5-(2-Aminoethyl)-2-oxazolidinones with Central Nervous System Depressant and Antiinflammatory Activity

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A series of 5-(2-aminoethyl)oxazolidinones has been prepared and tested for CNS depressant, analgetic, and antiinflammatory properties. Several of the compounds show moderate to potent activity.

The reaction of chloroethyloxazolidinones with amines as described in the preceding paper has led to compounds with interesting pharmacological activity.[1] In our continuing effort to uncover compounds with useful CNS depressant activity, we have extended this original exploratory work to include a series of aminoethyloxazolidinones prepared from aryl-substituted piperidines, pyrrolidines, and related cyclic amines. Several of the compounds prepared show CNS depressant activity in animal models while others show strong analgetic action. A few compounds demonstrate antiinflammatory activity.

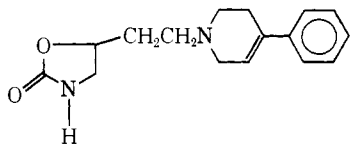
Chemistry. Most of the compounds described (Tables I–IV) were prepared by alkylating the appropriate amine with a 5-(2-chloroethyl)-2-oxazolidinone. The starting oxazolidinones were prepared from substituted pyrrolidinols by methods previously described.[1] Standard procedures described in the Experimental Section were used to prepare the amine oxides, acylated derivatives, and other related compounds.

Pharmacological Methods and Results. The pharmacological data for the compounds described in Tables I–IV are summarized in Table V. The specific assays are described below.

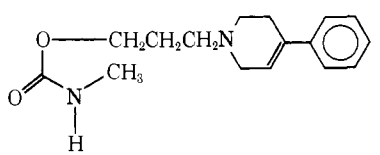
CNS Depressant Activity. The primary screen used for determining CNS depressant activity was the isolation-induced agressive behavior test of DaVanzo, *et al.*,[2] previously described. Tests were carried out 60 min after drug administration. Compounds were dissolved or suspended in physiological saline. Groups of five mice were tested initially with a dose of 20 mg/kg ip. ED_{50}'s were obtained on the most active compounds using the method of Litchfield and Wilcoxon.[3]

Among the most active compounds tested were the 4-phenyltetrahydropyridines **1**, **2**, and **7** with ED_{50}'s of 7, 13, and 6 mg/kg, respectively, compared to chlorpromazine and triperidol with activities of 2.5 and 2.2 mg/kg in the same assay. The ED_{50} of the corresponding phenylpiperazine analog described previously[1] was 12 mg/kg.

Compounds **21** and **22** may be considered ring-opened analogs of the cyclic oxazolidinones and are among the most active members of the series.



1, ED_{50} 7 mg/kg



21, ED_{50} 7 mg/kg

Analgetic Activity. Some of the compounds were tested for analgetic activity in mice using a modification of the method of Nilsen,[4] as previously described.[5] In addition, some of the compounds were also investigated for analgetic action in rats using the method of Randall and Selitto.[6] Compounds **24** and **26** were found to have potent analgetic action with ED_{50}'s of 1.6 and 1.2 mg/kg ip, compared to morphine with an ED_{50} in the same assay of 1.7 mg/kg.

Antiinflammatory Activity. The method used for determining antiinflammatory activity was the carrageenan-induced rat paw edema assay of Winter, *et al.*[7] Female rats of the Sprague–Dawley strain were obtained from Dublin Laboratories and weighed between 130 and 150 g. Five animals were used for each determination. The animals were housed in individual cages. All animals were fasted for 48 hr prior to administration of test materials with water *ad libitum* during the first 36 hr. Approximately 60 ml of a 10% glucose (in 0.5 *N* saline) solution was allowed *ad libitum* to each rat during the last 12 hr preceding administration of test materials. Any animals that did not consume approximately 60 ml of the solution were not used in the experiments.

The test compounds or saline (controls) were administered orally or by intraperitoneal injection 30 min prior to administration of the carrageenan. The dosages were calculated as the free base.

Carrageenan (0.1 ml of a 1% solution in saline) was injected into the plantar surface of the right hind paw. The left hind paw was injected with 0.1 ml of normal saline. Following carrageenan (4.5 hr) (5 hr postdrug) the animals were sacrificed with $CHCl_3$. The hind paws were immediately removed at the level of the lateral malleolus and weighed. Control and treated animal paws were then compared to determine drug effects.

