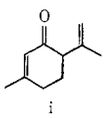
tention times 6, 8, and 10 min were detected. Gc-mass spectral analysis of the first component showed that it was identical with the hydrogenated photoproducts. The other two components were identified as products of partial hydrogenation.

Acknowledgment. Grateful acknowledgment is made to the Robert A. Welch Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Environmental Quality Program of Texas A&M University for generous support of this research. The authors would like to express their appreciation to Dr. Robert Stipanovic for many helpful discussions and for recording the gc–mass spectra.

Registry No.—1, 80-57-9; 11, 51911-75-2; 12, 51911-77-4; 14, 89-81-6; 15, 51911-80-9; 16, 51911-81-0; 17, 51911-82-1; 18, 17302-28-2.

References and Notes

(1) J. J. Hurst and G. H. Whitham, *Proc. Chem. Soc.*, 160 (1959); *J. Chem. Soc.*, 2864 (1960).
(2) Additional examples of this type of reaction are found in the studies of photorearrangements of bicyclo[3.2.0]hept-3-en-2-ones,[3] bicyclo[4.1.0]hept-4-en-3-ones,[4] and 4,5-diphenylcyclohex-2-en-1-one.[5]
(3) R. L. Cargill, B. M. Gimore, D. M. Pond, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Amer. Chem. Soc.*, **92**, 3809 (1970).
(4) T. Takino and H. Hart, *Chem. Commun.*, 450 (1970).
(5) H. E. Zimmerman and D. Sam, *J. Amer. Chem. Soc.*, **88**, 4905 (1966).
(6) W. F. Erman, *J. Amer. Chem. Soc.*, **89**, 3828 (1967).
(7) Schuster and Wildman[8] have shown that rearrangement to both chrysanthenone and ketene **3**, which can be trapped with alcohols or water, are triplet excited state reactions of verbenone and have proposed nonconcerted pathways for their production.
(8) D. I. Schuster and D. Widman, *Tetrahedron Lett.*, 3571 (1971).
(9) (a) H. E. Zimmerman, D. F. Juers, J. M. McCall, and B. Schroder, *J. Amer. Chem. Soc.*, **93**, 3662 (1971); (b) T. Tabata and H. Hart, *Tetrahedron Lett.*, 4929 (1969); (c) N. K. Hamer and M. Stubes, *Chem. Commun.*, 1013 (1970).
(10) R. C. Cookson, J. Hudec, and M. Sharma, *Chem. Commun.*, 107, 108 (1971).
(11) N. K. Hamer and A. J. Willis, *J. Chem. Soc., Chem. Commun.*, 458 (1973).
(12) 4-Metylverbenene has been prepared previously[13] by the reaction of verbenone with methyllithium followed by dehydration. The spectral and physical properties of material derived from our synthesis were identical with those previously reported.
(13) Y. Chretien-Bessiure and C. Grison, *Bull. Soc. Chim. Fr.*, **89**, 3103 (1970).
(14) Usual conditions were employed to ensure that no light is absorbed by diene **11** and that triplet, but not singlet, energy transfer is maximized.
(15) R. Mayer, K. Bochow, and W. Zieger, *Z. Chem.*, **4**, 348 (1964); P. J. Kropp, *J. Amer. Chem. Soc.*, **91**, 5783 (1969).
(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958.
(17) M. Bertrend, *C. R. Acad. Sci.*, **247**, 824 (1954).
(18) R. Dulou, P. Crabbe, and G. Dupount, *Bull. Soc. Chim. Fr.*, 1548 (1955).
(19) R. Escourrou, *Bull. Soc. Chim. Fr.*, **43**, 1101 (1928).
(20) G. Pattendon and B. C. L. Weedon, *J. Chem. Soc., C*, 1984 (1968).
(21) *Cf.* J. A. Berson and S. S. Olin, *J. Amer. Chem. Soc.*, **92**, 1986 (1970).
(22) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, Chapter 20.
(23) The results of Kochi and Krusic[24] indicate nearly no dependence of the odd-electron spin density in conjugated radicals on the extent or location of alkyl substituents.
(24) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **90**, 7157 (1968).
(25) Disproportionation of delocalized radicals is known to be less efficient than in localized tertiary radical systems.[26] However, in this system only one of the two radical centers is delocalized and the competing combination process leads to starting material. It should be noted that small



i

quantities of isopiperitenone (i) formed on photolysis of verbenone[6] probably results from disproportionation of the intermediate diradical **4** by pathway analogous to the production of **12.**
(26) S. F. Nelson and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).

