the reaction had reached equilibrium; higher temperatures either did not drive the reaction to completion or caused decomposition. This product was easily purified by crystallization. However, in order to identify positively the impurity and to achieve a synthesis for ^{14}C dimethobromide **31**, which precludes crystallization, this product was chromatographed on acid-washed alumina (70 wt) and eluted with *i*-PrOH–EtOAc (3:1) to yield the monomethobromide** **33** (60 mg); further elution with *i*-PrOH–EtOAc (3:1) and *i*-PrOH yielded pure dimethobromide **31** (1.04 g, 77%).

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That this methobromide has a 16-ammonio substituent was proved by its loss during the modified Hoffman degradation achieved by boiling a solution of the methobromide (100 mg) and NaOMe (300 mg) in DMF under reflux for 30 min. The sole product was crystallized from acetone to yield 2β-piperidino-5α-androstan-3α-ol-17-one (8b**, 60 mg).

Synthesis and Central Nervous System Depressant Activity of Some 5-(2-Substituted alkyl)-2-oxazolidinones[1]

Marvel L. Fielden,* William J. Welstead, Jr., Norman D. Dawson, Ying-Ho Chen, Richard P. Mays, John P. DaVanzo, and Carl D. Lunsford

Research Laboratories, A. H. Robins Company, Incorporated, Richmond, Virginia 23220.

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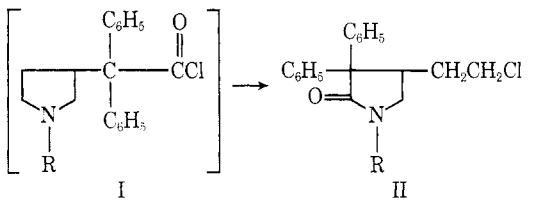
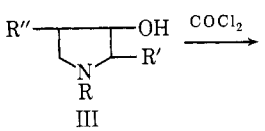
A novel method for preparing 5-(2-chloroalkyl)-2-oxazolidinones from 1-substituted 3-pyrrolidinols and phosgene is described. These compounds are intermediates for a series of 5-[2-(4-phenylpiperazino)alkyl]-2-oxazolidinones which are active CNS depressants.

A previous report from this laboratory described the conversion of α-(1-substituted 3-pyrrolidinyl)-1,1-diphenylacetic acids to the corresponding acid chlorides and their facile rearrangement to 1-substituted 4-(2-chloroethyl)-3,3-diphenyl-2-pyrrolidinones[2] (I → II).

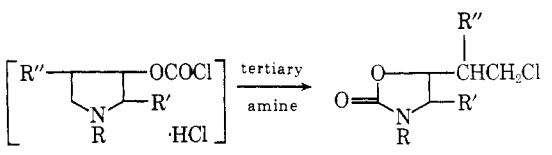


I II

By an analogous reaction a series of 3-substituted 2-oxazolidinones having a 2-substituted alkyl group in the 5 position has been prepared from 1-substituted 3-pyrrolidinols and phosgene.



III



IV V

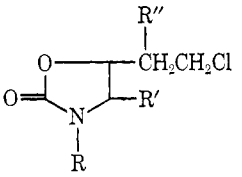
Compound V has been proven to be a useful intermediate to pharmacologically active compounds since the halogen of this molecule is easily replaced by various basic moieties. When the halogen of V is substituted by 4-phenylpiperazines, the resulting compounds (R equal to hydrogen or lower alkyl) exhibit major tranquilizing properties in animals. This has led to the preparation of a number of substituted 4-phenylpiperazine derivatives.

Chemistry. The 5-(2-chloroalkyl)-3-substituted 2-oxazolidinones were prepared by adding the properly substituted pyrrolidinol to a solution of phosgene in chloroform. The resulting carbonyl chloride hydrochloride (IV) was not isolated but its presence in solution was suggested by characteristic infrared absorption bands. When a solution containing IV was neutralized with triethylamine, the neutral oxazolidinone V was obtained. These 5-(2-chloroethyl)-2-oxazolidinones were stable in the presence of dilute acids or dilute alkali (when kept cold) and could be distilled with a minimum of decomposition at temperatures below 150°. The yield of purified products by this method ranged from approximately 35 to 70% of theoretical. The compounds of this type which have been prepared and identified are shown in Table I (compounds **1–7**).

