***N*-(2-Phenylethyl)-2-[(2-phenylethyl)amino]adenosine (35).** A reaction mixture of 2-fluoro-6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (**31**) (1.2 g, 2.7 mmol), 2-phenylethylamine (0.37 g, 3.0 mmol), and triethylamine (0.3 g, 3.0 mmol) in DME (20 mL) was stirred at room temperature for 20 h. TLC (5% MeOH–$CHCl_3$) showed the absence of starting material. The precipitated solid ($Et_3NH^+Cl^-$) was filtered and washed with DME, and the volatiles were removed from the filtrate. The residue was then dissolved in saturated methanolic ammonia (15 mL) and stirred at room temperature for 3 h. The volatiles were removed, and the residue was treated with $CHCl_3$–MeOH–ether. The solid (1.1 g) was filtered and dried. ^1H NMR $CDCl_3$ showed a 1:1 mixture of compounds **33** and **34**. All the sugar protons were duplicate and the C8 proton from both the compounds showed two separate singlets at δ 8.37 and 8.39 in a 1:1 ratio.

This 1:1 mixture of **33** and **34** was further reacted with an excess of 2-phenylethylamine in refluxing ethanol for 20 h. The volatiles were evaporated, and the residue upon crystallization from chloroform–ether (1:4) gave a solid, which was filtered and dried, affording 0.9 g (62.5% from **31** of *N*-(2-phenylethyl)-2-[(2-phenylethyl)amino]adenosine (**35**): mp 137–142 °C; ^1H NMR (DMSO-d_6) δ 2.7–3.0 (m, 4 H, CH_2Ph), 3.42–3.65 (m, 6 H, 2 CH_2NH and 2 $H_{5'}$), 3.88 (brd, 1 H, $H_{4'}$), 4.10 (brt, 1 H, $H_{3'}$), 4.57 (t, 1 H, $H_{2'}$), 4.6–5.5 (br, 3 H, 3 OH), 5.73 (d, 1 H, $H_{1'}$), 6.34 (s, 1 H, NH), 7.22 (brs, 10 H, aromatic), 7.29 (s, 1 H, NH), and 7.90 (s, 1 H, H_8); mass spectrum (FAB), *m/z* 491.1 (M^+). Anal. ($C_{26}H_{30}N_6O_4 \cdot 1.5H_2O$) C, H, N.

Receptor Binding. Affinities of compounds for inhibition of binding of [^{3}H]-N^6-cyclohexyladenosine to A_1 receptors in rat brain membranes and for inhibition of [^{3}H]NECA binding to A_2 receptors in rat striatal membranes in the presence of 50 nM N^6-cyclopentyladenosine were determined as previously described.[5]

Acknowledgment. We thank Jim Fergus and Gina Lu for providing A_1 and A_2 binding data and Sigrid Stork for chemical syntheses.

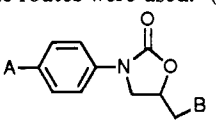
Registry No. 1, 58-61-7; **2**, 146-77-0; **3**, 1818-71-9; **4**, 58097-85-1; **5**, 120524-27-8; **6**, 37151-17-0; **7**, 53296-10-9; **8**, 41552-82-3; **9**, 36396-99-3; **10**, 38594-96-6; 11, 98383-40-5; **12**, 21924-65-2; **13**, 120524-28-9; **14**, 26783-44-8; **15**, 120524-29-0; **16**, 98383-43-8; **17**, 111864-02-9; 18 (R′ = H), 2004-07-1; **19**, 92123-05-2; **20**, 120524-30-3; **21**, 120524-31-4; **22**, 117325-43-6; **23**, 120524-32-5; **24**, 120524-33-6; **25**, 120524-34-7; **26**, 120524-35-8; **27**, 120524-36-9; **28**, 120524-37-0; **29**, 120524-38-1; **30**, 120524-39-2; **31**, 13276-51-2; **32**, 120524-40-5; **33**, 120524-41-6; **34**, 120524-42-7; **35**, 120524-43-8; **36**, 120524-44-9; **37**, 120524-45-0; **38**, 120524-46-1; **39**, 6979-94-8; **40**, 41623-91-0; **41**, 53296-13-2; **42**, 53296-14-3; **43**, 117325-41-4; **44**, 120524-47-2; **45**, 120524-48-3; **46**, 103450-84-6; **47**, 120524-49-4; **48**, 114675-13-7; **49**, 120524-50-7; **50**, 120442-40-2; **51**, 120524-51-8; **52**, 4294-16-0; **53**, 120524-52-9; **54**, 97374-48-6; **55**, 120524-53-0; **56**, 120524-54-1; **57**, 117773-72-5; **58**, 120524-55-2; **59**, 107656-16-6; **60**, 120524-56-3; **61**, 117325-42-5; **62**, 120524-57-4; cyclopentylamine, 1003-03-8; cyclohexylamine, 108-91-8; (*R*)-1-methyl-2-phenylethylamine, 156-34-3; 2,2-diphenylethylamine, 3963-62-0; 9-fluorenylmethylamine, 34577-90-7; 1-naphthylmethylamine, 118-31-0; benzylamine, 100-46-9; phenethylamine, 64-04-0; 2-(3,5-dimethoxyphenyl)-2-phenylethylamine, 120355-56-8; 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine, 120355-64-8; cyclopropylamine, 765-30-0; 2-*endo*-norbornylamine, 31002-73-0; (*S*)-2-hydroxypropylamine, 2799-17-9; pyrrolidine, 123-75-1.

Antibacterials. Synthesis and Structure–Activity Studies of 3-Aryl-2-oxooxazolidines. 1. The "B" Group

Walter A. Gregory,† David R. Brittelli,*† C.-L. J. Wang,† Mark A. Wuonola,† Ronald J. McRipley,‡ David C. Eustice,‡ Virginia S. Eberly,‡ P. T. Bartholomew,‡ Andrew M. Slee,‡ and Martin Forbes‡

Pharmaceutical and Biotechnology Research, Medical Products Department, E. I. du Pont de Nemours and Co., Medicinal Chemistry, Experimental Station, Wilmington, Delaware 19898, and Chemotherapy Research, Glenolden Laboratory, Glenolden, Pennsylvania 19036. *Received August 31, 1988*

The synthesis and structure/activity studies of the effect of varying the "B" group in a series of oxazolidinone antibacterials (I) are described. Two synthetic routes were used: (1) alkylation of aniline with glycidol followed

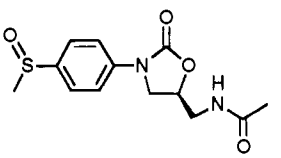


I

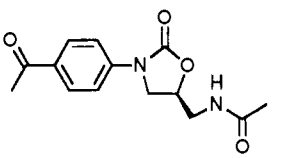
by dialkyl carbonate heterocyclization to afford I (A = H, B = OH), whose arene ring was further elaborated by using electrophilic aromatic substitution methodology; (2) cycloaddition of substituted aryl isocyanates with epoxides to give A and B with a variety of values. I with B = OH or Br were converted to other "B" functionalities by using S_N2 methodology. Antibacterial evaluation of compounds I with A = acetyl, isopropyl, methylthio, methylsulfinyl, methylsulfonyl, and sulfonamido and a variety of different "B" groups against *Staphylococcus aureus* and *Enterococcus faecalis* concluded that the compounds with B = aminoacyl, and particularly acetamido, were the most active of those examined in each A series, possessing MICs in the range of 0.5–4 μg/mL for the most active compounds described.

The oxazolidinones,[1] exemplified by DuP 105 (**1**) and DuP 721 (**2**), are a new class of orally active, synthetic antibacterial agents, derived from a random screening lead, whose in vitro spectrum includes activity against staphylococci, streptococci, enterococci, anaerobic bacteria, and mycobacteria.[2]

As a class, the oxazolidinones have equal activity against methicillin-sensitive and -resistant staphylococcal strains and β-lactamase positive and negative strains.[3,4] Pharmacokinetic studies on DuP 721 indicate that peak serum



1



2

levels exceeding the MIC_{90}'s can readily be achieved following single doses per os.[5] Mechanism of action studies

† Medicinal Chemistry, Experimental Station.
‡ Chemotherapy Research, Glenolden Laboratory.

(1) Fugitt, R. B.; Luckenbaugh, R. W. U.S. Patent 4,340,606, July 20, 1982. Gregory, W. A. U.S. Patent 4,461,773, July 24, 1984. Gregory, W. A. U.S. Patent, 4,705,799, November 10, 1987.

0022-2623/89/1832-1673$01.50/0

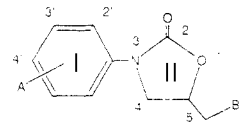
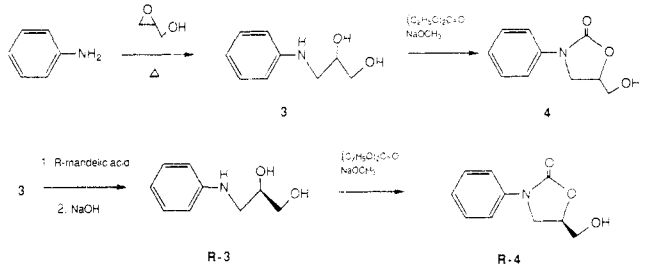


Figure 1.

Scheme I



have shown that the oxazolidinones inhibit protein synthesis, but not RNA or DNA synthesis, and suggest that inhibition occurs at an early event in the initiation phase of protein synthesis.[6]

In this and subsequent papers of this series, we describe the synthesis and systematically examine the structure–activity relationships of this novel class of antimicrobials. For purposes of discussion, the structural elements of the oxazolidinones are classified according to the following scheme and numbering system (Figure 1): the substituent on the aromatic ring is designated the "A" group, the aromatic ring "ring I", the heterocyclic ring "ring II", and the substituent on the 5-methylene the "B" group. To facilitate subsequent discussions, we will consider the structure/activity relationships of the "B" groups in the present investigation.