Oxazolines. IX. Synthesis of Homologated Acetic Acids and Esters

A. I. Meyers,* Davis L. Temple,[1] Robert L. Nolen,[2] and Edward D. Mihelich

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

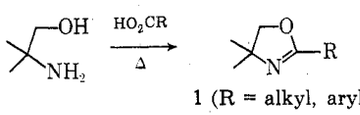
Received April 16, 1974

The lithio salt of 2,4,4-trimethyl-2-oxazoline (**1a**) reacts with alkyl halides affording the 2-alkyloxazolines **3** which may be hydrolyzed to homologated acetic acids. Dialkylation leads to α,α-dialkylacetic acids **5.** Alternatively, the alkylated oxazolines may be directly transformed into esters derived from the use of an appropriate alcoholic solvent. The lithio oxazolines also add smoothly to carbonyl compounds producing, after hydrolysis, α,β-unsaturated acids (**25**) or esters (**26**). Under certain conditions, the formation of β-hydroxy esters (**27**) is allowed, thus providing a convenient alternative to the Reformatsky reaction. The scope and limitations of this novel approach to alkylated acetic acids are also described.

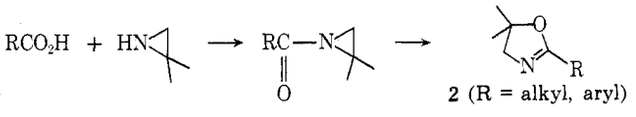
The recent surge of techniques developed for homologation of acetic acids has advanced synthetic methodology considerably. When one recalls that the only generally useful routes available prior to 1967 were the classical malonic and acetoacetic ester syntheses, these new methods involving alkali metalated acetic acids and esters,[3,5,6,8] organocopper derivatives,[7] and organoboranes[4] have all demonstrated that they are more versatile or superior in many respects. Thus, electrophiles may now be directly introduced onto $-CH_2CO_2R(H)$ or $RCHCO_2R(H)$ affording alkylated or dialkylated acetic acids or esters.

In 1970 a preliminary account appeared[9a] which described the potential utility of the simple 2-oxazoline **1** as a precursor to homologated acetic acids and esters. A more complete description of this method and its scope is now presented. Furthermore, the oxazoline precursor may also provide a useful alternative to the Reformatsky reaction (β-hydroxy esters) and, as described in the accompanying paper,[9b] to a variety of butyrolactones.

The requisite 2-oxazolines (**1**) are readily prepared by treating 2-amino-2-methyl-1-propanol with carboxylic acids and removal of the heterocycle by distillation.[10] An alternative technique involves the condensation of acids, acid chlorides, or esters with 2,2-dimethylaziridine followed by rearrangement.[11,12] The latter method leads to the iso-

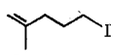


1 (R = alkyl, aryl)



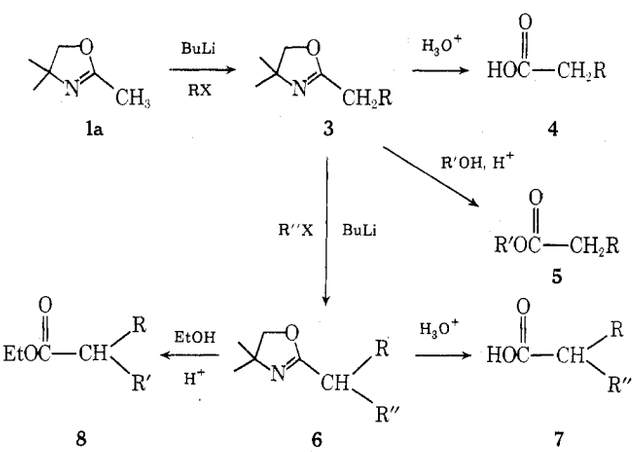
2 (R = alkyl, aryl)

Table I
Formation of Alkylated Acetic Acids and Esters from 2-Oxazolines

RX	R″X	% acid 4	% ester 5 (R′)	% acid 7	% ester 8
n-BuBr		80	84 (Et)		
$PhCH_2Cl$		95	98 (Et) 95 (Me) 99 (*i*-Pr) 85 (*sec*-Bu) 0.5 (*t*-Bu)		
$CH_2=C(Br)-CH_2Br$			86 (Et)		
$CH_2=CHCH_2Cl$		77	96 (Et) 95 (*i*-Pr)		
			94 (Et)		
$PhCH_2Cl$	MeI			89	80
$PhCH_2Cl$	$CH_2=CHCH_2Cl$			84	88
$PhCH_2Cl$	*n*-BuI			77	83

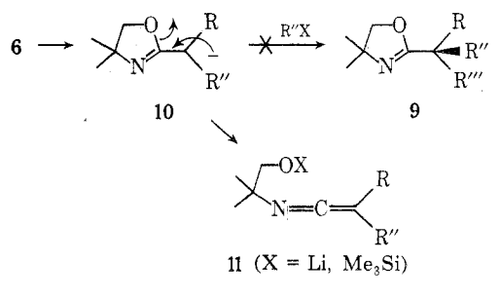
meric 2-oxazoline (**2**) which also serves as a precursor to homologated acetic and benzoic acids.[12b]