An intermediate of type V where R, R′, and R″ are hydrogen (compound 8) was prepared by the stepwise degradation of compound **10**.

Compound 8 was also prepared by reacting 1-chloro-3,4-epoxybutane with urethane and a catalytic amount of lithium amide.

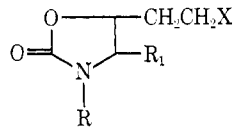
Table I



Compd	R	R′	R″	Mp, °C	Bp, °C (mm)	Yield, %	Empirical formula[b]
1	CH_3	H	H		120 (0.2)	52	$C_6H_{10}ClNO_2$[c]
2	C_2H_5	H	H		120–122 (0.2)	56	$C_7H_{12}ClNO_2$
3	n-C_4H_9	H	H		134–141 (0.2)	34	$C_9H_{16}ClNO_2$
4	Cyclohexyl	H	H	56–59		89[a]	$C_{11}H_{18}ClNO_2$
5	$CH_2C_6H_5$	H	H	51–52		81[a]	$C_{12}H_{14}ClNO_2$
6	CH_3	CH_3	H		120–125 (0.1)	70	$C_7H_{12}ClNO_2$
7	CH_3	H	CH_3		118–122 (0.1)	71	$C_7H_{12}ClNO_2$[d]
8	H	H	H	71–73		80	$C_5H_8ClNO_2$

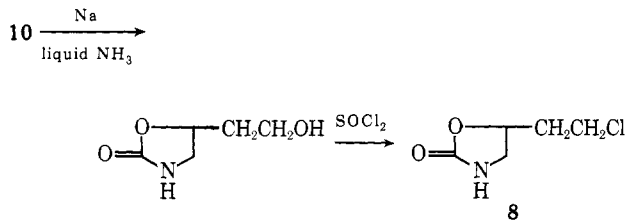
[a] Yield of crude oil used as intermediate. [b] All compounds were analyzed for C, H, and N. [c] C: calcd, 44.04; found, 44.59. [d] C: calcd, 47.33; found, 46.56.

Table II

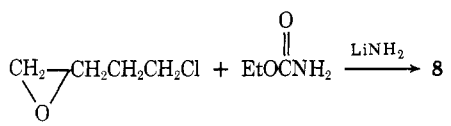


Compd	R	X	Method	Yield, %	Mp or bp (mm), °C	Recrystn solvent[d]	Empirical formula[e]
9	$CH_2C_6H_5$	I	*a*	51	42–43	IE	$C_{12}H_{14}INO_2$
10	$CH_2C_6H_5$	CH_3CO_2	*a*	25	172–176 (0.1)		$C_{14}H_{17}NO_4$
11	$CH_2C_6H_5$	3,5-$(CH_3)_2C_6H_3O$	*a*	23	70–71	IE	$C_{20}H_{23}NO_3$
12	H	3,5-$(CH_3)_2C_6H_3O$	C	43	106–108	EA	$C_{13}H_{17}NO_3$
13	CH_3	–C≡N	*a*	36	44–45	I–IE	$C_7H_{10}N_2O_2$
14	CH_3	–NHCH$_3$	*b*	95	110–112	I–IE	$C_7H_{13}ClN_2O_2$[f]
15	CH_3	–N(CH$_3$)$CH_2C_6H_5$	B	76	154–156	Ac–Et	$C_{14}H_{21}ClN_2O_2$[f]
16	CH_3	–N(CH$_3$)$_2$	*a*	71	198–200	I	$C_8H_{17}ClN_2O_2$[f]
17	$CH_2C_6H_5$	Pyrrolidino	B	60	145–147	MEK–M	$C_{16}H_{23}ClN_2O_2$[f]
18	CH_3	Piperidino	B	80	212–214	I	$C_{11}H_{21}ClN_2O_2$[f]
19	$CH_2C_6H_5$	Hexahydroazepino	B	24	133–135	Ac	$C_{18}H_{27}ClN_2O_2$[f]
20	$CH_2C_6H_5$	Morpholino	B	55	204–206	I	$C_{16}H_{23}ClN_2O_3$[f]
21	CH_3	Morpholino	B	88	242–244[c]	M	$C_{10}H_{19}ClN_2O_3$[f]
22	CH_3 (R_1 = CH_3)	Morpholino	B	56	218–220	E	$C_{11}H_{21}ClN_2O_3$[f]
23	CH_3	2-(2,3,4,5-Tetrahydro-1,4-benzoxazepinyl)	B	25	169–170	I–IE	$C_{13}H_{21}ClN_2O_3$[f]