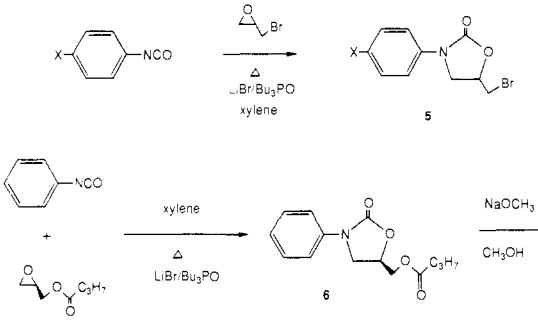
Chemistry

5-Substituted oxazolidinones have been prepared by many methods.[7] In this work, essentially two synthetic routes have been utilized.

In the first of these routes (Scheme I), alkylation of aniline to give **3** followed by dialkyl carbonate heterocyclization has been used to prepare the 5-hydroxymethyl compound **4**. Following the finding that only one enantiomer (e.g., that enantiomer represented by the (*S*)-5-(aminomethyl)oxazolidinone; the *R* or *S* designation for derivatives 5-substituted with other functionalities may differ) possessed antibacterial activity,[8] this scheme was modified to afford solely the desired stereoisomer by resolving **3** to *R*-**3** with (*R*)-mandelic acid. This scheme has been used primarily for preparing the parent phenyl compound, whose arene ring has been further elaborated by using electrophilic aromatic substitution methodology.

The other synthetic route used is more adaptable, particularly for preparing substituted-phenyl derivatives not obtainable by the first route, and employs as its key step the bromide-catalyzed cycloaddition reaction of isocyanates with epoxides[9] (Scheme II) to afford **5**. The required *R* isomers have been prepared with kinetically

Scheme II



Scheme III

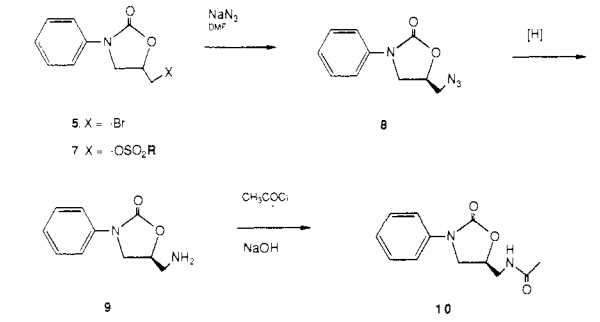
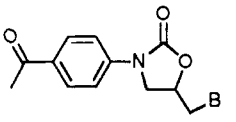
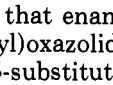
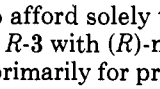
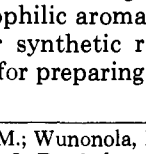
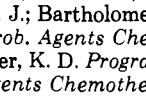


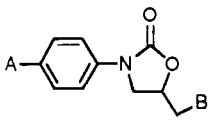
Table I. Antibacterial Activities of 5-Substituted 3-(4′-Acetylphenyl)oxazolidinones



no.	B	C-5 config	MIC, μg/mL: *Staphylococcus aureus* SFCO-1a	MIC, μg/mL: *Enterococcus faecalis* STCO-19
11	$=CH_2$	*R,S*	>128	>128
12	H	*R,S*	>128	>128
13	F	*R*	64	128
14	Cl	*R,S*	32	64
15	OH	*R*	16	16
16		*R*	>128	>128
17	$OC(=O)n\text{-}C_3H_7$	*R*	64	>128
18	$OP(=O)(OH)_2$	*R*	>128	>128
19	N_3	*R*	>128	>128
20		*R*	8	8
21	NH_2	*S*	>128	>128
22	$NH_3^+Cl^-$	*S*	>128	>128
2	$NHC(=O)CH_3$	*S*	0.5	1
23		*S*	>128	>128
24		*R*	>128	>128
	cephalexin		0.5	64
	vancomycin		0.5	2
	gentamycin		0.25	16

(2) Slee, A. M.; Wunonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Bartholomew, P. T.; Gregory, W. A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791.
(3) Stottmeier, K. D. *Program Abstr 27th Intersci. Conf. Antimicrob. Agents Chemother.* **1987**, Abstr. no. 243.
(4) Barry, A. L. *Antimicrob. Agents Chemother.* **1988**, *32*, 150. Neu, H. C.; Novelli, A.; Saha, G.; Chin, N.-X. *Ibid.* 580.
(5) Zajac, I.; Lam, G. N.; Hoffman, H. E.; Slee, A. M. *Program Abstr 27th Intersci. Conf. Antimicrob. Agents Chemother.* **1987**, Abstr. no. 247.
(6) Eustice, D. C.; Feldman, P. A.; Slee, A. M. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 965. Eustice, D. C.; Feldman, P. A.; Zajac, I.; Slee, A. M. *Antimicrob. Agents Chemother.* **1988**, *32*, 1218.
(7) Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197.
(8) Evidence will be presented in a subsequent paper in this series.
(9) Herweh, J. E.; Kauffmann, W. J. *Tetrahedron Lett.* **1971**, 809.

Table II. Antibacterial Activities of "A" Group Series with Varying "B" Groups



no.	B	C-5 config	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
		A = *i*-C_3H_7		
25	H	*R,S*	128	128
26	CH_3	*R,S*	>128	>128
27	Cl	*R,S*	64	64
28	OH	*R,S*	64	32
29	OC(=O)CH_3	*R,S*	128	128
30	N_3	*R,S*	>128	>128
31	NHC(=O)CH_3	*R,S*	4	4
		A = CH_3S		
32	H	*R,S*	>128	>128
33	Cl	*R,S*	>128	>128
34	OH	*R*	128	128
35	NHC(=O)CH_3	*S*	4	4
		A = CH_3SO		
36	Cl	*R,S*	32	32
37	OH	*R,S*	64	64
1	NHC(=O)CH_3	*S*	4	4
		A = CH_3SO_2		
38	H	*R,S*	64	128
39	CH_3	*R,S*	128	128
40	Cl	*R,S*	8	4
41	OH	*R,S*	16	16
42	N_3	*R*	16	8
43	NH_2	*S*	>128	>128
44	NHC(=O)CH_3	*S*	4	4
		A = H_2NSO_2		
45	Cl	*R,S*	16	>128
46	N_3	*R*	32	64
47	OH	*R*	128	128
48	NHC(=O)CH_3	*S*	32	16
		A = $CH_3C(=O)$		
14	Cl	*R,S*	32	64
19	N_3	*R*	>128	>128
15	OH	*R*	16	16
21	NH_2	*S*	>128	>128
2	NHC(=O)CH_3	*S*	0.5	1

resolved glycidyl butyrate[10] as the epoxide component of the cycloaddition reaction, followed by base-catalyzed ester exchange of the product **6** to give *R*-**4**.

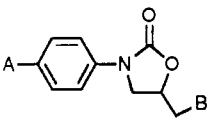
The 5-bromomethyl **5** and 5-hydroxymethyl **4** products of these synthetic schemes have been converted to other "B" groups principally by using S_N2 methodology. Amines **9** have been obtained by displacement of the hydroxyl sulfonate esters **7** or halo compounds **5** with sodium azide to give the azides **8**, followed by reduction; conversion of the amines **9** to amides **10** has employed conventional Schotten-Baumann techniques (Scheme III).

Structure–Activity Relationships

A large number of oxazolidinones with different "B" groups have been prepared and evaluated as antibacterials. As a representative set of examples, the in vitro antimicrobial activities of selected oxazolidinones with a common acetyl "A" group and a variety of functional "B" groups against *Staphylococcus aureus* and *Enterococcus faecalis* are summarized in Table I.

(10) Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* 1984, *106*, 7250.

Table III. Antibacterial Activity of "B" Group Series



no.	A	π	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
		B = Cl (π = 0.71)		
40	CH_3SO_2	−1.63	8	4
45	H_2NSO_2	−1.82	16	>128
36	CH_3SO	−1.58	32	32
14	$CH_3C(=O)$	−0.55	32	64
27	*i*-C_3H_7	1.53	64	64
33	CH_3S	0.61	>128	>128
		B = N_3 (π = 0.46)		
42	CH_3SO_2	−1.63	16	8
46	H_2NSO_2	−1.82	32	64
19	$CH_3C(=O)$	−0.55	>128	>128
30	*i*-C_3H_7	1.53	>128	>128
		B = OH (π = −0.67)		
41	CH_3SO_2	−1.63	16	16
15	$CH_3C(=O)$	−0.55	16	16
28	*i*-C_3H_7	1.53	32	32
37	CH_3SO	−1.58	64	128
34	CH_3S	0.61	128	128
47	H_2NSO_2	−1.82	128	128
		B = NHC(=O)CH_3 (π = −0.97)		
2	$CH_3C(=O)$	−0.55	0.5	1
31	*i*-C_3H_7	1.53	4	4
35	CH_3S	0.61	4	4
44	CH_3SO_2	−1.63	4	4
1	CH_3SO	−1.58	4	4
48	H_2NSO_2	−1.82	32	16

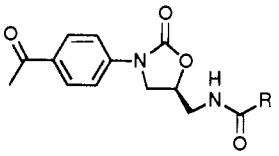
The antibacterial data in Table I clearly show that the acetamide group is by far the most active "B" group. Hydrocarbon and halo "B" groups generally confer weak antibacterial activity on oxazolidinones. The hydroxy compound **15** has modest activity, but its sulfonate, carboxylate, and phosphate esters are weakly active to inactive. Among nitrogen-containing "B" groups only the carboxamide derivative possesses good antibacterial activity. These generalizations hold as well for a variety of other "A" group series in which the effect of varying the "B" group has been extensively examined, although there is some dependence between the "A" and "B" groups in particular cases. This is illustrated in Table II, which summarizes briefly representative antimicrobial activity for some other "A" group functionality series. Relevant acetyl "A" group examples are included here to allow easy comparisons to be made.

