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Benzodiazepines. 4. 2-Oxyamino-5-phenyl-3H-1,4-benzodiazepines¹

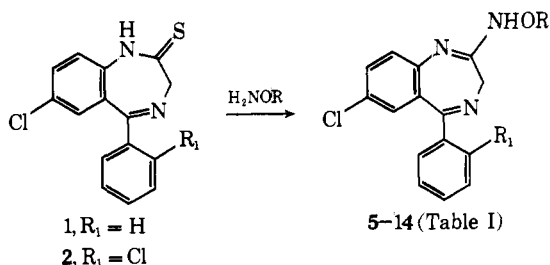
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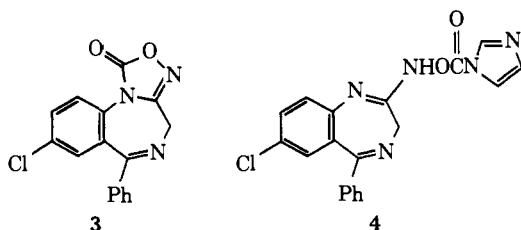
A series of 2-oxyamino-5-phenyl-3H-1,4-benzodiazepines has been prepared by the reaction of oxyamine derivatives with 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thiones. Pharmacologic testing in animals has shown that some of these compounds have interesting CNS depressant activity and suggests that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

Because of our interest¹⁻³ in the potential antianxiety activity of new 1,4-benzodiazepine derivatives,⁴⁻⁶ we have prepared a series of 5-phenyl-3H-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-2H-1,4-benzodiazepine-2-thiones (e.g., 1 and 2) and the condensation of these compounds with amines to give 2-amino-5-phenyl-



3H-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 1H,4H-[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 imidazole 4 rather than the expected cyclic product 3. The reaction of 5 with acetic anhydride in pyridine gave the acetate ester 16.



[†] 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 Me₄Si. 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-3H-1,4-benzodiazepine (5). **Procedure A.** A mixture of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-thione (1, 14.4 g, 0.05 mol), hydroxylamine hydrochloride (4.55 g), NaHCO₃ (5.45 g), and MeOH (250 ml) was refluxed for 1.5 hr with a stream of N₂ 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 Et₃N-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-3H-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 H₂O. The solid was collected by filtration, washed with H₂O, dissolved in CH₂Cl₂, 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 (CDCl₃) δ 4.33, 5.03 (broad singlets, 2, C-3), 10.69 (s, 1, NH). *Anal.* (C₁₉H₁₄ClN₅O₂) C, H, Cl, N.

8-Chloro-6-phenyl-1H,4H-[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 Et₃N (3.05 ml, 0.0220 mol) in dry toluene was cooled in an ice bath under N₂. 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 N₂ 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 CHCl₃. The extract was dried (Na₂SO₄) 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-Oxamino-5-phenyl-3H-1,4-benzodiazepines

No.	R	R ₁	Yield, %	Procedure	H ₂ NOR	Mp, °C	Recrystn solvent	Formula	Analyses
5	H	H	58.2	A ^d	NH ₂ OH ^a	126-130	EtOAc	C ₁₆ H ₁₂ ClN ₃ O	C, H, Cl, N
6	CH ₂ CH=CH ₂	H	36.5	A ^e	NH ₂ OCH ₂ CH=CH ₂ ^{a,c}	134-135.5	Et ₂ O-Sk B	C ₁₈ H ₁₆ ClN ₃ O	C, H, Cl, N ^b
7	C(CH ₃) ₃	H	14	A ^f	NH ₂ OC(CH ₃) ₃ ^{a,g}	251.5-252.5	EtOAc	C ₁₉ H ₂₀ ClN ₃ O	C, H, Cl, N
8	CH ₂ Ph	H	54	A ⁱ	NH ₂ OCH ₂ Ph ^{a,h}	180-181.5	MeOH	C ₂₂ H ₁₈ ClN ₃ O	C, H, Cl, N
9	CH ₃	H	62.5	A ^j	NH ₂ OCH ₃ ^a	185-186	MeOH	C ₁₆ H ₁₄ ClN ₃ O	C, H, Cl, N
10	(CH ₂) ₂ NEt ₂	H	91	A ^k	NH ₂ O(CH ₂) ₂ NEt ₂ ^l	99-100	EtOAc-Sk B	C ₂₁ H ₂₃ ClN ₃ O·0.5H ₂ O	C, H, Cl, N ^m
11	CH ₂ COOEt	H	31.3	A ⁿ	NH ₂ OCH ₂ COOEt ^o	113-114	Et ₂ O-Sk B	C ₁₉ H ₁₈ ClN ₃ O ₂	C, H, Cl, N
12	(CH ₂) ₂ -c-NC ₄ H ₉	H	42.2	A ^p	NH ₂ O(CH ₂) ₂ -c-NC ₄ H ₉ ^q	137.5-138.5	EtOAc	C ₂₁ H ₂₃ ClN ₃ O·H ₂ O	C, H, Cl, N ^r
13	CH ₃	Cl	70	d	NH ₂ OCH ₃ ^a	158.5-159.5	EtOAc	C ₁₆ H ₁₃ Cl ₂ N ₃ O	C, H, Cl, N
14	CH ₂ CH=CH ₂	Cl	37.8	A ^r	NH ₂ OCH ₂ CH=CH ₂ ^{a,c}	130-131	EtOAc-Sk B	C ₁₈ H ₁₅ Cl ₂ N ₃ O	C, H, Cl, N