[a] Preparation described in Experimental Section. [b] Prepared from **15** by reduction with H_2 and Pd/C. [c] With decomposition. [d] Solvent abbreviations: Ac, Me_2CO; B, C_6H_5; E, EtOH; EA, EtOAc; I, i-PrOH; IE, i-Pr_2O; M, MeOH; MEK, EtMeCO; O, isooctane; W, H_2O. [e] All compounds were analyzed for C, H, and N. [f] HCl salt.



Compound 8 prepared by this method has not been purified and characterized; however, amino products derived from this intermediate have been characterized. Compound **24** has been prepared both from the intermediate



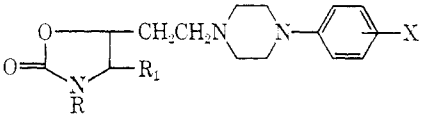
derived by this method and from intermediates starting with pyrridinol and phosgene.

One can imagine two possible courses for the reaction between 1-substituted 3-pyrrolidinols and phosgene. One is the reaction previously suggested to yield 2-oxazolidinones. It is conceivable that in the course of the rearrangement the pyrrolidine ring might open in a different manner which would yield a 6-chloromethyl-2-oxazinone. However, the fact that the same products are derived both from the 3-pyrrolidinols and phosgene and from the chlorobutoxide with urethane suggests that the products are 2-oxazolidinones.

The nuclear magnetic resonance spectra of the oxazolidinone derivatives are consistent with the proposed five-membered ring structure. In the unsubstituted oxazolidine ring, two nonequivalent methylene protons adjacent to the oxazolidinone nitrogen display a typical splitting pattern for the AB portion of an ABX system. The other ring proton on carbon 5 gives rise to a multiplet in the region γ 5.5.

The chlorine in 5-(2-chloroalkyl)-2-oxazolidinones is easily replaced with various reagents, such as secondary amines, sodium phenolate, carboxylate salts, or sodium cyanide, to yield the products shown in Table II. None of

Table III



Compd	R	X	Method	Yield, %	Mp, °C	Recrystn solvent[a]	Empirical formula[e]	"Fighting mice" screen: No. blocked (20 mg/kg ip)	"Fighting mice" screen: ED_{50} (confidence limits), mg/kg
24	H	H	C[a] (A_1)	24	151–152	I	$C_{13}H_{21}N_3O_2$		12.2 (6.1–24.4)
25	CH_3	H	*b*	34	151–154	I	$C_{20}H_{27}N_3O_6$[f]	3/5	
26	CH_3 (R_1 = CH_3)	H	B	18	169–175	MEK–M	$C_{21}H_{29}N_3O_6$[f]		5.9 (3.5–9.8)
27	C_2H_5	H	B	49	160–162	M	$C_{21}H_{29}N_3O_6$[f]		20.4 (15.1–27.5)
28	C_6H_{11}	H	B[a]	51	276–279[c]	E–W	$C_{21}H_{32}ClN_3O_2$[g]	2/5	
29	$-CH_2C_6H_5$	H	B	27	228–230[c]	E	$C_{22}H_{28}ClN_3O_2$[g]	0/5	
30	H	2-CH_3	C	25	182–185	M–E	$C_{20}H_{27}N_3O_6$[f]	3/5	
31	H	4-CH_3	C	30	144–145	I–M	$C_{20}H_{27}N_3O_6$[f]	2/5	
32	H	2-OCH_3	C	33	179–181	E	$C_{20}H_{27}N_3O_7$[f]	2/5	
33	H	2-Cl	A	24	166–168	MEK–M	$C_{19}H_{24}ClN_3O_6$[f]	2/5	
34	H	4-Cl	*a*	19	202–206	MEK	$C_{23}H_{28}ClN_3O_{10}$[h]	0/5	
35	H	2-F	A_1	11	121–124	EA	$C_{15}H_{20}FN_3O_2$[i]	1/5	
36	H	4-F	A_1	5	127–129	EA	$C_{15}H_{20}FN_3O_2$		10 (5.5–18.0)
37	H	3-CF_3	A	24	144–146	MEK–M	$C_{20}H_{24}F_3N_3O_6$[f]	3/5	