These data reveal that there is an interplay between the effects of "A" and "B" groups, evinced by a change in rank order of activity of the various "A" groups for a given "B" group, but in each series of compounds with common "A" groups, the acetamide is always the most active, with the exception of the sulfonamide series.

We would explain these data as reflecting a greater intrinsic "binding" attraction for compounds with the acetamide "B" group, while the changes in rank order for the other "B" groups possibly reflect enhancements in lipophilicity toward a more optimal value. The "A" groups in Table II span a wide range of lipophilicities, which range, in terms of the hydrophobic aromatic substituent parameter π,[11] from very hydrophilic for the sulfonamide, methyl

(11) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* 1971, *71*, 525.

Table IV. Antibacterial Activities of Amide Homologues



no.	R	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
49	H	4	8
2	CH_3	0.5	1
50	C_2H_5	4	4
51	n-C_3H_7	8	8
52	i-C_3H_7	8	16
53	c-C_3H_5	8	4

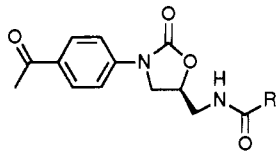
sulfone, and methyl sulfoxide groups, to modestly hydrophobic for acetyl, to modestly lipophilic for methylthio, to quite lipophilic for isopropyl (Table III). The relatively poor activity of **48** for an acetamide derivative could thus be rationalized in terms of being the result of a too hydrophilic combination of "A" and "B" group substituents. We would suggest that the relatively good activity of the chloro compounds in the methylsulfinyl and methyl sulfone series and azido compounds in the sulfonamide and sulfone series are reflections of this phenomenon as well. The changes in rank order in Table III, in which the entries for the better represented "B" groups in Table II are arranged in order of decreasing antibacterial activity, while not being by any means strictly quantitative, show qualitative trends that are roughly consistent with this notion. That is, the more hydrophilic "A" groups are relatively more active in the lipophilic azido and chloro "B" group series, and the more lipophilic "A" groups are more active in hydrophilic acetamide "B" group series. The key point not to be lost sight of is that, the exception of the sulfonamide "A" group series notwithstanding, our findings in more than 30 other series where comparisons among "B" groups have been made is that the amides, represented by the acetamide, have been the most active functional group class of substituents in this position of the molecule.

Further understanding of other physicochemical requirements for the "B" group are provided by examining the structure/activity relationships for various acetamide analogues, again comparing compounds carrying a common acetyl "A" group, in Tables IV and V.

In the homologous amide "B" group series with the acetyl "A" group (Table IV), the acetamide was most active, while the others were equivalent and less active. No physicochemical correlations are evident in this comparison. For example, the formyl compound **49** and the acetyl compound **2** have closely comparable lipophilicities, but quite different activities. We would suggest that the order of activity is possibly a consequence of a less than ideal "fit" for the formyl compound, while the lesser activity of the propionyl and butyryl amides perhaps reflects a larger than optimal substituent size in this position, a notion that is more evident by examining data in Table V, for example, comparing the activities of the methyl carbamate **54** with the *tert*-butyl carbamate **55** or with *N*-acetylglycyl amide **57**.

Perusal of the data in Table V reinforces the notion that no simple physicochemical parameter can explain the activity trends seen here. The hydrophilic ureido-substituted analogue **62** has activity nearly comparable to that of the much more lipophilic propionamide **50**. We conclude that the influence of the amide substituent in this position is not quantifiable in simple physicochemical terms; large substituents, e.g., *N*-alkylamide, *N*-arylamide, and imide "B" groups, provided analogues of **2** devoid of antibacterial activity (data not presented).

Table V. Antibacterial Activities of Representative Amide "B" Groups



no.	R	MIC, μg/mL *Staphylococcus aureus* SFCO-1a	MIC, μg/mL *Enterococcus faecalis* STCO-19
2	CH_3	0.5	1
54	OCH_3	4	4
55	$OC(CH_3)_3$	128	128
56	$CHCl_2$	2	2
57	$CH_2NH(C{=}O)(CH_3)$	128	>128
58	$CH_2(C{=}O)CH_3$	8	16
59	CH_2CN	16	8
60	CH_2SCN	32	32
61	CH_2OCH_3	32	32
62	NH_2	4	1
63	$N(CH_3)_2$	128	128

Summary

Oxazolidinone antibacterials bearing the acetamide "B" group are the most active analogues among a large number of compounds bearing a variety of different "B" groups.

Experimental Section

Chemistry. Melting points were determined on Thomas-Hoover and Meltemp capillary and Büchi 510 automatic melting point apparatus and are uncorrected. Infrared spectra were recorded in KBr disks with Perkin-Elmer Model 21 and 137 spectrophotometers and are reported in reciprocal centimeters. ^1H NMR spectra were determined in the indicated solvent on Varian A-60, Varian T-60, Varian EM-390, and Bruker WM-400 spectrometers and are reported in δ units (parts per million) downfield from tetramethylsilane as the internal reference. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Ultraviolet spectra were taken in absolute ethanol with a Cary 21 spectrophotometer.

(*R*,*S*)-3-(Phenylamino)-1,2-propanediol (3). To 1820 mL (20.0 mmol) of aniline heated to 80–88 °C with stirring under nitrogen was added slowly 265 mL (4.0 mol) of freshly distilled glycidol at a rate such that the temperature was maintained at 85–90 °C. After the first 40–100 mL of glycidol had been added, the external heat source was removed, and the reaction temperature was thereafter controlled by the rate of addition and if necessary by occasional cooling. After the addition was complete, the mixture was heated at 80–90 °C for 2.0 h. The product was distilled through a short wide-bore Vigreaux column to separate ~1.5 L of excess aniline, bp 50–55 °C (4.0–4.5 mm). When aniline distillation had ceased, the pressure was reduced to afford **3**, 588 g (88%), bp 132–125 °C (0.05–0.1 mm). The product crystallized on standing, mp 48.5–49.5 °C (lit.[12] mp 48–52 °C).

(*R*)-3-(Phenylamino)-1,2-propanediol (*R*-3). To a stirred solution of 1201 g (7.18 mol) of **3** in 1.9 L of $CHCl_3$ was added 600 g (3.95 mol) of (*R*)-(−)-mandelic acid. The mixture was heated to reflux to dissolve solids and then allowed to cool slowly. After the solution had cooled to ambient temperature, the solid was filtered and washed with three times with $CHCl_3$ and then dried to yield *R*-**3** (*R*)-mandelate: 868 g (38%); mp 87–88 °C; $[\alpha]^{25}_D = -58 \pm 0.4°$ (c = 1.0, ethanol). A suspension of 774 g (2.42 mol)

(12) Tam, W. *J. Org. Chem.* **1986**, *51*, 2977.

of *R*-3 (*R*)-mandelate in 2 L of methanol was stirred as 1.5 kg of methanol-washed IRA-400 ion exchange resin was added. The solution was stirred for 1.0 h at ambient temperature and then filtered, and the resin was washed well with methanol. The methanol filtrate was evaporated in vacuo to yield 366.6 g of a viscous liquid, which was dissolved in 700 mL of toluene, and the solution dried by azeotropic removal of water with a Dean–Stark water separator. The dry solution was concentrated and crystallized on standing to give 368 g (91%) of *R*-3: mp 38.5–39.5 °C; $[\alpha]^{25}_D$ = −24.0° ± 0.8° (*c* = 1.0, ethanol).

(*R*)-5-(Hydroxymethyl)-3-phenyl-2-oxooxazolidine (*R*-4). A mixture of 360 g (2.15 mol) of *R*-3, 252 mL (2.08 mol) of diethyl carbonate, and 1.0 g of sodium methoxide in 1 L of toluene was heated under reflux with azeotropic removal of ethanol. Toluene was added periodically to maintain solution volume. When ethanol distillation ceased and the head temperature reached a constant 110–111 °C, the mixture was cooled to 25 °C; the product that crystallized was filtered, washed with toluene and ether, and then dried to give 330 g (82%), mp 135.7–137.7 °C. The filtrate was concentrated to yield another 70.2 g crude *R*-4 containing some *R*-3. The product was purified by crystallization from ~1 L of 70% aqueous ethanol to give 281.7 g (70%), mp 139–140 °C. An additional 23.4 g was obtained by recrystallizing the second crop: total yield 305 g (76%); $[\alpha]^{25}_D$ = −71.8 ± 0.8° (*c* = 1, acetonitrile); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.56 and 3.70 (2, AB (J_{AB} = 14 Hz), CH_2O), 3.83 (1, dd (*J* = 7 Hz, *J* = 10 Hz), C-4 *H* trans to C-5 *H*), 4.08 (1, dd (*J* = 8, 10 Hz), C-4 *H* cis to C-5 *H*), 4.70 (m, 1, C-5 *H*), 7.12 (t (*J* = 9 Hz), 1, C′-4 *H*), and 7.40 and 7.57 (AB (J_{AB} = 9.0 Hz), 4, C′-3 and C′-5 H's and C′-2 and C′-6 H's, respectively). Anal. ($C_{10}H_{11}NO_3$) C, H, N.

