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Benzodiazepines. 4. 2-Oxyamino-5-phenyl-3*H*-1,4-benzodiazepines[1]

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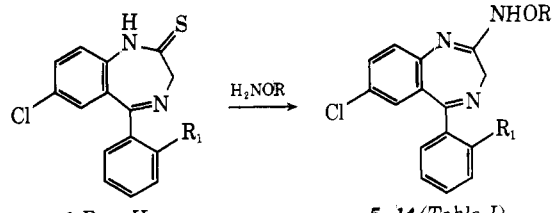
A series of 2-oxyamino-5-phenyl-3*H*-1,4-benzodiazepines has been prepared by the reaction of oxyamine derivatives with 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thiones. Pharmacologic testing in animals has shown that some of these compounds have interesting CNS depressant activity and suggests that they will have useful anxiolytic activity in man.

Because of our interest[1-3] in the potential antianxiety activity of new 1,4-benzodiazepine derivatives,[4-6] we have prepared a series of 5-phenyl-3*H*-1,4-benzodiazepines with oxyamino substituents at C-2.[7] Several of these compounds have excellent activity in our animal test systems which suggests that they will be useful anxiolytics in man.

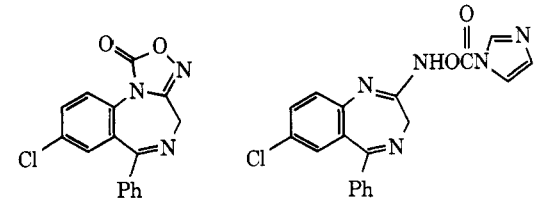
The preparation of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thiones (*e.g.*, **1** and **2**) and the condensation of these compounds with amines to give 2-amino-5-phenyl-



1, R_1 = H
2, R_1 = Cl

5–14 (Table I)

3*H*-1,4-benzodiazepines have been described by Archer and Sternbach.[8] We have utilized this method for the preparation of the 2-oxyamino derivatives shown in Table I. When the oxygen was unsubstituted (*viz.* **5**, Table I) the derivative could be condensed with phosgene in the presence of triethylamine to give the 1*H*,4*H*-[1,2,4]oxadiazolo-[4,3-*a*][1,4]benzodiazepin-1-one (**3**).† It is interesting that the reaction of **5** with carbonyldiimidazole gave the imidazolide **4** rather than the expected cyclic product **3**. The reaction of **5** with acetic anhydride in pyridine gave the acetate ester **16**.



3 **4**

† A preliminary report of this reaction has been published; see ref 2.

Experimental Section

Chemistry. Melting points, taken in a capillary tube, are corrected. The structures of all compounds were supported by ir, uv, and nmr spectra. Ir spectra were determined in Nujol using a Perkin-Elmer Model 421 recording spectrophotometer. Uv spectra were determined in 95% EtOH using a Cary Model 14 spectrophotometer. Nmr spectra were recorded on a Varian Model A-60A; chemical shifts were recorded in parts per million downfield from Me_4Si. 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°, made by Skelly Oil Co., Kansas City, Mo.

7-Chloro-2-(hydroxyamino)-5-phenyl-3*H*-1,4-benzodiazepine (5). Procedure A. A mixture of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepine-2-thione (**1**, 14.4 g, 0.05 mol), hydroxylamine hydrochloride (4.55 g), $NaHCO_3$ (5.45 g), and MeOH (250 ml) was refluxed for 1.5 hr with a stream of N_2 bubbling through the mixture. The cooled mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (750 g) with Et_3N-MeOH-EtOAc (2:13:85) and the product was crystallized from EtOAc to give 4.92 g, mp 122.5–130°, and 3.38 g, mp 128–132°, of **5**.

***N*-(7-Chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-*O*-(imidazol-1-ylcarbonyl)hydroxylamine (4).** A solution of carbonyldiimidazole (CDI, 2.62 g, 0.0162 mol) in dry THF (65 ml) was added to a stirred, ice-cold solution of **5** (2.32 g, 0.0081 mol) in THF (25 ml) and the resulting mixture was refluxed for 18 hr. Additional CDI (1.31 g, 0.0081 mol) was added and reflux was continued for 2 hr. The mixture was concentrated and the residue was suspended in H_2O. The solid was collected by filtration, washed with H_2O, dissolved in CH_2Cl_2, dried, concentrated, and crystallized from EtOAc–Skellysolve B to give 1.61 g (52.3%) of **4**, mp 105.5–106.5°. The analytical sample had mp 106.5°; uv end absorption, λ max 224.5 nm (ε 34,280), 250 (14,180), 300 (sh, 2350); ir 3140, 3120 (NH), sh 1795, 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.33, 5.03 (broad singlets, 2, C-3), 10.69 (s, 1, NH). *Anal.* ($C_{19}H_{14}ClN_5O_2$) C, H, Cl, N.