[a] Preparation described in Experimental Section. [b] Prepared by treating **24** with $NaNH_2$ and then Me_2SO_4. [c] With decomposition. [d] See footnote *d*, Table II, for solvent abbreviations. [e] All compounds were analyzed for C, H, and N. [f] Maleate salt. [g] HCl salt. [h] Difumarate salt. [i] C: calcd, 61.42; found, 60.69.

the compounds in this group have demonstrated any significant activity in the test for major tranquilizers.

The compounds containing an unsubstituted nitrogen on the oxazolidinone ring were prepared either from compound 8 or from corresponding compounds which contain a benzyl at this position by debenzylation with sodium in liquid ammonia.

The latter method, however, could not be used for some of the 4-phenylpiperazine derivatives which contained halogen or trifluoromethyl substituents on the phenyl ring since these halogens were replaced during the reduction. A method that was used for preparing one of the compounds of this type starting with 3-benzyl-5-[2-(2,2'-diethanolamino)ethyl]-2-oxazolidinone is shown below.

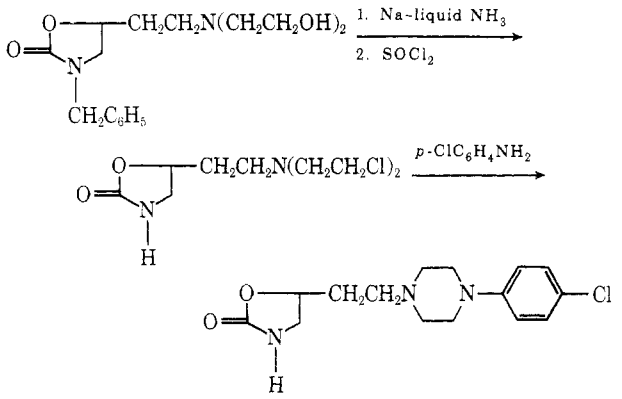


Table III shows the various phenylpiperazine derivatives which have been prepared, the method used in preparation, and their activity in the screen for major tranquilizers.

Piperazine derivatives with substituents other than phenyl on the N were prepared to determine if the phenyl group is essential for activity in the major tranquilizer screen. Compounds in this class are shown in Table IV. Because of the possible analogy of phenylpiperazine and 3-anilinopyrrolidine derivatives, the substituted 3-aminopyrrolidines represented in Table V were prepared as indicated. None of the compounds in either group had significant activity in the screen for major tranquilizer.

Pharmacological Testing Methods. The isolation-induced aggressive behavior test[3] was used as a primary screen to determine tranquilizing activity of the compounds described here. Male albino mice were used. Following development of the behavior, normal mice were exposed to the isolated, aggressive animals. A well-directed attack on the normal animals was used as the end point of the test. Blockade of this attack was regarded as evidence of tranquilizing action. Tests were conducted 60 min after drug administration.

Compounds were dissolved or suspended in physiological saline. With each compound, groups of five mice were tested initially at 20 mg/kg ip. In those cases where aggressive behavior was prevented in all animals, additional doses were used to allow estimation of the effective dose by the statistical method of Litchfield and Wilcoxon.[4]

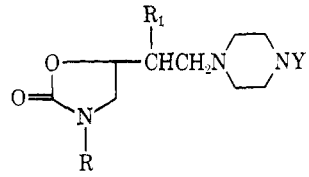
Results and Discussion

None of the compounds in Tables I, II, IV, or V showed significant activity in the "fighting mice" screen for major tranquilizers at 20 mg/kg. This indicates that within this series the presence of the 4-phenylpiperazine moiety is necessary for this activity.