Reaction of Lithio Oxazoline with Alkyl Halides. Homologated Acetic Acids and Esters. Treatment of the 2-methyloxazoline **1a** with *n*-butyllithium at −78° in THF produces, within a few minutes, the lithio oxazoline as a yellow suspension, which was then alkylated with a variety of alkyl halides, furnishing the elaborated oxazoline **3.** In all cases 2–7% of dialkylated oxazoline **6** (R = R″) accompanied the major product. The removal of the dialkyloxazoline did not present any serious experimental difficulty, since direct acid hydrolysis gave the homologated carboxylic acid **4,** which was then purified by distillation (Table I). However, if a subsequent alkylation was carried out using a different alkyl halide, it was necessary to first purify **3** by distillation. Repeating the metalation of **3** with *n*-butyllithium and a second equivalent of alkyl halide produced the dialkylated oxazoline **6,** which was smoothly cleaved to the α,α-dialkylcarboxylic acid **7.**

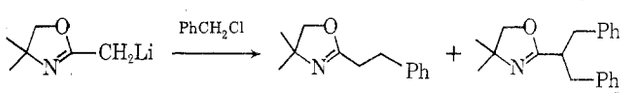


Of further value in this scheme was the fact that the elaborated oxazolines **3** and **6** could be converted directly to their corresponding esters **5** and **8** by performing the cleavage in an alcohol containing 5–10% sulfuric acid. Methyl, ethyl, isopropyl, and *sec*-butyl esters are formed in excellent yields, whereas the *tert*-butyl esters virtually resist formation (Table I).

Attempts to alkylate oxazolines **6** to their trialkylated derivative **9** were not successful owing mainly to the fact that the tertiary proton is not removed by the base (*n*-butyllithium, *tert*-butyllithium, or lithium diisopropylamide) until the solution is warmed to approximately 20°. At this temperature, the anion **10** is not stable and rapidly rearranges to the ketenimine **11** (X = Li). The latter was successfully trapped as its trimethylsilyl derivative **11** (X = Me_3Si).[13b] This behavior is similar to that of tertiary anions derived from dihydro-1,3-oxazines.[13a]

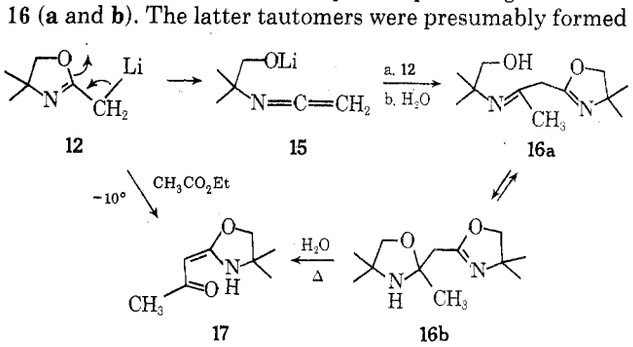


A study to evaluate the stability of the primary and secondary carbanions derived from the 2-alkyloxazolines was also performed. When the anion **12** was alkylated with benzyl chloride (1.0 equiv) at −78° the ratio of monoalkylated derivative **13** to dialkylated derivative **14** was 95:5 with an overall yield of 93%. However, when alkylation was per-



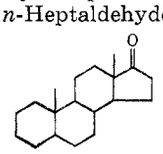
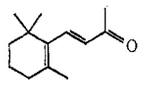
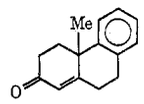
12	13	14
	(−78°) 95%	5%
	(0°) 58%	42%

formed at −10 to 0°, the ratio of **13** to **14** was 58:42 in an overall yield of 45%. If the anion **12** was allowed to warm to room temperature in the absence of an external electrophile, there was obtained after aqueous quenching the dimer **16** (**a** and **b**). The latter tautomers were presumably formed



via the transient ketenimine **15** and rapid sequential reaction with unrearranged **12.**[14] Isolation of **16** could be readily achieved by distillation below 100°, whereas heating above 150° resulted in thermal reversion of **16** to starting 2-methyloxazoline **1a.** On the other hand, heating an aqueous suspension of **16** led to removal of the oxazolidine moi-

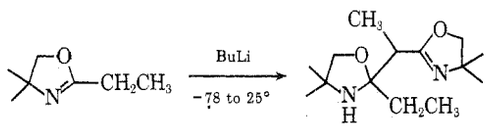
Table II
Unsaturated and β-Hydroxy Acids and Esters from 1a

Carbonyl	% acid (25)	% ester (26)	% hydroxy ester (27)
Acetone			55
3-Heptanone		80[a]	91
Cyclohexanone	84	88	
Cycloheptanone	90[c]	69[b]	80[d]
n-Heptaldehyde			74
	96		
		68[e]	
		78[f]	