(*R*)-[5-(Hydroxymethyl)-3-phenyl-2-oxooxazolidinyl]methyl 4-Methylbenzenesulfonate (7). To a solution of 259 g (1.34 mol) of *R*-4 in 800 mL of dry pyridine at 0–5 °C was added a solution of 270 g (1.42 mol) of 4-methylbenzenesulfonyl chloride in 250 mL of pyridine, and the mixture was stirred at 15 °C or less until all the *R*-4 had been consumed. The mixture was then poured into 3 L of an ice/water mixture with stirring, and the precipitated product was filtered, washed well with water, and dried; 405 g (87%), mp 153–154 °C. This was satisfactory for subsequent transformations but could be crystallized from acetonitrile to afford material with mp 155–155.5 °C; $[\alpha]^{25}_D$ = −65.5 ± 0.4° (*c* = 1, acetonitrile); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.43 (s, 1, CH_3), 3.73 (1, dd (*J* = 5.6 Hz, *J* = 8.0 Hz), C-4 *H* trans to C-5 *H*), 4.13 (1, dd (*J* = 8.0 Hz, *J* = 8 Hz), C-4 *H* cis to C-5 *H*), 4.92 (2, d (*J* = 4 Hz), CH_2O), 4.92 (m, 1, C-5 *H*), 7.13 (t (*J* = 7 Hz), 1, C′-4 *H*), and 7.33–7.53 (m, 6, aromatic) and 7.80 (AB (J_{AB} = 8.0 Hz), 2, C′-2 and C′-6 H's on sulfonylaryl). Anal. ($C_{17}H_{17}NO_5S$) C, H, N.

(*R*)-(3-Phenyl-2-oxo-5-oxazolidinyl)methyl Azide (8). A mixture of 404.9 g (1.166 mol) of 8, 5.0 g of 18-crown-6, and 80.0 g of sodium azide in 600 mL of DMF was stirred at 70 °C under nitrogen for 5 h. The mixture was then cooled to 0 °C and treated with 500 mL of water. The resulting mixture was poured into 1 L of water to crystallize the product. Filtration yielded 225.5 g (88%), which was pure enough for further use. A sample was recrystallized from *n*-butyl chloride/petroleum ether: mp 76–77.5 °C; $[\alpha]^{25}_D$ = −160.0 ± 0.9° (*c* = 0.93, ethanol); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.73 (m, 4, CH_2N$_3$ and C-4 *H* trans to C-5 *H*), 4.13 (dd (*J* = 8, 8 Hz), 1, C-4 *H* cis to C-5 *H*), 4.87 (m, 1, C-5 *H*), 7.12 (t (*J* = 9 Hz), 1, C′-4 *H*), and 7.38 and 7.53 (AB (J_{AB} = 9.0 Hz), 4, C′-3 and C′-5 H's and C′-2 and C′-6 H's, respectively). Anal. ($C_{10}N_{10}N_4O_2$) C, H, N.

(*S*)-5-(Aminomethyl)-3-phenyl-2-oxooxazolidine Hydrochloride (9). A solution of 225.5 g (1.033 mol) of 8 in 500 mL of 1,2-dimethoxyethane (glyme) was heated to 50 °C and a solution of 145 mL of trimethyl phosphite was added at a rate such that nitrogen evolution did not become too vigorous; the temperature was moderated to a gentle reflux by occasional cooling. When the addition was complete, the mixture was heated under reflux for 1.5 h and then treated with 200 mL of 6 N HCl. The mixture was then heated under reflux for 8.0 h. The product crystallized on cooling and was filtered and washed with glyme to afford 155 g (66%): mp 225 °C dec; $[\alpha]^{25}_D$ = −75.0 ± 0.8° (*c* = 1.00, water); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.23 (d (*J* = 5 Hz), 2, CH_2NH$_3$), 3.77 (dd (*J* = 9, 6 Hz), 1, C-4 *H* trans to C-5 *H*), 4.20 (dd (*J* = 9, 9 Hz), 1, C-4 *H* cis to C-5 *H*), 5.00 (m, 1, C-5 *H*), 7.13 (t (*J* = 9 Hz), 1, C′-4), and 7.42 and 7.53 (AB (J_{AB} = 7.0 Hz), 4, C′-3 and C′-5 H's and C′-2 and C′-6 H's, respectively), and 8.60 (br, 3, NH$_3$).

(*S*)-*N*-(3-Phenyl-2-oxo-5-oxazolidinylmethyl)acetamide (10). To a solution of 130 g (0.568 mol) of 9 in 100 mL of water and 500 mL of THF at 0–5 °C was added a solution of 23 g of NaOH in 20 mL of water. The solution was stirred well and the temperature maintained at 0–5 °C as a solution of 65 mL of acetic anhydride in 65 mL of THF was added, with 200 mL of 25% aqueous NaOH solution being added simultaneously as necessary to keep the pH at 9–10. After all the acetic anhydride had been added, the mixture was allowed to stir until the pH reached approximately 7. The THF portion of the solvent was then removed in vacuo, and the residue was triturated with water and the product filtered to yield 131 g (98%), mp 130–131 °C. The product was purified further by crystallization from acetonitrile to afford 120 g (90%): mp 131–131.5 °C; $[\alpha]^{25}_D$ = −40.0 ± 0.8° (*c* = 1.00, acetonitrile); ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.03 (s, 3, CH_3CONH), 3.65 (m, 2, CH_2NHAc), 3.83 (dd (*J* = 9, 6 Hz), 1, C-4 *H* trans to C-5 *H*), 4.07 (dd (*J* = 9, 9 Hz), 1, C-4 *H* cis to C-5 *H*), 4.80 (m, 1, C-5 *H*), 6.63 (m, 1, *H*NCOCH$_3$), 7.13 (t (*J* = 9 Hz), 1, C′-4 *H*), and 7.37 and 7.47 (AB (J_{AB} = 9.0 Hz), 4, C′-3 and C′-5 H's and C′-2 and C′-6 H's, respectively). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

(*R*)-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl Butyrate (17). A mixture of 1.45 g (0.016 mol) of anhydrous LiBr, 3.64 g (0.016 mol) of tri-*n*-butylphosphine oxide, and 50 mL of xylene was azeotropically dried for 1 h, and then the heat source was removed and a solution of 44.7 g of 4-acetylphenyl isocyanate (0.277 mol) and 40 g (0.277 mol) of (*R*)-glycidyl butyrate in 50 mL of xylene was added at a rate such that the mixture maintained gentle reflux. The resulting solution was refluxed for 2.0 h, and then the solvent was removed in vacuo and the crude product was crystallized from ethanol to give 69.29 g (82%) of 17: mp 89.5–90 °C; $[\alpha]^{25}_D$ = −63° (*c* = 1, acetonitrile). Anal. ($C_{16}H_{19}NO_5$) C, H.

(*R*)-3-(4-Acetylphenyl)-5-(hydroxymethyl)-2-oxooxazolidine (15). A solution of 55 g (0.18 mol) of 17 and 0.980 g (0.018 mol) of sodium methoxide in 180 mL of methanol was stirred at ambient temperature for 2 h. The solution was then neutralized with 10% aqueous HCl, and the solvent was removed in vacuo to afford 43.7 g (100%) of 15, which was crystallized from ethanol/water: mp 175–176 °C; $[\alpha]^{25}_D$ = −67.8° (*c* = 1, acetone). Anal. ($C_{12}H_{13}NO_4$) C, H.

(*R*)-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl 4-Methylbenzenesulfonate (20). By the general tosylation procedure described for 7, 4.70 g (0.020 mol) of 15 and 6.80 g (0.020 mol) of 4-methylbenzenesulfonyl chloride in 65 mL of pyridine afforded 7.11 g (91%) of 16: mp 140–141.5 °C; $[\alpha]^{25}_D$ = −59.1 ± 0.8° (*c* = 0.98, DMSO). Anal. ($C_{19}H_{19}NO_6$) C, H, N.

(*S*)-5-(Morpholinomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (16). A. (*R*)-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl Methanesulfonate. By the general sulfonation procedure described for the preparation of 7, 32.79 g (0.139 mol) of 15 and 20.93 g (0.180 mol) of methanesulfonyl chloride afforded 41.2 g (96%) of the title mesylate.

B. (*R*)-5-(Iodomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine. A mixture of 0.500 g (0.0016 mol) of the mesylate described in part A above, 0.960 g (0.0064 mol) of NaI, and 5 mL of acetone was heated under reflux for 18 h. The solvent was removed in vacuo, the residue dissolved in CHCl$_3$ and washed with brine, and the CHCl$_3$ layer dried (Na$_2$SO$_4$) and evaporated in vacuo to yield 0.514 g (94%) of the iodide.

C. (*R*)-5-(Morpholinomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (16). A solution of 0.490 g (1.4 mmol) of the iodide from part B, 0.620 g (7.1 mmol) of morpholine, and 5 mL of THF containing 0.6 mL of triethylamine was refluxed for 18 h. The solvent was then removed in vacuo, and the residue was taken up in CH$_2$Cl$_2$, washed with brine, dried (MgSO$_4$), and evaporated in vacuo; the residue was purified by flash chromatography using ethyl acetate as the eluent to afford 0.300 g (70%): mp 154–155°; $[\alpha]^{25}_D$ = −48° (*c* = 1, acetonitrile); ^{1}H NMR (200 MHz CDCl$_3$) δ 2.61 (s, 3, CH_3CO), 2.63 (m, 4, CH_2NCH_2), 2.75 (m, 2, CH_2N), 3.72 (4, dd (*J* = *J*′ = 6 Hz), CH_2OCH_2), 3.87 (dd (*J* = 9.0, 6.5 Hz), 1, C-4 *H* trans to C-5 *H*), 4.13 (dd (*J* = 9.0, 9.0 Hz), 1, C-4 *H* cis to C-5 *H*), 4.82 (m, 1, C-5 *H*), 7.67 and 8.00 (AB (J_{AB} = 8.9 Hz), 4, aryl H). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

5-(Aminomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (21). A. 3-[(4-Acetylphenyl)amino]-1,2-propanediol. To a stirred solution of 100 g (0.740 mol) of 4-aminoacetophenone in 500 mL of ethanol heated to reflux under nitrogen was added dropwise 50 mL (0.754 mol) of glycidol. The mixture was heated under reflux for 18 h, at which time an additional 25 mL (0.377 mol) of glycidol was added and the mixture was refluxed an additional 8 h. The mixture was then cooled and the product filtered: 87.0 g (56%); mp 136–137 °C.