The results shown in Table III illustrate the effects of various substituents on the 3 position of the oxazolidinone and on the phenyl attached to the piperazine. As seen in compounds **24–29**, where the phenyl is unsubstituted, either H or CH_3 on the oxazolidinone N gave the more active compounds. From compounds **30–37** where the 3 position of the oxazolidinone is unsubstituted it appears that substitution on the phenyl generally decreases the activity as compared to the unsubstituted **24**. The only exception to this among those prepared was 4-fluorophenyl- (**36**), which had activity comparable to **24**.

The most active compound in the series with albino mice, which were routinely used, was **26** with an ED_{50} of 5.9 mg/kg. Under similar conditions chlorpromazine had an ED_{50} of 2.5 mg/kg (confidence limits 1.5–4.6). However, with black mice (C-57, Jackson Memorial Laborato-

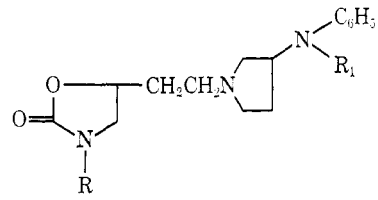
Table IV



Compd	R	Y	Method	Yield, %	Mp, °C	Recrystn solvent[a]	Empirical formula[b]
38	CH_3	CH_3	B	72	262–264	E–IE	$C_{11}H_{23}Cl_2N_3O_2$[c]
39	H	-*n*-C_6H_{13}	A_1	20	119–121	W–M	$C_{15}H_{29}N_3O_2$
40	CH_3	$-CH_2CH_2OH$	B	75	251–253	M–IE	$C_{12}H_{25}Cl_2N_3O_3$[c]
41	H	-2-Pyridyl	A_1	36	130–132	EA	$C_{14}H_{20}N_4O_2$
42	CH_3 (R_1 = CH_3)	2,3,4-$(CH_3O)C_6H_2CH_2$	B	7	238–240	E–W	$C_{21}H_{37}Cl_2N_3O_6$[d]

[a] See footnote *d*, Table II, for solvent abbreviations. [b] All compounds were analyzed for C, H, and N. [c] DiHCl salt. [d] DiHCl salt hydrate.

Table V



Compd	R	R_1	Method	Yield, %	Mp, °C	Recrystn solvent[c]	Empirical formula[d]
43	$-CH_2C_6H_5$	$-CH_3$	B	25	179–182	Ac–M	$C_{23}H_{31}Cl_2N_3O_2$[e]
44	H	$-CH_3$	C	39	*b*		$C_{16}H_{23}N_3O_2$
45	$-CH_2C_6H_5$	H	B	73	*b*		$C_{22}H_{27}N_3O_2$
46	H	H	C	80	110–120	B–O	$C_{15}H_{21}N_3O_2$
47	H	$-COC_2H_5$	*a*	45	*b*		$C_{18}H_{25}N_3O_3$

[a] Prepared from **46** and EtCOCl. [b] Product was purified by column chromatography using Florisil eluting with C_6H_6–Me_2CO. [c] See footnote *d*, Table II, for solvent abbreviations. [d] All compounds were analyzed for C, H, and N. [e] DiHCl salt.

ries) compound **24** was more active than chlorpromazine with an ED_{50} of 2.9 mg/kg (confidence limits 1.7–4.8) compared with 4.8 mg/kg (confidence limits 4.2–5.6).

Experimental Section

The procedures for preparations given below are representative of the methods used for the compounds described in Tables I–V. Physical properties and yields are given in the tables. All compounds were analyzed for C, H, and N and, unless otherwise noted in the tables, were within ±0.4% of theoretical values. Melting points were taken in a Thomas-Hoover capillary apparatus. Temperatures are uncorrected.