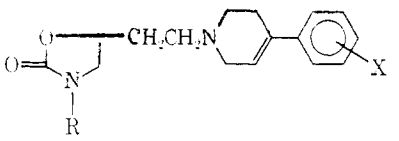
The three most active compounds tested in this assay were compounds **2**, **4**, and **20** with 37, 26, and 39% inhibition of foot edema, respectively, at 20 mg/kg po. Phenylbutazone at 40 mg/kg po gave a 27% inhibition in the same assay.

Aggregated Mice. Some of the compounds were studied in grouped white mice for possible antagonistic action to *d*-amphetamine.[8] Groups of ten mice each were placed in 6 × 10 × 4 in. wire mesh cages. The mice were given 21 mg/kg of *d*-amphetamine by ip injection and various amounts of the test compounds also by ip injection. The number of animals dead was determined 22 hr later. Approximately 90% of the control animals given 21 mg/kg of *d*-amphetamine died. Haloperidol gives complete protection at 5 mg/kg.

Electroencephalographic Study. Compound **2** was investigated further using electroencephalographic techniques described previously.[9]

The compound produced generalized slowing of cortical potentials after a transient increase in low voltage fast activity. The waves became progressively slower following the administration of 1, 3, 5, and 10 mg/kg of the compound. The activity became disorganized after an additional 20 mg/kg and isolated spikes appeared in the EEG.

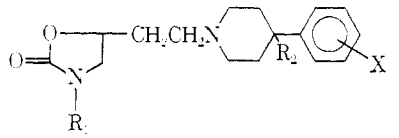
Table I



Compd	R	X	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Analyses[c]
1	H	H	16	B–O	143–145	$C_{16}H_{20}N_2O_2$
2	CH_3	H	82	E–W	102–104	$C_{17}H_{22}N_2O_2$
3	H	4-F	59	B	138–140	$C_{16}H_{19}FN_2O_2$
4	CH_3	4-F	63	B–O	98–100	$C_{17}H_{21}FN_2O_2$
5	H	4-OCH_3	30	M	172–174	$C_{17}H_{22}N_2O_3$
6	CH_3	4-OCH_3	38	EA	119–121	$C_{18}H_{24}N_2O_3$
7	CH_3	3-CF_3	28	I	207–209	$C_{18}H_{22}ClF_3N_2O_2$[d]

[a] Solvent abbreviations: B, C_6H_6; Bu, MeCOEt, C, $CHCl_3$; E, EtOH; EA, EtOAc; I, *i*-PrOH; IE, *i*-Pr_2O; M, MeOH; O, isooctane; W, H_2O. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, and N. [d] HCl salt.

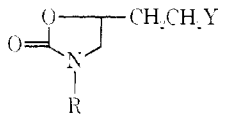
Table II

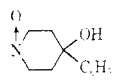
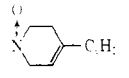
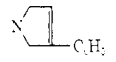
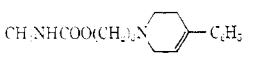
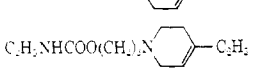
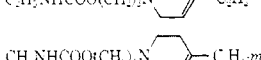


Compd	R_1	R_2	X	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Analyses[c]
8	$C_6H_5CH_2$	H	H	67	B–O	96–98	$C_{23}H_{28}N_2O_2$
9	H	H	H	35	EA	134–137	$C_{16}H_{22}N_2O_2$
10	CH_3	H	*m*-CF_3	43	I	229–231	$C_{18}H_{24}ClF_3N_2O_2$[d]
11	$C_6H_5CH_2$	OH	H	72	B–O	108–110	$C_{23}H_{28}N_2O_3$
12	H	OH	H	68	B–E	180–183	$C_{16}H_{22}N_2O_3$
13	CH_3	OH	H	50	B	128–130	$C_{17}H_{24}N_2O_3$
14	H	OH	*p*-CH_3O	31	M–EA	178–180	$C_{17}H_{24}N_2O_4$
15	CH_3	OH	*p*-CH_3O	59	C–EA	150–152	$C_{18}H_{26}N_2O_4$
16	CH_3	OH	*m*-CF_3	75	I	221–223	$C_{18}H_{24}ClF_3N_2O_3$[d]

[a] See footnote *a*, Table I, for solvent abbreviations. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, and N. [d] HCl salt.