[a] Contained 54% of β,γ isomer. [b] Contained 78% β,γ isomer. [c] Mp 75–78°, mixture contains 60–70% β,γ isomer. [d] β-Hydroxy acid obtained from alkaline cleavage of methiodide salt. [e] Contained >90% β,γ-retro ester: W. Oroshnik, G. Karmas, and A. D. Mebane, *J. Amer. Chem. Soc.*, **74**, 3807 (1952). [f] Contains β,γ,δ,ε-unsaturated ester.

ety and provided the vinylogous amide **17** which contains ~10% of the β-keto-2-oxazoline. Structure proof for **17** was gathered by its synthesis *via* an alternate route. Addition of ethyl acetate to the lithio oxazoline furnished **17**, which was identical with the sample obtained from hydrolysis of **16**.

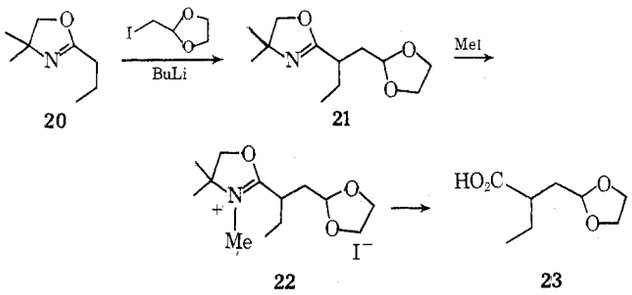
In a similar fashion the 2-ethyloxazoline **18**, when treated with *n*-butyllithium at −78° and then allowed to warm to ambient, gave the dimer **19** after quenching. Thus, pri-



18 **19**

mary, secondary, and tertiary lithio carbanions of oxazolines all appear to have one trait in common: they are unstable at or near room temperature and rearrange to ketenimines. The primary and secondary carbanions ultimately lead to dimers, whereas the tertiary carbanions may be too bulky to dimerize. This behavior, since it was also observed in the dihydro-1,3-oxazines,[13] may be a general property of cyclic imino ethers and thio ethers.

In cases where the elaborated oxazoline carries acid-sensitive groups, it was found feasible to perform the cleavage to carboxylic acids under alkaline conditions. Thus, the 2-(*n*-propyl)oxazoline **20** (obtained from *n*-butyric acid and 2-amino-2-methyl-1-propanol) was converted to the dioxalane derivative **21** using *n*-butyllithium and the dioxalane of iodoacetaldehyde. Treatment with methyl iodide fur-

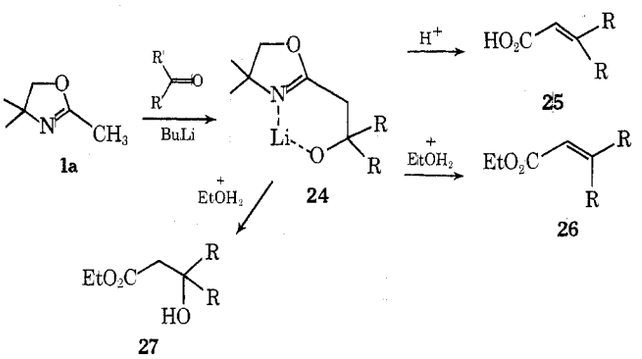


20 **21**

22 **23**

nished the methiodide salt **22** which was transformed quantitatively to the dioxalane acid **23** by stirring in aqueous sodium hydroxide at room temperature. This alkaline release of the carboxylic acids was found to be general for a number of elaborated oxazoline methiode salts and should provide additional latitude in the preparation of substituted aliphatic carboxylic acids. In a subsequent report,[12b] the utility of the oxazoline as a masking group for preconstructed carboxylic acids and the eventual alkylation to homologated derivatives will be described.

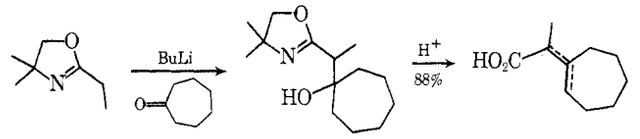
Reaction of Lithio Oxazolines with Carbonyl Compounds. Unsaturated and β-Hydroxy Acids and Esters. The 2-methyloxazoline **1a** was found to react *via* its lithio salt with a variety of carbonyl compounds, leading to the adducts **24** in high yield. Acidic hydrolysis provided the unsaturated carboxylic acids **25**, whereas acidic ethanolysis afforded the corresponding unsaturated esters **26**. In all