5-(2-Chloroethyl)-3-methyl-2-oxazolidinone (1) (Representative Method for Compounds 1–7, Table I). To 198 g (2 mol) of $COCl_2$, dissolved in 800 ml of cold $CHCl_3$ contained in a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, pot thermometer, and condenser, was added 204 g (2 mol) of 1-methyl-3-pyrrolidinol† in 450 ml of $CHCl_3$. The reaction mixture was cooled in an ice bath and the addition was at such a rate that the pot temperature was kept below 10°. After the addition of pyrrolidinol was completed, stirring was continued in cold for 0.75 hr. Then, with continuing cooling and stirring, 270 ml (2 mol) of Et_3N was added and the reaction mixture allowed to warm to room temperature. The $CHCl_3$ solution was extracted with dilute HCl, then dilute NaOH, and finally water. The $CHCl_3$ layer was dried (Na_2SO_4). The $CHCl_3$ was removed at reduced pressure on a rotary evaporator. The weight of the neutral residual oil was 238 g. This product was distilled *in vacuo* (0.3–0.6 mm). (During the distillation there was evidence of some decomposition.) After a small forerun, 200 g (60% yield) of distillate (bp 120–135°) containing a small amount of crystalline solid was collected. This was redistilled using a 6-in. heated column. The product boiled at 120° (0.2 mm), wt 169 g (52%).

†1-Alkyl-3-pyrrolidinols were prepared according to Lunsford, *et al.*[5]

Method A. 5-(2-Chloroethyl)-2-oxazolidinone (8) (Procedure 1). A solution of 11 g (0.05 mol) of **10** dissolved in THF was slowly added to a solution of 3.68 g (0.16 mol) of Na in 200 ml of liquid NH_3. The reaction was stirred 1 hr after the addition was complete and 10.6 g (0.2 mol) of NH_4Cl was added in small portions. The NH_3 was then allowed to evaporate. The THF solution was filtered and concentrated at reduced pressure. The residual oil weighed 5.4 g and gave nmr spectra consistent with the expected 5-(2-hydroxyethyl)-2-oxazolidinone. This oil was refluxed with 1 equiv of $SOCl_2$ in $CHCl_3$. The solvent was removed at reduced pressure and the residual oil (6.0 g, 80%) crystallized on standing and was used without further purification as an intermediate to react with various amines by a procedure similar to method B. An analytical sample was recrystallized from EtOH–Et_2O, mp 71–73°.

Method A_1. 5-(2-Chloroethyl)-2-oxazolidinone (Procedure 2). A mixture of 89 g (1 mol) of urethane and 1.5 g of $LiNH_2$ was heated in a three-neck flask equipped with a mechanical stirrer, a dropping funnel, and a distilling column. When the temperature of the mixture reached 120°, 107 g (1 mol) of 1-chloro-3,4-epoxybutane was added dropwise with vigorous stirring. When the temperature reached approximately 140–150°, EtOH began distilling. Heating was continued for 2 hr and 35 ml of EtOH was collected. The mixture was cooled to 90° and 300 ml of an *i*-PrOH–H_2O (5:1) mixture was added with stirring. This mixture was then extracted with 300 ml of $CHCl_3$. The $CHCl_3$ solution was washed twice with 50 ml of H_2O, dried (Na_2SO_4), and concentrated with water pump vacuum at 80°. The residue (wt 125 g, 83%) was a viscous oil and was used without further purification to react with various amines by a procedure similar to method B.

3-Benzyl-5-(2-iodoethyl)-2-oxazolidinone (9). A solution of 12.0 g (0.05 mol) of **5** and 10.5 g (0.07 mol) of NaI in 100 ml of Me_2CO was heated at gentle reflux with mechanical stirring for 20 hr. The reaction mixture was cooled and a white precipitate was separated by filtration and washed with Me_2CO. The precipitate weighed 2.8 g (95.5% of theoretical yield of NaCl). The combined filtrate and Me_2CO wash were concentrated on a rotary

evaporator. A brown oil remained, wt 16.8 g. The oil was repeatedly extracted with hot *i*-Pr_2O leaving a dark insoluble residue. The *i*-Pr_2O solution deposited on cooling a slightly colored solid which, on recrystallization from *i*-Pr_2O, yielded 8.5 g (51%) of a white crystalline solid, mp 42–43°.