B. 3-(4-Acetylphenyl)-2-oxo-5-(hydroxymethyl)oxazolidinone. By the general diethyl carbonate cyclization procedure described for the preparation of *R*-4, 34 g (0.162 mol) of the aminopropanediol described in part A and 30 mL of diethyl carbonate afforded 36.6 g (96%) of the title compound, mp 153–154 °C.

C. [3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl Methanesulfonate. By the general sulfonation procedure described for the preparation of **7**, 30 g (0.127 mol) of the alcohol described in part B above yielded 35 g (88%) of the mesylate.

D. [3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide. By the general azide displacement procedure described for the preparation of **8**, 10 g (0.032 mol) of the mesylate from part C afforded 4.80 g (55%), mp 101–102 °C.

E. 5-(Aminomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (21). By the general azide reduction procedure described in the preparation of **9**, 4.80 g (0.018 mol) of the azide from part B above yielded 1.6 g (37%) of **21**, mp 115–116 °C (benzene). Anal. ($C_{12}H_{14}N_2O_3$) C, H, N.

(*R*)-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide (19). By the general procedure for preparation of azides described for **8**, a mixture of 47.45 g (0.139 mol) of **16**, 0.500 g 18-crown-6, and 14.7 g of sodium azide in 600 mL of DMF yielded 31.44 g (87%) of **19**, pure enough for further use. A sample was crystallized from 1:2 petroleum ether/ethyl acetate: mp 79–80 °C; $[\alpha]^{25}_D = -150.0 \pm 0.9°$ (c = 0.93, acetonitrile). Anal. ($C_{12}H_{12}N_4O_3$) C, H.

(*S*)-5-(Aminomethyl)-3-(4-acetylphenyl)-2-oxooxazolidine Hydrochloride (22). By the general procedure for azide reduction described for **8**, a solution of 6.0 g (0.0231 mol) of **19** and 3.0 mL (0.0570 mol) of trimethyl phosphite in 500 mL of glyme afforded 5.14 g (82%), mp 256–257 °C dec. Anal. ($C_{12}H_{15}N_2O_3Cl$) C, H, N, Cl.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]-methyl]acetamide (2). Via the general Schotten-Baumann procedure described for the preparation of **10**, 16.96 g (0.0627 mol) of **22** and 6.5 mL (0.069 mol) of acetic anhydride yielded 12.0 (70%) of **2**: mp 189.5–190 °C (acetonitrile); $[\alpha]^{25}_D = -51.1 \pm 0.4°$ (c = 1.00, DMF); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.83 (s, 3, CH_3CONH), 2.55 (s, 3, CH_3CO), 3.44 (m, 2, CH_2NHAc), 3.81 (dd (J = 9.0, 6.5 Hz), 1, C-4 *H* trans to C-5 *H*), 4.18 (dd (J = 9.0, 9.0 Hz), 1, C-4 *H* cis to C-5 *H*), 4.76 (m, 1, C-5 H), 7.68 and 7.99 (AB (J_{AB} = 8.9 Hz), 4, aryl H), and 8.24 (m, 1, *H*NCOCH$_3$); ^{13}C NMR 100.6 MHz (DMSO-d_6) δ 22.3 (CH_3CONH), 26.3 (CH_3CO aryl), 41.3 and 47.1 (CH_2's), 71.7 (CH), 117.0, 129.2, 131.6, and 142.4 (aromatic), 153.8 (oxazolidinone carbonyl), 169.9 (acetamide carbonyl), and 196.4 (keto carbonyl); IR (Nujol mull) 3270, 1755, 1666, 1650, 1608, and 1567 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 283 (4.33) nm. Anal. ($C_{14}H_{16}N_2O_4$) C, H, N.

3-(4-Acetylphenyl)-2-oxo-5-vinyloxazolidine (11). By the general epoxide–isocyanate procedure described for the preparation of **17**, 11.50 g (0.071 mol) of 4-acetylphenyl isocyanate and 5.0 g (0.071 mol) butadiene monoxide yielded 7.335 g of **11**, which was crystallized from *n*-butyl chloride: mp 118–119.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.58 (s, 3, CH_3CO), 3.82 (dd (J = 8.0, 7.0 Hz), 1, C-4 *H* trans to C-5 *H*), 4.22 (dd (J = 8.0, 8.0 Hz), 1, C-4 *H* cis to C-5 *H*), 5.11 (q (J = 8.0 Hz)), 1, C-5 *H*), 5.43 (d (J = 10 Hz), 1, =CH_2 *Z*-*H*), 5.54 (d (J = 17 Hz), =CH_2 *E*-*H*), 5.99 (ddd (J = 8.0 Hz, J' = 10 Hz, J'' = 17 Hz), 1, C*H*=), and 7.62 and 7.95 (AB (J_{AB} = 8.1 Hz), 4, aryl H). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

3-(4-Acetylphenyl)-2-oxo-5-methyloxazolidine (12). By the general epoxide–isocyanate procedure described for the preparation of **17**, 7.20 mL (0.10 mol) of propylene oxide and 8.06 g (0.050 mol) of 4-acetylphenyl isocyanate yielded 10.334 g (94%), which was crystallized from methanol and recrystallized from *n*-butyl chloride three times to give 2.258 g, mp 127–127.5 °C. Anal. ($C_{12}H_{12}NO_3$) C, H, N.

(*R*)-5-(Fluoromethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (13). A. Preparation of (*R*)-5-(Fluoromethyl)-3-phenyl-2-oxooxazolidine. To a solution of 15 mL (0.114 mol) of (diethylamido)sulfur trifluoride in 50 mL of CH_2Cl_2 at 10 °C under nitrogen was added in portions 10.0 g (0.516 mol) of **7**, and the mixture was allowed to stand for 7 days. The solvent was removed in vacuo, the residue was short-path distilled with a Kugelrohr distillation apparatus, and the distillate was crystallized from methanol to afford 6.9 g (69%), mp 113–113.5 °C.

B. (*R*)-5-(Fluoromethyl)-3-(4-acetylphenyl)-2-oxo-oxazolidine (13). To a mixture of 50 mL of methanesulfonic acid containing 5.0 g of methanesulfonic anhydride that had been stirred for 0.5 h was added 6.9 g (0.035 mol) of (*R*)-5-(fluoromethyl)-3-phenyl-2-oxooxazolidine. The mixture was stirred for 1.0 h and then treated with 10 mL of acetic anhydride and stirred at ambient temperature for 18 h. The mixture was then poured over ice and extracted with 85:15 $CHCl_3$/*i*-PrOH. The organic phase was washed with 5% $NaHCO_3$ solution and saturated brine, dried (Na_2SO_4), and evaporated in vacuo; the residue was chromatographed (60:40 toluene/ethyl acetate, silica gel), and the product fractions were crystallized from toluene to afford 2.9 g (37%) of **13**: mp 119–120 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.18 (s, 3, CH_3CO), 3.91 (dd (J = 9.0, 6.5 Hz), 1, C-4 *H* trans to C-5 *H*), 4.25 (dd (J = 9.0, 7.0 Hz), 1, C-4 *H* cis to C-5 *H*), 4.72 (d (J_{HF} = 47 Hz), 2, CH_2F), 4.99 (m, 1, C-5 *H*), and 7.71 and 8.00 (AB (J_{AB} = 8.8 Hz), 4, aryl H). Anal. ($C_{10}H_{10}NO_2F$) C, H, N.

5-(Chloromethyl)-3-(4-acetylphenyl)-2-oxooxazolidine (14). By the general epoxide–isocyanate procedure described for the preparation of **17**, 4.0 mL (0.050 mol) of epichlorohydrin and 8.06 g (0.050 mol) of 4-acetylphenyl isocyanate afforded 3.927 g (31%) of **14**, mp 94–95 °C (*n*-butyl chloride). Anal. ($C_{12}H_{12}NO_3Cl$) C, H, N, Cl.

(*R*)-[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl Phosphate (18). To a solution of 2.35 g (0.010 mol) of **17** in 20 mL of dry THF in a round-bottomed flask with a side arm and septum under nitrogen was added 1.08 g (0.015 mol) of tetrazole followed by 4.21 g (0.0116 mol) of bis[2-(trimethylsilyl)ethoxy]-*N*,*N*-diisopropylaninophosphine.[13] The mixture was stirred for 1.0 h, cooled to 0 °C, and treated with 5.0 mL of water, followed by 5.0 mL of 30% hydrogen peroxide. The mixture was stirred for 1.0 h, diluted with ethyl acetate, washed with 10% aqueous sodium bisulfite solution and then with saturated NaCl solution, dried ($MgSO_4$), and evaporated in vacuo; 5.689 g. To a solution of this material in 40 mL of acetonitrile under nitrogen was added dropwise 1.7 mL of 50% HF. The mixture was stirred for 3.0 h. The product was filtered and crystallized from acetonitrile/methanol; 1.989 g (59%) of **18** was isolated: mp 201.5–202.5 °C dec; ^{1}H NMR (90 MHz, DMSO-d_6) δ 2.57 (s, 3, CH_3CO), 4.01, (m, 4, C-4 *H* trans to C-5 *H*, C-4 *H* cis to C-5 *H*, and CH_2OP), 4.93 (m, 1, C-5 H), 7.67 and 7.87 (AB (J_{AB} = 7.8 Hz), 4, aryl H) and 8.62 (br, 2, P(O*H*)2). Anal. ($C_{12}H_{14}O_7NP$) C, H, N, P.