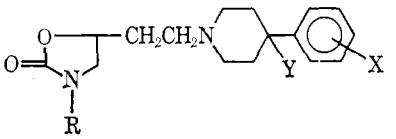
Table III



Compd	R	Y	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Analyses[c]
17	CH_3		51	M–Bu	169–170	$C_{17}H_{24}N_2O_4$
18	CH_3		68	M	163–164	$C_{23}H_{35}N_3O_6S$[d]
19	CH_3		78	I–IE	215–217	$C_{11}H_{19}ClN_2O_2$[e]
20	H		20	EA	105–107	$C_{13}H_{16}N_2O_2$
21[f]			37	I	167–168	$C_{16}H_{23}ClN_2O_2$[e]
22[f]			72	I–IE	157–158	$C_{17}H_{25}ClN_2O_2$[e]
23[f]			88	I–IE	159–161	$C_{17}H_{22}ClF_3N_2O_2$[e]

[a] See footnote *a*, Table I, for solvent abbreviations. [b] Melting points are uncorrected. [c] All compounds analyzed for C, H, and N. [d] Hexamate salt. [e] HCl salt. [f] Compounds **21**, **22**, and **23** are ring-opened analogs of the cyclic oxazolidinones.

Table IV



Compd	R	X	Y	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Analyses[c]
24	H	H	$OCOC_2H_5$	61	I	186–188	$C_{19}H_{27}ClN_2O_4$[d,e]
25	CH_3	H	$OCOC_2H_5$	70	I–IE	201–203	$C_{20}H_{29}ClN_2O_4$[d]
26	$C_6H_5CH_2$	H	$OCOC_2H_5$	73	I–IE	156–158	$C_{30}H_{36}N_2O_8$[f]
27	CH_3	*m*-CF_3	$OCOC_2H_5$	69	I–IE	188–190	$C_{21}H_{28}ClF_3N_2O_4$[d]
28	H	H	$COOC_2H_5$	26	EA–M	203–205	$C_{19}H_{29}ClN_2O_5$[g]
29	$C_6H_5CH_2$	H	$COOC_2H_5$	37	B–O	90–92	$C_{26}H_{32}N_2O_4$

[a] See footnote *a*, Table I, for solvent abbreviations. [b] Melting points are uncorrected. [c] All compounds were analyzed for C, H, and N. [d] HCl salt. [e] C: calcd, 59.60; found, 58.91. [f] Fumarate salt. [g] HCl salt monohydrate.

Table V. Pharmacological Data[a]

	Fighting mouse				Rat paw edema		Aggregated mice	
Compd	No. blocked/ no. tested	ED_{50}, mg/kg ip	Randall-Selitto ED_{50}, mg/kg	Nilsen ED_{50}, mg/kg ip	% inhibition	mg/kg (route)	No. protected/ no. tested	mg/kg ip
1		7 (5.0–9.9)			12	20 (po)	8/10	5
2		13 (8.7–20.1)			37	20 (po)	10/10	5
3	2/5							
4	3/5				26	20 (po)		
5	1/5							
6	1/5							
7		6 (3.4–10.0)					6/6	5
8	2/5				2	20 (ip)		
9	2/5				12	20 (ip)	10/10	10
10		11 (8.0–15.0)						
11								
12	0/5						10/10	10
13	0/5				5	20 (po)	0/10	10
14	0/5							
15	0/5							
16	0/5							
17	0/5							
18	1/5				4	20 (po)		
19	0/5				14	40 (po)		
20		12 (7.0–20.4)			39	20 (po)		
21		7 (5.0–9.9)			21	20 (po)		
22		6 (3.6–9.3)						
23		9 (5.0–14.4)						
24	0/5		6 (3.5–8.9) ip 19 (13–29) po	1.6 (0.9–2.5)	2	20 (ip)	0/10	10
25				4.4 (3.2–6.0)	11	20 (po)		
26	2/5		0.6 (0.4–1.0) ip 8 (5.2–12.1) po	1.2 (0.8–1.6)			0/10	10
27	0/5			18 (10.3–32.4)				
28	1/5		43 (19–96) po	11 (7.1–16.5)	30	40 (ip)		
29	0/5			11 (8.1–14.6)	8	20 (ip)		

[a] See text for experimental details and doses where not shown.

After another 40 mg/kg, the EKG was altered and the cortex became isoelectric for a short time. Electrical signs of a convulsion with postictal depression followed this dose. The actions are similar to those of chlorpromazine.