5-(2-Acetoxyethyl)-3-benzyl-2-oxazolidinone (10). A mixture of 36 g (0.15 mol) of **5** and 32.8 g (0.4 mol) of NaOAc in 100 ml of DMSO was heated in a steam bath for 18 hr with stirring. After separating the insoluble salts by filtration, the DMSO was distilled from the filtrate at water pump vacuum. The residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ layer was separated and dried (Na_2SO_4) and the solvent removed on a rotary evaporator. The residual oil was twice distilled *in vacuo* collected 9.8 g (25% yield); bp 172–176° (0.1 mm).

3-Benzyl-5-[2-(3,5-dimethylphenoxy)ethyl]-2-oxazolidinone (11). In a 2-l., three-necked flask equipped with a mechanical stirrer, condenser, thermometer, and dropping funnel was placed 500 ml of EtOH (absolute). With cooling there was added 11.5 g (0.5 mol) of Na. To this solution was added 68 g (0.55 mol) of 3,5-xylenol in 100 ml of EtOH (absolute) followed by dropwise addition of 112 g (0.5 mol) of **5**. The solution was heated at reflux 4 hr during which time a white precipitate of NaCl formed, which was separated by filtration and dried: wt 17 g (58.5% of theoretical amount). The filtrate was concentrated on a rotary evaporator to remove the alcohol. The residue was then partitioned between cold water and Et_2O. The ether layer was washed with dilute NaOH and dried (Na_2SO_4). Cooling this ether solution produced a crystalline solid: wt 37.6 g (23%); mp 65–68°. Recrystallization from *i*-Pr_2O gave a product which melted at 70–71°.

5-(2-Cyanoethyl)-3-methyl-2-oxazolidinone (13). A mixture of 8.2 g (0.05 mol) of **1** and 3.8 g (0.075 mol) of NaCN in 50 ml of DMSO was heated on a steam bath overnight. The reaction mixture was filtered to remove the insoluble, inorganic salts and most of the DMSO was distilled at reduced pressure. The residue was dissolved in approximately 60 ml of H_2O and the solution was extracted with $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and the solvent removed on a rotary evaporator. The weight of the residual oil was 7.6 g (99%). This oil was distilled *in vacuo* and 4.2 g of slightly yellow oil, bp 165–175° (0.2–0.4 mm), was collected. The oil crystallized after standing for several days exposed to air and was recrystallized from a mixture of *i*-PrOH-*i*-Pr_2O: yield 2.8 g (36%); mp 44–45°.

5-(2-Dimethylaminoethyl)-3-methyl-2-oxazolidinone Hydrochloride (16). Dimethylamine, 18 g (0.4 mol), was dissolved in 125 ml of anhydrous EtOH contained in a cold stainless steel bomb. To this solution was added 33 g (0.2 mol) of **1**. The bomb was sealed and heated at 90° for 15 hr. The resulting clear yellow solution was concentrated to dryness on a rotary evaporator. The residual waxy solid was dissolved in dilute NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated on a rotary evaporator. The oily residue was dissolved in 175 ml of *i*-PrOH and made acid with ethereal HCl. The solid precipitate was separated by filtration, washed with *i*-Pr_2O, and dried in air: yield 29.7 g (71%); mp 197–199°. Recrystallization from *i*-PrOH gave a white crystalline solid, mp 198–200°.