(*R*)-2-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]-methyl]phthalimide (23). A. (*R*)-2-[(3-Phenyl-2-oxo-5-oxazolidinyl)methyl]phthalimide. A mixture of 270 g (0.777 mol) of **7**, 151.7 g (0.819 mol) of potassium phthalimide, and 800 mL of DMF was stirred at 50 °C for 48 h. The cooled mixture was then slowly poured onto 3 L of ice/water and stirred vigorously for 0.5 h. The product was filtered, washed well with water, and dried. The crude solid was crystallized from acetonitrile: 203.7 g (81%); mp 167–168 °C; $[\alpha]^{23}_D = -73.4 \pm 0.5°$ (c = 0.93, acetonitrile).

B. (*R*)-2-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]-methyl]phthalimide (23). By the general electrophilic acetylation procedure described for the preparation of **13** above, from 15.1 g (0.043 mol) of (*R*)-2-[(3-phenyl-2-oxo-5-oxazolidinyl)-methyl]phthalimide and 15.0 mL of acetic anhydride in 70 mL of methanesulfonic acid there was obtained 12.47 g (76%) of **23**, mp 224–225 °C (acetonitrile). Anal. ($C_{20}H_{16}N_2O_5$) C, H, N.

Dimethyl (*R*)-1-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (24). A solution of 2.60 g (0.010 mol) of **2** and 1.8 mL (0.015 mol) of dimethyl acetylenedicarboxylate in 25 mL of glyme was heated under reflux and nitrogen for 7.0 h. Upon cooling, the product crystallized:

(13) Seitz, S. P. Personal communication.

2.80 g (70%); mp 157–158 °C. Anal. ($C_{18}H_{18}N_4O_7$) C, H, N.

3-(4-Isopropylphenyl)-2-oxo-5-methyloxazolidine (25). By the general epoxide–isocyanate procedure described for the preparation of **17**, 8.06 g (0.050 mol) of 4-isopropylphenyl isocyanate and 3.60 mL (0.050 mol) of propylene oxide yielded 6.234 g (57%) of **25**, mp 33–34 °C (petroleum ether (−78 °C)). Anal. ($C_{13}H_{17}NO_2$) C, H, N.

3-(4-Isopropylphenyl)-2-oxo-5-ethyloxazolidine (26). By the general epoxide–isocyanate procedure described for the preparation of **17**, 0.806 g (0.005 mol) of 4-isopropylphenyl isocyanate and 0.430 mL (0.005 mol) of 1,2-epoxybutane yielded 1.012 g (86%) of a liquid, **26**, which was shown to be one material by HPLC: mass spectrum ($C_{14}H_{19}NO_2$) calcd *m/e* 233.1416, measured *m/e* 233.2429 (M^+).

3-(4-Isopropylphenyl)-2-oxo-5-(chloromethyl)oxazolidine (27). By the general epoxide–isocyanate procedure described for the preparation of **17**, 8.06 g (0.050 mol) of 4-isopropylphenyl isocyanate and 4.0 mL (0.050 mol) of epichlorohydrin yielded 9.350 g (74%) of **27**, mp 78.5–79 °C (*n*-butyl chloride). Anal. ($C_{13}H_{16}NO_2Cl$) C, H, N, Cl.

3-(4-Isopropylphenyl)-2-oxo-5-(hydroxymethyl)oxazolidine (28). A. [3-(4-Isopropylphenyl)-2-oxo-5-oxazolidinyl]methyl Butyrate. By the general epoxide–isocyanate procedure described for the preparation of **17**, 8.06 g (0.050 mol) of 4-isopropylphenyl isocyanate and 7.0 mL (0.050 mol) of *d,l*-glycidyl butyrate afforded 15.28 g (100%) of the product.

B. 3-(4-Isopropylphenyl)-2-oxo-5-(hydroxymethyl)oxazolidine (28). By the general procedure for methanolysis of the butyrate described for the preparation of **15** above, the material prepared in part A yielded 9.675 g (82%) of **28**, mp 100–101 °C (methanol/water). Anal. ($C_{13}H_{17}NO_3$) C, H, N.

[3-(4-Isopropylphenyl)-2-oxo-5-oxazolidinyl]methyl Acetate (29). To 5.88 g (0.025 mol) of **28** were added 15 mL of acetic anhydride, 15 mL of pyridine, and dropwise 8 mL of acetyl chloride, in that order, and the mixture was heated under reflux and nitrogen for 1 h, poured into a suspension of 100 g of ice in 400 mL of acetone, and stirred for 2 h. The resulting solution was diluted with 200 mL of water and extracted with 2–300-mL portions of ethyl acetate. The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated in vacuo: 5.47 g (79%), mp 95–96 °C (*n*-butyl chloride). Anal. ($C_{15}H_{19}NO_4$) C, H, N.

[3-(4-Isopropylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide (30). A. 3-(4-Isopropylphenyl)-2-oxo-5-(bromomethyl)oxazolidinone. By the general epoxide–isocyanate procedure described for the preparation of **17**, 48.5 g (0.300 mol) of 4-isopropylphenyl isocyanate and 26 mL (0.300 mol) of epibromohydrin afforded 62.9 g (70%) of the title compound, mp 84–85 °C (70% aqueous ethanol).

B. [3-(4-Isopropylphenyl)-2-oxo-5-oxazolidinyl]methyl Azide (30). By the general sodium azide displacement procedure described for the preparation of **8** above, 59.64 g (0.200 mol) of the above bromide and 15 g of sodium azide afforded 51.7 g (99%) of **30**, mp 63–64 °C (di-*n*-butyl ether). Anal. ($C_{13}H_{16}N_4O_2$) C, H, N.

***N*-[[3-(4-Isopropylphenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide (31).** A mixture of 48.5 g (0.212 mol) of **30**, 60 mL of triethylamine, and 25 mL of propane-1,3-dithiol was stirred and gradually warmed to 40 °C over the period of 1 h, as nitrogen evolved. The mixture was then heated at 50 °C for 1 h and then allowed to stir at ambient temperature for 18 h. The solvent was removed in vacuo, and the residue was dissolved in aqueous HCl and washed with CH_2Cl_2. The aqueous layer was adjusted to pH 8 by adding aqueous NaOH solution, and the product was extracted with 1:1 ether/THF. The extracts were dried (Na_2SO_4) and evaporated in vacuo to yield 44.2 g of crude amine. By the general Schotten-Baumann procedure described in the preparation of **10**, 5.21 g (0.022 mol) of this amine and 2.3 mL of acetic anhydride afforded 3.12 g (50%) of **31**, mp 142.5–143.5 °C (acetonitrile). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

3-[4-(Methylthio)phenyl]-2-oxo-5-methyloxazolidine (32). By the general epoxide–isocyanate procedure described for the preparation of **17**, 3.6 mL (0.050 mol) of propylene oxide and 8.26 g (0.050 mol) of 4-(methylthio)phenyl isocyanate yielded 11.8 g (100%) of **32**, mp 115.5–116.5 °C (*n*-butyl chloride). Anal. ($C_{11}H_{13}NO_2S$) C, H, N, S.

3-[4-(Methylthio)phenyl]-2-oxo-5-(chloromethyl)oxazolidine (33). By the general epoxide–isocyanate procedure described for the preparation of **17**, 4.0 mL (0.050 mol) of epichlorohydrin and 8.26 g (0.050 mol) of 4-(methylthio)phenyl isocyanate yielded 3.927 g (30%) of **33**, mp 106–107 °C (*n*-butyl chloride). Anal. ($C_{11}H_{12}ClNO_2S$) C, H, N, S, Cl.

(*R*)-3-[4-(Methylthio)phenyl]-2-oxo-5-(hydroxymethyl)oxazolidine (34). A. (*R*)-[3-[4-(Methylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl Butyrate. By the general epoxide–isocyanate procedure described for the preparation of **17**, 25 g (0.151 mol) of 4-(methylthio)phenyl isocyanate and 21.2 mL of (*R*)-glycidyl butyrate afforded 47.6 g (100%) of the product.

B. (*R*)-3-[4-(Methylthio)phenyl]-2-oxo-5-(hydroxymethyl)oxazolidine (34). By the general procedure for methanolysis of the butyrate described for the preparation of **15** above, the material prepared in part A yielded 33.820 g (100%) of **34**, mp 139–140 °C (methanol/water). Anal. ($C_{11}H_{13}NO_3S$) C, H, N, S.

(*S*)-*N*-[[3-[4-(Methylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (35). A. (*R*)-[3-[4-(Methylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl 4-Methylbenzenesulfonate. By the general procedure for tosylation described for the preparation of **7**, 50.5 g (0.209 mol) of **34** and 44.0 g (0.220 mol) of 4-methylbenzenesulfonyl chloride afforded 61.24 g (74%) of the title compound, mp 151.5–152 °C (acetonitrile).

B. (*R*)-[3-[4-(Methylthio)phenyl]-2-oxo-5-oxazolidinyl]-methyl Azide. By the general azide displacement procedure described for the preparation of **8**, 50.0 g (0.1272 mol) of the above 4-methylbenzenesulfonate and 11.1 g of sodium azide yielded 31.3 g (93%) of the title compound, mp 75–76 °C (70:20 ethanol/water).

C. (*S*)-3-[4-(Methylthio)phenyl]-2-oxo-5-(aminomethyl)-oxazolidine. By the general azide reduction procedure described for the preparation of **31** above, 30.3 g (0.1147 mol) of the above azide and 13.1 mL of 1,3-propanedithiol afforded 16.50 g (60%) of the title amine.

D. (*S*)-*N*-[[3-[4-(Methylthio)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (35). By the general Schotten-Baumann acetylation procedure described for the preparation of **10**, 6.8 g (0.0303 mol) of the above amine and 3.4 mL of acetic anhydride afforded 7.1 g (84%) of **35**: mp 166.5–167 °C (THF/water); $[\alpha]^{25}_D$ = −44.2 ± 0.4° (*c* = 0.98, DMF). Anal. ($C_{13}H_{16}N_2O_3S$) C, H, N, S.