1a **24** **25** **26** **27**

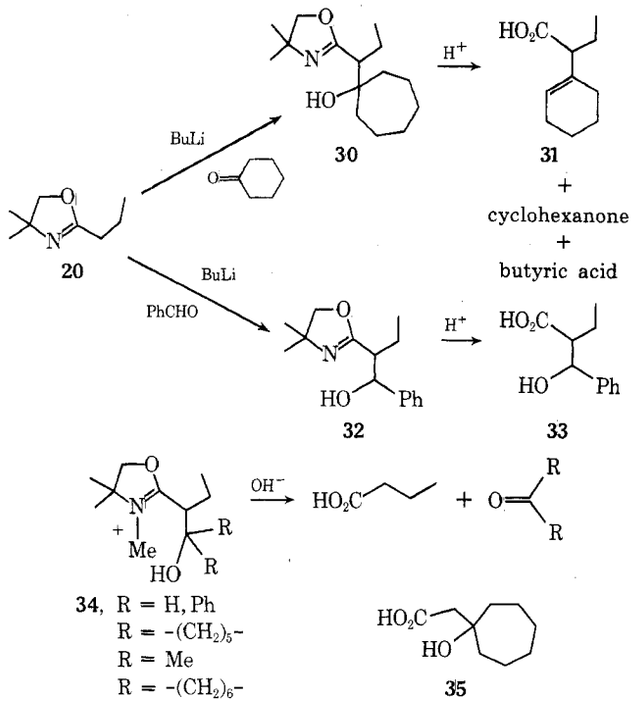
cases, a thermodynamic mixture of unsaturated acids and esters was formed containing various amounts of the β,γ isomers (Table II). By employing lower concentrations of sulfuric acid in the ethanol, the cleavage of the oxazoline adduct **24** leads to the β-hydroxy esters in good yield, thus introducing a viable alternative to the Reformatsky reaction (Table II).[15]

When the oxazoline contained a 2-alkyl group other than methyl, α-alkyl derivatives may be obtained. For example, the 2-ethyloxazoline **18** was alkylated with cycloheptanone, affording a high yield of the adduct **28**. Hydrolysis in aqueous acid provided the 2-cycloheptylidinepropionic acid **29**,

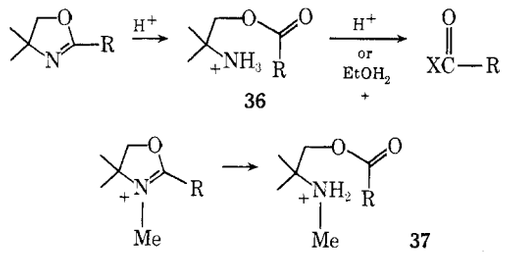


18 **28** **29** (α,β 21%) (β,γ 79%)

which existed mainly as the β,γ isomer. This result, however, was not general with other ketones. Repeating this sequence using cyclohexanone gave much lower yields (25–50%) of the corresponding cyclohexylidine acid. In order to assess the nature of this alkylation in more general terms, a study was performed on the 2-(*n*-propyl)oxazoline **20**. Although reaction of the lithio salt of **20** with carbonyl compounds proceeded in high yield to **30** and **32**, hydrolysis to the respective esters **31** and **33** took place in poor to moderate yields, the main products being reversion to the starting carbonyl compounds and butyric acid. This behavior has been noted previously on the facile reversion of α-alkyl-β-hydroxy acids and esters to their carbonyl precursors.[16,17] When the hydrolysis was carried out on the *N*-methyl salts of **30** and **32** (*e.g.*, **34**), complete reversion occurred to the starting carbonyl and butyric acid. Only in the case of the cycloheptanone adduct was the β-hydroxy acid **35** obtained (55%, see Table II) *via* alkaline hydrolysis.



The mechanism of oxazoline hydrolysis has been studied extensively[17] and found to proceed to the amino ester salts in acidic medium but undergoes more complicated reactions above pH 5. The reversion of the β-hydroxy oxazolines **28, 30, 32,** and **34** must have therefore taken place through their amino ester derivatives (*i.e.*, **36** and **37**), in a manner similar to the reversion in simple esters.



Thus, β-hydroxy esters and acids containing an α-alkyl substituent are formed in less than satisfactory yields under acidic cleavage conditions, and virtually not at all under alkaline conditions.

Experimental Section[18]

Butyllithium was obtained from Lithium Corp., Bessemer City, N. C. The infrared spectra were taken on a Perkin-Elmer 257 grating instrument and the nmr spectra were taken on a Varian T-60. Mass spectra were taken on a AEI-MS-9 or MS-12 instrument at 70 eV.