Method B. 3-Cyclohexyl-5-[2-(4-phenylpiperazino)ethyl]-2-oxazolidinone Hydrochloride (28). A solution of 11.5 g (0.5 mol) of **4** and 16.0 g (0.10 mol) of 4-phenylpiperazine (an equivalent amount of K_2CO_3 may be substituted for the excess of amine) in 100 ml of EtOH (or *i*-PrOH) was heated at reflux for 8 hr. The dark solution was dehydrated by distilling with C_6H_6 on a rotary evaporator. On cooling, a white precipitate formed which was separated by filtration and dried in air. This was the hydrochloride of the starting amine (4 g, mp 235–238°). The filtrate was concentrated on a rotary evaporator to remove the EtOH. The residue was suspended in H_2O and made alkaline with dilute NaOH. A viscous brown oil precipitated. The supernatant was decanted and the oil washed several times with water and finally dissolved in EtOH and dried by distilling with C_6H_6 on the rotary evaporator. The volume was brought to 100 ml with absolute EtOH. The solution was made acid with ethereal HCl. The white solid precipitate was separated by filtration and washed with EtOH and with *i*-Pr_2O: yield 12.4 g; mp 270–280° dec. Recrystallization of the product from an EtOH-H_2O mixture gave 10.1 g (51%), mp 276–279° dec.

Method C. 5-[2-(4-Phenylpiperazino)ethyl]-2-oxazolidinone (24). Na (1.7 g, 0.075 mol) was dissolved in approximately 75 ml of liquid NH_3. To this deep blue colored solution was added dropwise 14.7 g (0.04 mol) of **29** in 100 ml of toluene. When approximately 80% of the toluene solution had been added, the blue color disappeared. An additional 0.2 g of Na was added to the reaction mixture and the addition of the toluene solution was continued. Before all of this solution had been added, a solid formed in the reaction flask and thorough mixing became difficult. After the addition was complete, stirring was continued for 1 hr and 5.4 g (0.1 mol) of NH_4Cl was then added. With continued stirring the NH_3 was allowed to evaporate. The reaction mixture was then extracted with dilute HCl. To this aqueous extract was carefully added aqueous NH_4OH with stirring. The first precipitate was a brownish gummy oil from which the supernatant liquid was decanted. Continued addition of NH_4OH to the supernatant yielded a crystalline solid which was separated by filtration, washed with H_2O, and dried *in vacuo*: yield 6.8 g; mp 135–140°. After two recrystallizations from *i*-PrOH, 2.8 g (24%) of a white crystalline solid was obtained, mp 151–152°.

5-[2-[4-(4-Chlorophenyl)-1-piperazino]ethyl]-2-oxazolidinone Difumarate (34). A mixture of 173 g (0.722 mol) of 3-benzyl-5-(2-chloroethyl)-2-oxazolidinone, 2,2′-diethanolamine (76 g, 0.722 mol), anhydrous K_2CO_3 (100 g, 0.722 mol), and 500 ml of *n*-BuOH was stirred and refluxed for 18 hr. The reaction mixture was suction filtered while hot and the *n*-BuOH removed on a steam bath at reduced pressure (approximately 100 mm). A quantitative yield of crude 3-benzyl-5-[2-(2,2′-diethanolamino)ethyl]-2-oxazolidinone was obtained. A solution of 30.8 g (0.1 mol) of this product was debenzylated according to method C. The residual base was dissolved in anhydrous EtOH and the solution was made acid with anhydrous HCl and the acidic solution was concentrated to an oily residue consisting of crude 5-[2-(2,2′-diethanolamino)ethyl]-2-oxazolidinone hydrochloride. This crude product was stirred 15 min at room temperature with 100 ml of $SOCl_2$ and then heated 2 hr at 60°. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. The residue consisting of 18.1 g (0.062 mol) of crude 5-[2-[*N*-(2,2′-dichlorodiethylamino)]ethyl]-2-oxazolidinone hydrochloride was dissolved with 26 g (0.2 mol) of *p*-chloroaniline in 250 ml of *i*-PrOH and stirred at reflux for 18 hr. The reaction mixture was treated with NH_3 at 5–10°, the NH_4Cl removed by filtration, and the *i*-PrOH was evaporated at reduced pressure. Unreacted *p*-chloroaniline was removed by vigorous stirring of the residue with 200 ml of isooctane at 60°. The dried residue (18.3 g, 0.0586 mol) was dissolved in 50 ml of EtOAc and treated with 6.9 g (0.0594 mol) of fumaric acid dissolved in a minimum of MeOH. Recrystallization of the crude fumarate from EtCOMe gave 4.7 g (19%) of **34**, mp 202–206°.

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