3-[4-(Methylsulfinyl)phenyl]-2-oxo-5-(chloromethyl)oxazolidine (36). To a solution of 2.58 g (0.010 mol) of **33** in 100 mL of methylene chloride at −30 °C under nitrogen was added 2.15 g (0.010 mol) of 85% *m*-chloroperbenzoic acid and the mixture was stirred at −30 °C for 30 min and then allowed to stir and warm slowly. When the temperature reached −20 °C, the mixture was evaporated in vacuo and the residue was triturated with 200 mL of ether: 2.758 g (100%), mp 85–86 °C. Anal. ($C_{11}H_{12}NO_3SCl$) C, H, N, S, Cl.

3-[4-(Methylsulfinyl)phenyl]-2-oxo-5-(hydroxymethyl)-oxazolidine (37). By the general sulfide monooxidation procedure described for the preparation of **36** above, 23.9 g (0.10 mol) of **34** and 21.6 g (0.10 mol) of 85% *m*-chloroperbenzoic acid afforded 6.8 g of **37** as a mixture of diastereomers. Chromatography (70% CH_2Cl_2/30% acetonitrile) afforded 1.8 g (7%) of a fraction of **37**, mp 145–153 °C (acetonitrile). Anal. ($C_{11}H_{13}NO_4S$) C, H, N, S.

(*S*)-*N*-[[3-[4-(Methylsulfinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (1). By the general sulfide monooxidation procedure described for the preparation of **36**, 2.00 g (0.07 mol) of **35** and 1.512 g (0.007 mol) of *m*-chloroperbenzoic acid afforded, after purification by HPLC (90% acetonitrile/methanol), 0.73 g (35%) of **1** as a mixture of diastereomers: mp 146–155 °C; $[\alpha]^{25}_D$ = −44.4 ± 0.4° (*c* = 1.01, water); ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.84 (s, 3, CH_3CONH), 2.72 (s, 3, CH_3SO), 3.43 (m, 2, CH_2NHAc), 3.79 (dd (*J* = 8.9, 6.6 Hz), 1, C-4 *H* trans to C-5 *H*), 4.17 (dd (*J* = 8.9, 8.9 Hz), 1, C-4 *H* cis to C-5 *H*), 4.75 (m, 1, C-5 *H*), 7.70 and 7.74 (AB (J_{AB} = 9.0 Hz), 4, aryl *H*), and 8.25 (m, 1, *H*NCOCH$_3$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 22.7 (CH_3CONH), 42.2 (CH_3SO aryl), 42.6 and 48.7 (CH_2's), 73.6 (*C*H), 120.4, 126.3, 138.8, and 141.5 (aromatic), 156.9 (oxazolidinone carbonyl), and 175.4 (acetamide carbonyl); IR (Nujol mull) 3450, 1757, 1675, and 1596, cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 257 (4.29) nm. Anal. ($C_{13}H_{16}N_2O_4S$) C, H, N, S.

3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-methyloxazolidine (38). To a suspension of 2.23 g (0.01 mol) of **32** in 100 mL of methylene chloride at ambient temperature under nitrogen was added 4.31 g (0.02 mol) of *m*-chloroperbenzoic acid, the mixture was stirred for 2 h and then evaporated to dryness in vacuo, and the residue was triturated with 200 mL of ether: 2.46 g (96%); mp 194–194.5 °C (acetonitrile). Anal. ($C_{11}H_{13}NO_4S$) C, H, N, S.

3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-ethyloxazolidine (39). A. 3-[4-(Methylthio)phenyl]-2-oxo-5-ethyloxazolidine. By the general epoxide–isocyanate procedure described for the preparation of **17**, 8.26 g (0.05 mol) of 4-(methylthio)phenyl isocyanate and 4.30 mL (0.05 mol) of 1,2-epoxybutane yielded 4.676 g (48%) of the title oxazolidinone, mp 87–88 °C.

B. 3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-ethyloxazolidine (39). By the general sulfide oxidation procedure described for the preparation of **38**, 2.37 g (0.01 mol) of the sulfide from part A and 4.31 g (0.020 mol) of 85% *m*-chloroperbenzoic acid afforded 2.63 g (98%) of **39**, mp 179–180.5 °C (acetonitrile). Anal. ($C_{12}H_{15}NO_4S$) C, H, N, S.

3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-(chloromethyl)oxazolidine (40). By the general sulfide oxidation procedure described for the preparation of **38**, 2.58 g (0.01 mol) of **33** and 4.31 g (0.02 mol) of 85% *m*-chloroperbenzoic acid afforded 2.89 g (99%) of **40**; mp 171.5–172 °C (acetonitrile). Anal. ($C_{11}H_{12}NO_4SCl$) C, H, N, S, Cl.

3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-(hydroxymethyl)oxazolidine (41). By the general sulfide oxidation procedure described for the preparation of **38**, 2.39 g (0.01 mol) of **34** and 4.31 g (0.02 mol) of 85% *m*-chloroperbenzoic acid afforded 2.72 g (100%) of **41**, mp 181–182 °C (acetonitrile). Anal. ($C_{11}H_{13}NO_5S$) C, H, N, S.

(*R*)-[3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl Azide (42). A. (*R*)-3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-(hydroxymethyl)oxazolidine. By the general sulfide oxidation procedure described for the preparation of **38**, 130.0 g (0.504 mol) of **34** and 225 g (1.108 mol) of 85% *m*-chloroperbenzoic acid afforded 98.4 g (67%) of the title compound: mp 189.5–190 °C (70% aqueous ethanol); $[\alpha]^{25}_D = -60.2 \pm 0.4°$ (c = 1, methanol).

B. (*R*)-[3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl 4-Methylbenzenesulfonate. By the general tosylation procedure described above for the preparation of **7**, 5.0 g (0.018 mol) of the above alcohol and 3.7 g of 4-methylbenzenesulfonyl chloride yielded 4.02 g (50%) of the title compound, mp 185.5–187 °C.

C. (*R*)-[3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl Azide (42). By the general azide displacement procedure described for the preparation of **8**, 3.5 g (0.08 mol) of the above sulfonate and 2.0 g of sodium azide afforded 1.25 g (53%) of **42**, mp 146.5–148 °C. Anal. ($C_{11}H_{12}N_4O_4S$) C, H, N, S.

(*R*)-3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-(aminomethyl)oxazolidine (43). By the general azide reduction procedure described for the preparation of **31** above, 1.4 g (5.2 mmol) of the above azide and 4.4 mL of 1,3-propanedithiol afforded 0.87 g (62%) of the title amine, mp 146.5–147 °C (ethanol). Anal. ($C_{11}H_{14}N_2O_4S$) C, H, N, S.

(*S*)-*N*-[[3-[4-(Methylsulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (44). By the general azide reduction procedure and Schotten-Baumann acetylation described for the preparation of **31**, 10.37 g (0.035 mol) of **42**, 4.0 mL of 1,3-propanedithiol, and 5.0 mL of triethylamine yielded 6.2 g (54%) of the acetic acid salt of the amine, mp 143–145 °C, 2.0 g (0.007 mol) of which upon acetylation afforded 1.01 g (45%) of **44**, mp 192.5–193.5 °C (acetonitrile). Anal. ($C_{13}H_{16}N_2OS$) C, H, N, S.

4-[5-(Chloromethyl)-2-oxo-3-oxazolidinyl]benzenesulfonamide (45). To 15 mL of chlorosulfuric acid at 5 °C under nitrogen was added with stirring 6.35 g of 3-phenyl-2-oxo-5-(chloromethyl)oxazolidine. The mixture was stirred at room temperature for 1.0 h and then poured into ice with good stirring (caution: splatters!), and the solid was filtered and added to a mixture of 25 mL of concentrated ammonium hydroxide in 50 mL of THF. The mixture was stirred for 10 min and then the THF portion of the solvent was removed in vacuo, and the residue was triturated with water and filtered: 3.581 g (41%); mp 140–141 °C (ethyl acetate/*n*-butyl chloride). Anal. ($C_{10}H_{11}N_2O_4SCl$) C, H, N, S, Cl.

(*R*)-4-[5-(Azidomethyl)-2-oxo-3-oxazolidinyl]benzenesulfonamide (46). By the general electrophilic sulfonation/amidation procedure described for the preparation of **45**, 2.0 g (9.0 mmol) of **8** afforded 1.16 g (43%) of **46**, mp 140–140.5 °C (acetonitrile). Anal. ($C_{10}H_{11}N_5O_4S$) C, H, N, S.

(*R*)-4-[5-(Hydroxymethyl)-2-oxo-3-oxazolidinyl]benzenesulfonamide (47). By the general electrophilic sulfonation/amidation procedure described for the preparation of **45**, 41 g (0.212 mol) of **4** yielded 15.8 g (27%) of **47**: mp 167–169 °C (acetonitrile); $[\alpha]^{25}_D = -62.1 \pm 0.4°$ (c = 1.01, acetonitrile). Anal. ($C_{10}H_{12}N_2O_5S$) C, H, N, S.