2,4,4-Trimethyl-2-oxazoline (1a). The procedure was essentially that of Allen and Ginos.[10] Thirty grams (0.50 mol) of glacial acetic acid was added with stirring to 44.5 g (0.50 mol) of 2-amino-2-methyl-1-propanol. The mixture was heated and the temperature (pot) rose to 120° and then slowly declined to 110°. The mixture was distilled azeotropically at 98–110° through a 6-in. Vigreux column into 200 ml of hexane. The upper hexane layer was separated and the water layer was extracted repeatedly with hexane. The combined hexane extracts were dried ($MgSO_4$) and evaporated to yield 41.3 g (73%). The material was pure enough to use (>99%), but was fractionated (bp 75°) to yield a colorless oil which formed a yellow picrate: mp 162–164°; tlc (ether–silica gel) showed one spot, R_f 0.37; ir (film) 1670 cm^{-1} (C=N); nmr ($CDCl_3$) δ 3.82 (s, 2), 1.82 (s, 3), 1.20 (s, 6).

2-(*n*-Propyl)-4,4-dimethyl-2-oxazoline (20) was prepared in 88% yield from *n*-butyric acid as described above: bp 152°; ir (film) 1650 cm^{-1}; nmr ($CDCl_3$) δ 3.82, 2.10, 1.57, 1.11, 0.85; tlc (silica gel–ether) R_f 0.50.

General Method for Alkylation of Lithio Oxazolines. 2-(Phenethyl)-4,4-dimethyl-2-oxazolines (13). 2,4,4-Trimethyl-2-oxazoline (5.0 g, 0.044 mol) in 40 ml of dry THF under nitrogen was cooled to −78° (Dry Ice–acetone bath) and 41 ml of 1.22 *M* *n*-butyllithium in pentane–hexane was added with a syringe through a rubber septum. There was an immediate precipitation of the yellow anion, and benzyl chloride (6.2 g, 0.049 mol) in 20 ml of dry THF was added over a 10-min period. The Dry Ice–acetone bath was removed and the mixture was allowed to return to room temperature and then poured into 100 ml of cold water. The water was made acidic with HCl and extracted with ether. The acid portion was then neutralized with 40% NaOH with cooling and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to yield 8.80 g (99%) of a yellow oil: bp 168° (20 mm); ir (film) 1660 cm^{-1}; nmr (CCl_4) δ 7.18 (br s, 5), 3.82 (s, 2), 2.82 (t, 2), 2.32 (t, 2), 1.20 (s, 6). The sample was sufficiently pure (95–97%) for hydrolysis or alcoholysis.

General Method for Hydrolysis to Carboxylic Acids. 3-Phenylpropionic Acid. The alkylated oxazoline from above was dissolved in 40 ml of 3 *N* hydrochloric acid and heated to reflux for 15–20 min. The oily layer was taken up in chloroform or dichloromethane, dried ($MgSO_4$), and concentrated to give the carboxylic acid (80%). The product was >95% pure prior to distillation. If the carboxylic acid was solid, it was removed by filtration, washed and dried.

General Method for Alcoholysis of Oxazolines. 3-Phenylpropionic Esters (5). Twenty millimoles of 2-phenethyl-4,4-dimethyl-2-oxazoline was heated to reflux (15 hr) in 100 ml of 95% alcoholic sulfuric acid (prepared by mixing 50 ml of alcohol, 4 ml of concentrated sulfuric acid, and 5 ml of water and bringing the total volume to 100 ml with additional alcohol). After cooling, the solution was concentrated to *ca.* 25 ml and poured into 200 ml of ether. The ethereal solution was washed with saturated brine until no further solid material separated and was then dried (K_2CO_3) and concentrated. The purity was checked by vpc.

Methyl ester: 95% yield (95% purity).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32. Found: C, 73.39; H, 7.51.

Ethyl ester: 99% yield (98% purity).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.22; H, 7.87.

Isopropyl ester: 99% yield (96–98% purity).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 74.77; H. 8.47.

***sec*-Butyl ester:** 85% yield (95–98% purity).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74. Found: C, 75.57; H, 8.53.

Ethyl 2-Methyl-3-phenylpropionate. General Procedure for Alkylation of a Secondary Carbanion and Conversion to Ethyl Ester (3 to 8). Five grams (25 mmol) of **3** (R = benzyl) was dissolved in 40 ml of dry THF and cooled to −78° under a dry nitrogen atmosphere. To the magnetically stirred solution was added 11 ml (27 mmol) of *n*-butyllithium in hexane. The solution immediately assumed a deep red color and was stirred for an additional 30 min to ensure complete anion formation. Methyl iodide (7.00 g, 49 mmol) in 20 ml of THF was added in a dropwise manner and the resulting solution (yellow) was stirred at −78° for 30 min and then allowed to warm to room temperature. The mixture was poured into 100 ml of cold saturated brine and extracted with three 100-ml portions of ether. The ether extract was dried ($MgSO_4$) and evaporated to yield 4.79 g (91%) of **6** (R = $PhCH_2$; R″ = Me). The crude material was used without further purification in the next step.