8-Chloro-6-phenyl-1*H*,4*H*-[1,2,4]oxadiazolo[4,3-*a*][1,4]benzodiazepin-1-one (3). A stirred solution of **5** (2.86 g, 0.0100 mol) and Et_3N (3.05 ml, 0.0220 mol) in dry toluene was cooled in an ice bath under N_2. Phosgene (0.795 ml, 0.011 mol) was evaporated into this mixture during 20 min. Excess phosgene was removed by bubbling a slow stream of N_2 through the mixture which was removed from the ice bath and allowed to stand at ambient temperature for 1 hr 15 min. The mixture was then poured into ice water and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was crystallized from EtOAc–Skellysolve B to give 1.56 g, mp 193–194°, and 0.80 g, mp 191–192° (75.6% yield), of **3**. The analytical sample

Table I. Physical and Analytical Data for the 2-Oxyamino-5-phenyl-3*H*-1,4-benzodiazepines

No.	R	R_1	Yield, %	Procedure	H_2NOR	Mp, °C	Recrystn solvent	Formula	Analyses
5	H	H	58.2	A[d]	NH_2OH[a]	126–130	EtOAc	$C_{15}H_{12}ClN_3O$	C, H, Cl, N
6	$CH_2CH{=}CH_2$	H	36.5	A[e]	$NH_2OCH_2CH{=}CH_2$[a,c]	134–135.5	Et_2O–Sk B	$C_{18}H_{16}ClN_3O$	C, H, Cl; N[b]
7	$C(CH_3)_3$	H	14	A[f]	$NH_2OC(CH_3)_3$[a,g]	251.5–252.5	EtOAc	$C_{19}H_{20}ClN_3O$	C, H, Cl, N
8	CH_2Ph	H	54	A[i]	NH_2OCH_2Ph[a,h]	180–181.5	MeOH	$C_{22}H_{18}ClN_3O$	C, H, Cl, N
9	CH_3	H	62.5	A[j]	NH_2OCH_3[a]	185–186	MeOH	$C_{16}H_{14}ClN_3O$	C, H, Cl, N
10	$(CH_2)_2NEt_2$	H	91	A[k]	$NH_2O(CH_2)_2NEt_2$[l]	99–100	EtOAc–Sk B	$C_{21}H_{25}ClN_4O \cdot 0.5H_2O$	C, H, Cl, N[m]
11	CH_2COOEt	H	31.3	A[n]	NH_2OCH_2COOEt[o]	113–114	Et_2O–Sk B	$C_{19}H_{18}ClN_3O_3$	C, H, Cl, N
12	$(CH_2)_2$-c-NC_4H_8	H	42.2	A[p]	$NH_2O(CH_2)_2$-c-NC_4H_8[q]	137.5–138.5	EtOAc	$C_{21}H_{23}ClN_4O \cdot H_2O$	C, H, Cl, N[r]
13	CH_3	Cl	70	*d*	NH_2OCH_3[a]	158.5–159.5	EtOAc	$C_{16}H_{13}Cl_2N_3O$	C, H, Cl, N
14	$CH_2CH{=}CH_2$	Cl	37.8	A[s]	$NH_2OCH_2CH{=}CH_2$[a,c]	130–131	EtOAc–Sk B	$C_{18}H_{15}Cl_2N_3O$	C, H, Cl, N

[a]Hydrochloride salt. [b]N: calcd, 12.90; found, 12.43. [c]A. C. Cope and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3427 (1949). [d]See Experimental Section. [e]EtOH solvent, reflux 4.5 hr. [f]MeOH–DMSO solvent, reflux 7 hr. [g]W. Theilacker and K. Ebke, *Angew. Chem.*, **68**, 303 (1956). [h]E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964). [i]Reflux 10 hr. [j]Reflux 5.5 hr. [k]EtOH solvent, reflux 7 hr. [l]D. O. Holland and F. A. Robinson, *J. Chem. Soc.*, 182 (1948). [m]H_2O: calcd, 2.29; found, 2.70. [n]EtOH–DMSO (10:1 v/v) solvent, reflux 7 hr. [o]E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. daVanzo, and M. E. Greig, *J. Med. Pharm. Chem.*, **5**, 464 (1962). [p]Reflux 2 hr. [q]Dihydrochloride salt: L. A. Paquette, *J. Org. Chem.*, **29**, 3545 (1964). [r]H_2O: calcd, 4.49; found, 3.54. [s]EtOH solvent, reflux 5 hr.