^aHydrochloride salt. ^bN: calcd, 12.90; found, 12.43. ^cA. C. Cope and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3427 (1949). ^dSee Experimental Section. ^eEtOH solvent, reflux 4.5 hr. ^fMeOH-DMSO solvent, reflux 7 hr. ^gW. Theilacker and K. Ebke, *Angew. Chem.*, **68**, 303 (1956). ^hE. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964). ⁱReflux 5.5 hr. ^jEtOH solvent, reflux 7 hr. ^kD. O. Holland and F. A. Robinson, *J. Chem. Soc.*, 182 (1948). ^lH₂O: calcd, 2.29; found, 2.70. ^mEtOH-DMSO (10:1 v/v) solvent, reflux 7 hr. ⁿE. 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). ^oReflux 2 hr. ^pDihydrochloride salt: L. A. Paquette, *J. Org. Chem.*, **29**, 3545 (1964). ^qH₂O: calcd, 4.49; found, 4.49. ^rEtOH 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 [(CD₃)₂SO] δ 4.73 (br s, 2, C-3). *Anal.* (C₁₆H₁₀ClN₃O₂) C, H, Cl, N.

O-Acetyl-N-(7-chloro-5-phenyl-3H-1,4-benzodiazepin-2-yl)-hydroxylamine (16). A stirred solution of Ac₂O (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 N₂ 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 (H₂O), and dissolved in CH₂Cl₂. The solution was dried (K₂CO₃) 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 (CDCl₃) δ 2.23 (s, 3, COCH₃), 4.42 (s, 2, C-3). *Anal.* (C₁₇H₁₄ClN₃O₂) C, H, Cl, N.

7-Chloro-2-(methylthio)-5-(o-chlorophenyl)-3H-1,4-benzodiazepine (15). A solution of 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-2H-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 (CH₃)₂SO₄ (3.35 g) in MeOH (12 ml). This mixture was stirred for 10 min, diluted with H₂O, made strongly alkaline with NaOH, and extracted with Et₂O. The extract was washed (H₂O), dried (K₂CO₃), and concentrated. The residue was chromatographed on silica gel (500 g) with EtOAc-cyclohexane (25:75). The resulting product was crystallized from Et₂O at 0° to give 3.71 g (45%) of 15, mp 113-118.5°. The analytical sample was crystallized from CH₂Cl₂-Et₂O and had mp 118-120°. *Anal.* (C₁₆H₁₂Cl₂N₂S) H, Cl, N; C: calcd, 57.32; found, 57.82; S: calcd, 9.57; found, 8.97.

7-Chloro-5-(o-chlorophenyl)-2-(methoxyamino)-3H-1,4-benzodiazepine (13). A mixture of 15 (1.60 g, 0.00476 mol), methoxyamine hydrochloride (0.794 g), NaHCO₃ (0.794 g), and absolute EtOH (50 ml) was refluxed for 4 hr with a slow stream of N₂ flowing through the reaction mixture. This mixture was concentrated *in vacuo*; the residue was mixed with H₂O and extracted with CH₂Cl₂. The extract was washed (H₂O), dried (K₂CO₃), 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 nicotinic-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 ED₅₀ 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-3H-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 oxamino 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						Potentiation		Antagonism, foot shock
			Nicotine		Thiosemicarbazide	Strychnine	Electroshock	Pentylenetetrazole	Ethanol	Pentobarbital	
			TE	D							
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

^aSee Experimental Section for explanation of the symbols. Values are ED₅₀'s expressed in mg/kg. ^bSamples 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 diazepam⁶ or on the 6-phenyl moiety of the 4-*H*-s-triazolo[4,3-*a*][1,4]benzodiazepines¹ 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 anti-anxiety 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 anti-anxiety drug with low sedative and muscle relaxant potential.

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