Oxazoline **6** (4.68 g, 0.022 mol) was dissolved in 60 ml of ethanolic sulfuric acid and heated to reflux for 16 hr. The mixture was cooled to room temperature, poured into 100 ml of cold saturated brine and extracted with three 100-ml portions of ether. Pentane (100 ml) was added to the ether extract and the cloudy solution was washed successively with saturated brine, 10% bicarbonate, and saturated brine. After drying and concentration, 3.32 g (80%) of the ester **8** was obtained, bp 76–79° (0.75 mm),[19] ir (film) 1730 cm^{-1}.

2-Ethyl-3-(2-dioxalanyl)propionic Acid (23). General Method for Alkaline Cleavage. Thirty grams (0.210 mol) of propyloxazoline **20** was magnetically stirred in 80 ml of dry tetrahydrofuran at −78°. To this solution 133.2 ml (0.231 mol, 1.80 *M*) of *n*-butyllithium (hexane) was added dropwise. The yellow solution was stirred for 30 min before 53.93 g (0.252 mol) of 2-iodoacetaldehyde ethylene acetal[20] was added dropwise. The mixture was stirred for 30 min at −78° and then allowed to slowly reach room

temperature. The mixture was poured into 300 ml of saturated brine and extracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated. Distillation of the residue gave 33.2 g (65%) of **21**: bp 92° (0.25 mm); ir (film) 1675 cm^{-1}; nmr (CCl_4) δ 0.9 (t, 3), 1.20 (s, 6), 1.35–2.65 (m, 5), 3.65–4.00 (m, 6), 4.80 (d of d, 1).

The oxazoline was converted to the methiodide salt by stirring in excess methyl iodide overnight at room temperature and evaporating the volatiles *in vacuo*. The methiodide **22** was recrystallized from acetonitrile–ether, mp 119–120°.

The oxazoline methiodide **22** (8.6 g, 23.3 mmol) was added to 50 ml of 1 *N* sodium hydroxide and the mixture was stirred for 15 hr at room temperature. The solution was acidified with 10% hydrochloric acid (pH 2) and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to leave an oil: bp 115–118 (0.4 mm), 3.9 g (94%) of the β-dioxalane acid **23**; ir (film) 1700, 1740, 3000 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (t, 3), 1.18–2.75 (m, 5), 3.80 (m, 4), 4.95 (t, 1), 8.60 (s, 1, exchangeable with D_2O).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.27; H, 8.21.

General Method for Preparation of β-Hydroxy Esters. Ethyl (3-Hydroxy-3-*n*-propyl)caproate (27, R = *n*-Propyl). A solution of oxazoline **1a** (6 g) in dry tetrahydrofuran (20 ml) was treated dropwise with stirring under nitrogen with *n*-butyllithium (29.4 ml, 2.25 *M*) at −78°. The resulting yellow suspension was stirred for 30 min and then a solution of 4-heptanone (7.55 g) in tetrahydrofuran (10 ml) was added over a 15-min period. The green solution was allowed to warm gradually to room temperature and then poured into 100 ml of ice–water, neutralized with 9 *N* hydrochloric acid, and extracted with ether. The aqueous solution was carefully neutralized with 40% sodium hydroxide and the oil was removed by ether extraction. Drying (Na_2SO_4) and concentration left the colorless hydroxy oxazoline in high purity: ir (film) 1670, 3400 cm^{-1}; nmr (CCl_4) δ 4.2 (s, 1, exchangeable with D_2O), 3.92 (s, 2), 2.30 (s, 2), 0.6–1.7 (m, 20).

A solution of the hydroxy oxazoline above (5.15 g) in 1.5 *N* ethanolic sulfuric acid (50 ml, prepared by diluting 2 ml of concentrated sulfuric acid to 50 ml with absolute ethanol) was heated at reflux for 18 hr. On cooling, the solution was poured into 300 ml of ether and extracted with saturated brine to remove the amino alcohol. The ethereal solution was dried and concentrated to give the hydroxy ester: 4.3 g (91%); ir (film) 1740, 3515 cm^{-1}; nmr ($CDCl_3$) δ 0.68–1.5 (m, 17), 2.48 (s, 2), 3.90 (s, 1, exchangeable with D_2O), 4.18 (q, 2).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.43; H, 11.02.

General Method for Preparation of Unsaturated Acids. $\Delta^{17,20}$-Allopregn-21-oic Acid (25). The general method for alkylation of the lithio oxazoline with a carbonyl compound as given above was employed using androstan-17-one (0.327 g, 0.98 mmol). Work-up yielded 457 mg (96%) of a crystalline compound: mp 158–159° (petroleum ether); ir (Nujol) 1650, 3300 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 2), 2.40 (s, 2), 1.21 (s, 6), 0.86 (s, 3), 0.75 (s, 3), and the usual broad signals of the steroidal skeleton.