had mp 191–192°; uv λ max 226 nm (ε 31,200), 252 (13,100), 300 (sh, 2250); ir 1795 (sh), 1770, 1725 cm^{-1} (sh) (C=O); nmr [$(CD_3)_2SO$] δ 4.73 (br s, 2, C-3). *Anal.* ($C_{16}H_{10}ClN_3O_2$) C, H, Cl, N.

***O*-Acetyl-*N*-(7-chloro-5-phenyl-3*H*-1,4-benzodiazepin-2-yl)-hydroxylamine (16).** A stirred solution of Ac_2O (1.02 g, 0.01 mol) in pyridine (10 ml) was cooled in an ice bath and treated with **5** (1.44 g, 0.005 mol). The resulting mixture was allowed to stand under N_2 at ambient temperature for 18 hr and was poured into ice water. This mixture was stirred for 2 hr. The solid product was collected by filtration, washed (H_2O), and dissolved in CH_2Cl_2. The solution was dried (K_2CO_3) and concentrated *in vacuo*. Crystallization of the residue from MeOH–EtOAc gave 0.92 g (56%) of **16**, mp 217–218°. The analytical sample had mp 212.5–213.5°; uv (EtOH) end absorption, λ max 248 nm (ε 33,400), 329 (2350), 210 (sh 32,350), 233 (29,800); ir (Nujol) 3310 (NH), 1745, 1705 (C=O), 1655, 1635 cm^{-1} (C=N); nmr ($CDCl_3$) δ 2.23 (s, 3, $COCH_3$), 4.42 (s, 2, C-3). *Anal.* ($C_{17}H_{14}ClN_3O_2$) C, H, Cl, N.

7-Chloro-2-(methylthio)-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepine (15). A solution of 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepine-2-thione (**2**, 7.42 g, 0.0244 mol) in 1 *N* NaOH solution (28.9 ml) and MeOH (36 ml) was treated during 20 min with a solution of $(CH_3)_2SO_4$ (3.35 g) in MeOH (12 ml). This mixture was stirred for 10 min, diluted with H_2O, made strongly alkaline with NaOH, and extracted with Et_2O. The extract was washed (H_2O), dried (K_2CO_3), and concentrated. The residue was chromatographed on silica gel (500 g) with EtOAc–cyclohexane (25:75). The resulting product was crystallized from Et_2O at 0° to give 3.71 g (45%) of **15**, mp 113–118.5°. The analytical sample was crystallized from CH_2Cl_2–Et_2O and had mp 118–120°. *Anal.* ($C_{16}H_{12}Cl_2N_2S$) H, Cl, N; C: calcd, 57.32; found, 57.82; S: calcd, 9.57; found, 8.97.

7-Chloro-5-(*o*-chlorophenyl)-2-(methoxyamino)-3*H*-1,4-benzodiazepine (13). A mixture of **15** (1.60 g, 0.00476 mol), methoxyamine hydrochloride (0.794 g), $NaHCO_3$ (0.794 g), and absolute EtOH (50 ml) was refluxed for 4 hr with a slow stream of N_2 flowing through the reaction mixture. This mixture was concentrated *in vacuo*; the residue was mixed with H_2O and extracted with CH_2Cl_2. The extract was washed (H_2O), dried (K_2CO_3), and concentrated. Crystallization of the residue from EtOAc gave 1.11 g (70%) of **13**, mp 157–159°.

Pharmacology. Methods. Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all studies reported here. Unless otherwise indicated the test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered intraperitoneally to groups of six mice per dose, at multiple dose levels distributed at 0.3 log intervals. Procedures for measuring the effect of test compounds on overt behavior: loss of righting reflex (LRR) and traction (Tr); antagonism of nicotine-induced tonic extensor convulsions (TE) and death (D); potentiation of EtOH and pentobarbital-induced narcosis; antagonism of thiosemicarbazide- and strychnine-induced convulsions and lethality. Antagonism of electroshock convulsions, pentylenetetrazole-induced clonic convulsions, and foot shock-induced aggression have been described previously.[1,9-11] ED_{50} values were calculated by the method of Spearman and Karber.[12]

Results and Discussion

The pharmacologic results are presented in Table II. Data obtained for diazepam (**17**) and chlordiazepoxide (**18**) in the same test systems are included for comparison. In general, although the toxicity data are not reported here, the compounds were relatively nontoxic; the neurotoxic dose as reflected by LRR was greater than the highest dose tested.