Like chlorpromazine, doses of 3 or 5 mg/kg of **2** decreased responses to stimulation of the ascending activating system but higher doses of 10 or 20 mg/kg did not completely abolish the response. This compound produced a diphasic response to stimulation of midline nuclei of the thalamus similar to that produced by chlorpromazine. Low doses up to 5 mg/kg increased the pattern of thalamic recruitment and higher doses depressed the response.

Also like chlorpromazine, doses of 1 and 3 mg/kg of the compound prolonged hippocampal after-discharge and facilitated the spread of the discharges to the cortex. Electrodes placed in the amygdaloid complex showed that convulsions produced by the compound originated in this area as they apparently do when chlorpromazine is used as the convulsant.

The only area in which **2** differed in its action from that of chlorpromazine was in the study of the cortical after-discharge. Low doses of chlorpromazine tended to prolong this evoked potential while low doses of **2** reduced the response and 10 mg/kg abolished it. It is, however, interesting to note that one group of major tranquilizers, the butyrophenones, also abolish this cortical response.[10]

The acute ip LD_{50}'s in mice and rats of compound **1** are 180 (160–202) and 140 mg/kg (118–165), respectively. Metabolism studies on compound **2** have been reported previously.[11]

Experimental Section

The procedures given below are representative for the preparation of the compounds listed in Tables I–IV. Analyses, yields, and physical properties are recorded in the tables. Temperatures are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3-Methyl-5-[2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)ethyl]-2-oxazolidinone (2). A stirred mixture of 8.35 g (0.05 mol) of 3-methyl-5-(2-chloroethyl)-2-oxazolidinone, 10 g (0.05 mol) of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride, and 20 g of $NaHCO_3$ in 75 ml of 2-butanol was refluxed under N_2 for 24 hr. The mixture was cooled and the precipitate was removed by filtration. The precipitate was added to water and the insoluble product (8.9 g) was filtered off and washed with water. The original filtrate was concentrated to an oil, dissolved in C_6H_6, and dried ($MgSO_4$). The hot benzene solution was treated with isooctane and after cooling yielded 2.9 g of additional product. The combined product was recrystallized.

5-[2-[4-(4-Fluorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]ethyl]-2-oxazolidinone (3). A stirred mixture of 4.9 g (0.03 mol) of 5-(2-chloroethyl)-2-oxazolidinone, 6.9 g (0.03 mol) of 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride, and 15 g of $NaHCO_3$ in 60 ml of 2-butanol was refluxed for 24 hr. The inorganic salts were filtered off from the hot solution and, after cooling, the filtrate yielded 1.5 g of product. The filtrate was evaporated to dryness and the residue was dissolved in $CHCl_3$ and extracted several times with H_2O. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated to a solid. The product fractions were combined and recrystallized.

3-Benzyl-5-[2-(4-hydroxy-4-phenyl-1-piperidinyl)ethyl]-2-oxazolidinone (11). A mixture of 35 g (0.14 mol) of 3-benzyl-5-(2-chloroethyl)-2-oxazolidinone, 25 g (0.14 mol) of 4-hydroxy-4-phenylpiperidine, and 20 g (0.14 mol) of K_2CO_3 in 300 ml of *n*-butanol was refluxed under N_2 for 16 hr. After cooling, the inorganic salts were filtered off and the filtrate was concentrated under reduced pressure to an oil. Trituration with dry Et_2O gave crude product which was recrystallized.

5-[2-(4-Phenyl-1-piperidinyl)ethyl]-2-oxazolidinone (9). A suspension of 18 g (0.05 mol) of 3-benzyl-5-[2-(4-phenyl-1-piperidinyl)ethyl]-2-oxazolidinone in 30 ml of THF was added slowly to a stirred solution of 3 g (0.17 mol) of Na in 200 ml of liquid NH_3. After stirring 30 min NH_4Cl was added until the blue color disappeared; then the ammonia was allowed to evaporate overnight. The resulting solid was treated with H_2O and extracted into $CHCl_3$. The $CHCl_3$ layer was extracted several times with 3 *N* HCl. Neutralization of the acid extract gave impure product which was recrystallized from EtOAc.