(*S*)-*N*-[[3-[4-(Aminosulfonyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (48). By the general electrophilic sulfonation/amidation procedure described for the preparation of **45**, 7.91 g (0.034 mol) of **10** gave 6.85 g (64%), mp 236–236.5 °C (acetonitrile). Anal. ($C_{12}H_{15}N_3O_5S$) C, H, N, S.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]formamide (49). To 10 mL of THF and 10 mL of phenyl formate at 10 °C was added 2.08 g (9.0 mmol) of **22** free base and the mixture was stirred for 18 h. The THF was removed in vacuo, and the resulting solution was treated with ether and the solid filtered to yield 1.86 g (80%), mp 146–147 °C (acetonitrile). Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]propanamide (50). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 2.35 g (10 mmol) of **22** free base and 2.0 mL of propanoic anhydride afforded 2.33 g (80%) of **50**, mp 209.5–210.5 °C (THF/water). Anal. ($C_{15}H_{18}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]butanamide (51). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 1.40 g (5 mmol) of **22** free base and 0.87 mL of butanoic anhydride afforded 1.10 g (70%) of **51**, mp 198–199 °C (THF/water). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-methyl-2-propanamide (52). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 1.40 g (5 mmol) of **22** free base and 0.87 mL of 2-methyl-2-propanoic anhydride afforded 1.10 g (70%) of **52**, mp 218–219 °C (THF/water). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide (53). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 1.40 g (5 mmol) of **22** free base and 0.87 mL of cyclopropanecarboxylic anhydride afforded 0.900 g (57%) of **53**, mp 229–230 °C (acetonitrile/ether); ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.66 (m, 4, cyclopropyl CH_2), 1.60 (m, 1, cyclopropyl CH), 2.55 (s, 3, CH_3CO), 3.48 (t (J = 5 Hz), 2, CH_2NH), 3.82 (dd (J = 9.0, 6.4 Hz), 1, C-4 H trans to C-5 H), 4.18 (dd (J = 9.0, 9.0 Hz), 1, C-4 H cis to C-5 H), 4.78 (m, 1, C-5 H), 7.68 and 7.99 (AB (J_{AB} = 8.5 Hz), 4, aryl H), and 8.52 (m, 1, NHCO). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

Methyl (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]carbamate (54). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 5.0 g (19 mmol) of **22** and 2.15 mL (28 mmol) of methyl chloroformate afforded 4.23 g (78%) of **34**: mp 167.5–168 °C (acetonitrile); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.57 (s, 3, CH_3CO), 3.34 (m, 2, CH_2NHAc), 3.54 (s, 3, CH_3CO$_2$NH), 3.85 (dd (J = 9, 7 Hz), 1, C-4 H trans to C-5 H), 4.20 (dd (J = 9, 9 Hz), 1, C-4 H cis to C-5 H), 4.75 (m, 1, C-5 H), 7.1 (m, 1, HNCO$_2$), and 7.70 and 8.00 (AB (J_{AB} = 8 Hz), 4, aryl H). Anal. ($C_{14}H_{16}N_2O_5$) C, H, N.

***tert*-Butyl (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]carbamate (55).** By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 1.0 g (3.7 mmol) of **22** and 1.18 mL (4.8 mmol) of 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile afforded 1.03 g (83%) of **55**, mp 187 °C dec. Anal. ($C_{17}H_{22}N_2O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]dichloroacetamide (56). By the general Schotten-Baumann acetylation procedure described for the preparation of **10**, 1.5 g (6 mmol) of **22** and 2.20 mL of dichloroacetyl chloride afforded 1.7 g (86%) of **56**: mp 209.5–210.5 °C (toluene); ^{1}H NMR

(200 MHz, DMSO-d_6) δ 2.57 (s, 3, CH_3CO), 3.57 (m, 2, CH_2NH), 3.80 (dd (J = 9.0, 6.5 Hz), 1, C-4 *H* trans to C-5 *H*), 4.22 (dd (J = 9.0, 9.0 Hz), 1, C-4 *H* cis to C-5 *H*), 4.83 (m, 1, C-5 *H*), 6.50 (s, 1, $CHCl_2CON$), 7.67 and 8.00 (AB (J_{AB} = 10 Hz), 4, aryl H), and 9.00 (m, 1, N*H*). Anal. ($C_{14}H_{14}N_2O_4Cl$) C, H, N, Cl.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-(acetylamino)acetamide (57). A. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]chloroacetamide. Via the general Schotten-Baumann procedure described for preparation of **10**, 7.47 g (28 mol) of **22** and 9.43 g of chloroacetic anhydride yielded 7.9 g (92%) of the title compound, mp 171–172 °C (THF/water).

B. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-azidoacetamide. By the general azide displacement procedure described for preparation of **8**, 3.10 g (10 mmol) of the chloroacetamide from part A yielded 2.75 g (87%) of the title azide, mp 143.5–144 °C.

C. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-aminoacetamide Hydrochloride. By the general reduction procedure described for the preparation of **9**, 2.5 g (7.8 mmol) of the azidoacetyl compound described in part B afforded 1.2 g (47%) of the title amine hydrochloride, mp >250 °C.

D. (*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-(acetylamino)acetamide (57). By the general Schotten-Baumann acetylation procedure described for the preparation of **10**, 0.500 g (1.5 mmol) of the amide hydrochloride described in part C above yielded 0.360 g (71%) of **57**, mp 234–235 °C (acetonitrile/ether). Anal. ($C_{16}H_{19}N_3O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-3-oxobutanamide (58). By the general Schotten-Baumann acylation procedure described for the preparation of **10**, 6.17 g (0.023 mol) of **22** and 2.2 mL of diketene afforded 3.99 g (54%) of **58**, mp 160–161 °C (acetonitrile). Anal. ($C_{16}H_{18}N_2O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-cyanoacetamide (59). By the general displacement procedure described for **8**, 2.1 g (0.0068 mol) of (*S*)-*N*-[[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]chloroacetamide, prepared as described in the preparation of **57**, and 0.500 g of potassium cyanide yielded 1.40 g (68%) of **59**, mp 169–170 °C (20:1 ethanol/acetonitrile). Anal. ($C_{15}H_{15}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-thiocyanoacetamide (60). By the general displacement procedure described for **8**, 2.1 g (0.0068 mol) of (*S*)-*N*-[[3-(4-acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]chlorothioacetamide, prepared as described in the preparation of **57**, and 0.700 g of potassium cyanide yielded 1.70 g (75%) of **60**, mp 144 °C dec (ethanol). Anal. ($C_{15}H_{15}N_3O_4S$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-2-methoxyacetamide (61). By the general Schotten-Baumann procedure described for **10**, 1.4 g (5 mmol) of **22** and 0.43 mL of methoxyacetyl chloride yielded 1.10 g (69%) of **61**, mp 155.5–157 °C (acetonitrile). Anal. ($C_{15}H_{18}N_2O_5$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]urea (62). To 2.00 g (0.007 mol) of **22** free base in 100 mL of glyme was added 1.3 g of phenyl carbamate, and the mixture was refluxed under nitrogen for 3.0 h. The solution was then cooled, concentrated in vacuo, and diluted with ether and filtered: 1.98 g (84%); mp 180.5–182 °C (acetonitrile). Anal. ($C_{12}H_{15}N_3O_4$) C, H, N.

(*S*)-*N*-[[3-(4-Acetylphenyl)-2-oxo-5-oxazolidinyl]methyl]-*N'*,*N'*-dimethylurea (63). By the general Schotten-Baumann procedure described for **10**, 1.4 g (5 mmol) of **22** and 0.51 mL of *N*,*N*-dimethylcarbamoyl chloride yielded 0.400 g (25%) of **63**, mp 203–205 °C dec (acetonitrile). Anal. ($C_{15}H_{19}N_3O_4$) C, H, N.

In Vitro Susceptibility Tests. MICs of the compounds for the various bacterial strains were determined by a microtiter broth dilution assay.[2,14] For comparative purposes, MICs of racemic compounds were divided by 2 to reflect the fact that only one oxazolidinone enantiomer possesses antibacterial activity.

(14) National Committee for Clinical Laboratory Standards. 1982. Tentative standard M7-T. National Committee for Clinical Laboratory Standards, Villanova, PA.

Cholecystokinin Antagonists. Synthesis and Biological Evaluation of 3-Substituted Benzolactams

W. H. Parsons,*,† A. A. Patchett,† M. K. Holloway,‡ G. M. Smith,‡ J. L. Davidson,† V. J. Lotti,§ and R. S. L. Chang§

Department of Exploratory Chemistry, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065, and Departments of Microbial Pharmacometrics and Molecular Systems, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received December 12, 1988*

A series of 1,3-substituted benzolactams are reported that are potent nonpeptidal antagonists of the peptide hormone cholecystokinin (CCK). Design considerations were based upon the natural product CCK antagonist asperlicin and the potent benzodiazepine antagonist series exemplified by L-364,718 (1). Compound **19**, the most potent compound in the benzolactam series, had an IC_{50} = 3 nM for inhibition of binding of ^{125}I-CCK-8 to CCK receptors in rat pancreatic tissue, and its racemic analogue **8** was found to be orally active in inhibiting CCK-induced gastric emptying in mice, with an ED_{50} = 2.6 mg/kg po. The effects of ring size, substitution at positions 1 and 3, and stereochemistry at position 3 are discussed. Conformational studies of compound **19** and L-364,718 have delineated similarities that these molecules share in their core conformations and substituent orientations.

The peptide cholecystokinin (CCK) is a hormone and proposed neutrotransmitter found in gut and brain. This peptide has been reported to stimulate pancreatic and biliary secretion, produce gall bladder contraction, increase gut motility, induce satiety, and antagonize the analgesic effects of opiates.[1-3] The search for CCK antagonists has accelerated in recent years to produce agents useful in clarifying these various roles of CCK in physiology and to provide possible therapeutic applications. Several years ago the isolation and properties of the natural product CCK antagonist asperlicin were announced.[4] It is a se-

† Department of Exploratory Chemistry.
‡ Molecular Systems Department.
§ Department of Microbial Pharmacometrics.

(1) Williams, J. A. *Biomed. Res.* **1982**, *3*, 107.
(2) Smith, G. P. In *Eating and Its Disorders*; Stunkard, A. J., Steller, E., Eds.; Raven: New York, 1984; p 67.
(3) Watkins, L. R.; Kinscheck, I. B.; Mayer, D. J. *Science* 1984, *224*, 395.
(4) Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schonberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177.

0022-2623/89/1832-1681$01.50/0