Our initial observation that 7-chloro-2-(methoxyamino)-5-phenyl-3*H*-1,4-benzodiazepine (**9**), which coincidentally has the same empirical formula as chlordiazepoxide, was moderately active in our test systems prompted us to study the structure–activity relationships in this series. As might be expected the size and type of substituent on oxygen of the oxyamino function was important for biological activity. Thus the hydroxy derivative **5** was more potent than the methoxy derivative **9** which in turn was more active than compounds with larger substituents (*viz.* **6** and **7**); the benzyloxy derivative **8** had little activity.

Table II. Pharmacological Data[a]

No.	LRR	Tr	Antagonism: Nicotine TE	Antagonism: Nicotine D	Antagonism: Thiosemicarbazide	Antagonism: Strychnine	Antagonism: Electroshock	Antagonism: Pentylenetetrazole	Potentiation: Ethanol	Potentiation: Pentobarbital	Antagonism, foot shock
3	>200	>200	23	20	45	178	>200	>50	>100	>100	
4	>200	>200	3.1	3.1	10	178	50	12	36		
5	>200	>200	2.5	2.5	8	>100	100	12.5	16		
6	>200	>200	16	20	14	126	>100	50	45		
7	>200	>200	50	56	>100	>100	>100	>100	>50		
8	>200	>200	>200	>200							
9	>100	>100	4	4	45	>100	>100	22	29		
10	>200	>200	6.3	6.3	>100	>100	>100	>50	>100		>40
11	>200	>200	>200	>200	>100	>100	>100	>100	>100		
12	>200	>200	28	40	100	>200	>200	89	>100		
13	>100	>100	1.2	1.4	0.7	40	>100	2.1	25	25	
14	>200	89	0.2	0.2	0.5	36	>200	0.8	36	36	2.5
16	>200	>200	23	23	14	>100	>100	5.6	>50		
17[b]	50	7	0.28	0.28	0.7	8.0	50	0.8	0.9	5.0	1.8
18[b]	126	18	1.4	1.8	1.1	16	28	3.1	12.5	11	7.0

[a] See Experimental Section for explanation of the symbols. Values are ED_{50}'s expressed in mg/kg. [b] Samples of diazepam (**17**) and chlordiazepoxide (**18**) were obtained from Hoffmann-La Roche, Inc.

The acetoxy derivative **16** retained activity in the pentylenetetrazole and thiosemicarbazide tests but was less active than **5** for antagonizing nicotine induced TE and D. The high activity of the imidazolide **4** was interesting; however, this may have been an artifact since compounds of this type are often readily hydrolyzed in aqueous systems. In this case the hydrolysis product would be the active compound **5**.

The oxadiazole **3** was less active than the acyclic hydroxyamine derivative **5**. This result was surprising since the isosteric 2,4-dihydro-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepin-1-ones are highly active in these test systems.[13]

It has been noted previously that incorporation of an ortho halogen substituent on the 5-phenyl ring of diazepam[6] or on the 6-phenyl moiety of the 4-*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines[1] enhances the biological activity of the resulting analog. This effect was, however, not observed for 7-chloro-2-(methylamino)-5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepine 4-oxide which was somewhat less active than chlordiazepoxide. It is particularly noteworthy, therefore, that in the present series an *o*-chloro substituent on the 5-phenyl moiety markedly enhances the biological activity (compare compounds **6** and **9** with **14** and **13**, respectively). This effect was particularly apparent in tests which are believed to indicate potential antianxiety activity in man. Thus compound **14** was as active as diazepam (**17**) in the nicotine, thiosemicarbazide, pentylenetetrazole, and foot-shock tests. It was, however, less active than diazepam in its ability to potentiate the hypnotic effects of ethanol and pentobarbital and to antagonize strychnine-induced convulsions and the traction response in mice. These results suggest that compound **14** (U-31,920) will be an effective antianxiety drug with low sedative and muscle relaxant potential.

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