5-[2-[3-Phenyl-1-(3-pyrrolinyl)]ethyl]-2-oxazolidinone (20). A stirred mixture of 7.35 g (0.05 mol) of 5-(2-chloroethyl)-2-oxazolidinone, 8 g (0.05 mol) of 3-phenyl-3-pyrrolidinol, and 14 g of $NaHCO_3$ in 50 ml of 2-butanol was refluxed for 18 hr. The mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure to an oil (14 g). The crude oil was dissolved in 50 ml of 6 *N* HCl and heated on a steam bath for 30 min. The acidic solution was cooled in ice, diluted with 100 ml of ice-H_2O, and treated slowly with cold 25% NaOH until basic. The resulting gum was extracted into $CHCl_3$, dried ($MgSO_4$), and concentrated under reduced pressure to an oil (13 g). The oil was dissolved in a small amount of C_6H_6 and chromatographed on 300 g of 60–100 mesh Florisil. The column was eluted with C_6H_6 containing increasing amounts of Me_2CO up to pure Me_2CO. The fractions containing the desired product were combined and concentrated and the product was recrystallized: uv λ max (EtOH) 251 mμ (ε 12,650).

1-(3-Hydroxypropyl)-4-phenyl-1,2,3,6-tetrahydropyridine Hydrochloride. A mixture of 79.5 g (0.5 mol) of 4-phenyl-1,2,3,6-tetrahydropyridine, 69.5 g (0.5 mol) of trimethylene bromohydrin, 50 g of K_2CO_3, and 400 ml of absolute EtOH was refluxed for 3 hr, filtered, and concentrated. The residual oil was made basic with 50% NaOH and extracted with $CHCl_3$. After the combined extracts were washed with H_2O, the solvent was evaporated. The residual oil was distilled at reduced pressure and the fraction boiling at 138–140° (0.01 mm) collected. The viscous oil crystallized on standing: mp 45–47°. The product was converted to an HCl salt. *Anal.* ($C_{14}H_{20}ClNO$) C, H, N.

1-(3-Methylcarbamoyloxypropyl)-4-phenyl-1,2,3,6-tetrahydropyridine Hydrochloride (21). To a solution of 15.2 g (0.07 mol) of 1-(3-hydroxypropyl)-4-phenyl-1,2,3,6-tetrahydropyridine in 200 ml of dry C_6H_6 was added slowly a solution of 4.0 g (0.07 mol) of CH_3NCO in 30 ml of dry C_6H_6. The solution was stirred for 16 hr at room temperature and then the solvent was evaporated. The resulting product was converted to a crystalline HCl salt.

3-Benzyl-5-[2-(4-carbethoxy-4-phenyl-1-piperidinyl)ethyl]-2-oxazolidinone (29). A mixture of 22.6 g (0.094 mol) of 3-benzyl-5-(2-chloroethyl)-2-oxazolidinone, 27.0 g (0.097 mol) of 4-phenyl-4-carbethoxypiperidine carbonate, and 40.5 g of K_2CO_3 was refluxed with stirring in 300 ml of absolute EtOH under N_2 for 5 days. After cooling, the inorganic salt was filtered off and the filtrate was treated with several pieces of Dry Ice to precipitate the remaining starting amine. The amine carbonate was removed by filtration and the filtrate was concentrated yielding 9.7 g of impure product. The product was purified by column chromatography (350 g of Florisil using C_6H_6-Me_2CO to elute), followed by recrystallization.

3-Methyl-5-[2-(4-propionoxy-4-phenyl-1-piperidinyl)ethyl]-2-oxazolidinone Hydrochloride (25). A stirred mixture of 15 g (0.049 mol) of 3-methyl-5-[2-(4-hydroxy-4-phenyl-1-piperidinyl)ethyl]-2-oxazolidinone and 30 g (0.22 mol) of K_2CO_3 in 100 ml of $CHCl_3$ was treated dropwise with 6 g (0.065 mol) of EtOCl in 10 ml of $CHCl_3$. After stirring 4 hr at room temperature 100 ml of H_2O was added and the mixture was stirred an additional 30 min. The $CHCl_3$ layer was separated, dried ($MgSO_4$), and concentrated to an oil which was converted to a crystalline HCl salt.

3-Methyl-5-[2-(4-phenyl-1-oxido-1,2,3,6-tetrahydro-1-pyridyl)ethyl]-2-oxazolidinone (18). A mixture of 5 g of 3-methyl-5-[2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)ethyl]-2-oxazolidinone, 35 ml of 30% H_2O_2, and 50 ml of MeOH was stirred overnight at room temperature. The excess H_2O_2 was decomposed with PtO_2 and the mixture was filtered. The filtrate was treated with 1 equiv of hexamic acid and concentrated, and the residue was recrystallized from MeOH. The nmr spectrum and tlc ($CHCl_3$–$HCONH_2$ on Avicel) indicated a single diastereomer was isolated.

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