A solution of 71 mg of the steroid oxazoline in 20 ml of 3 *N* hydrochloric acid containing sufficient ethanol to effect solution was heated to reflux for 15–20 min. The cloudy solution, after cooling, was extracted with chloroform–ether (1:1) and dried ($MgSO_4$). The residue after evaporation was a crystalline solid, mp 250–252° (lit.[21] mp 242–244°), obtained in 97% yield.

General Method for Preparation of Unsaturated Esters. β-Ionylidene Acetic Esters (26). The lithium salt of oxazoline **1a** (5.0 g, 44 mmol) was alkylated with β-ionone (9.6 g, 50 mmol) in the manner described above and gave 9.8 g (73%) of a viscous yellow oil, single spot on tlc, R_f 0.72 (ether), ir (film) 1650, 3350 cm^{-1}. The crude oxazoline–β-ionone adduct (9.5 g) was hydrolyzed in ethanolic sulfuric acid (10% concentrated sulfuric in 95% ethanol) by heating under reflux for 7 hr and gave 8.8 g (93%) of an equal mixture of β-ionylidene ester and *retro*-β-ionylidene ester:[22] ir (film) 1735 (unconjugated C=O) and 1710 cm^{-1} (conjugated C=O); nmr spectrum ($CDCl_3$) showed a ~1:1 mixture of the two isomers; λ_{max} 292 nm (EtOH). The mixture was purified by passing through Woelm Grade I neutral alumina with ether and gave ~90% of the retro isomer, rearrangement to the latter taking place during chromatography.

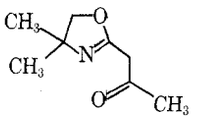
Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.50; H, 9.89.

Unsaturated Acids from 2-Ethyl-2-oxazoline (18). 2-Cycloheptylidenepropionic Acid and Its Endo Isomer (29). The lithio salt of 2-ethyl-2-oxazoline **18** was alkylated with 1.0 equiv of cycloheptanone in the usual fashion (THF, −78°) to give the adduct **28** in 67% yield, ir (film) 1650, 3400 cm^{-1}. The product was hydrolyzed in 40 ml of 3 *N* hydrochloric acid by heating for 20 min. The solution was saturated with salt and extracted with chloroform, dried, and concentrated. The unsaturated acid (96%) was obtained as an oil, R_f 0.83 (ether). It was found convenient to convert the acids to their ethyl esters for vpc analysis. This was done by successive treatment with thionyl chloride and ethanol. Vpc (Chromosorb P, 10% SE-30) at 180° showed the esters to be a 79:21 mixture of endo and exo double-bond isomers, ir (film) 1710, 1740 cm^{-1}.

Dimerization of 2,4,4-Trimethyl-2-oxazoline (1a) to 16b. The anion **1a**, prepared in the usual manner (BuLi, THF, −78°), was allowed to warm to room temperature (18 hr). The resulting brown mixture was poured into saturated brine and extracted several times with ether. Evaporation of the dried extracts left a dark-colored oil, 3.3 g (66%), which was distilled: bp 64–67° (0.25 mm); *m/e* 226; nmr ($CDCl_3$) δ 1.29 (s, 12), 1.40 (s, 3), 2.47 (s, 2), 2.7 (br s, exchangeable with D_2O), 3.52 (d of d, 2), 3.90 (s, 2).

Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80. Found: C, 62.66; H, 10.06.

Hydrolysis of Dimer to 17. The dimer **16b** (0.913 g) was dissolved in 10 ml of water and heated on a hot plate at 60° for 2 hr. The solution was cooled and extracted with ether. The dried (K_2CO_3) extracts were concentrated to give a solid: 0.401 g (70%); mp 124–126°; nmr ($CDCl_3$) δ 1.42 (s, 6), 2.01 (s, 3), 4.05 (s, 2), 4.83 (s, 1), 8.85 (br, 1, exchangeable with D_2O). These nmr signals integrated to ~90% of the indicated values while weak signals were observable as singlets at δ 1.3, 2.2, 3.4, and 4.0 which are consistent with the structure below.



Alternatively, **17** was prepared by treating the lithio oxazoline **12** with 1.0 equiv of ethyl acetate at −78°. This was performed *via* inverse addition as follows.

The lithio oxazoline (22 mmol) was prepared in the usual manner and transferred using a cold syringe to a solution of ethyl acetate (3.9 g, 44 mmol) in 10 ml of tetrahydrofuran cooled to −10°. The yellow color of the anion solution was immediately discharged and the solution was allowed to warm to room temperature and stirred for 30 min. Quenching in water, followed by ether extraction, gave, after concentration, a semisolid material. Washing with pentane resulted in crystallization of **17**, mp 123–126°. The pentane solution was evaporated, leaving an oil which was shown to be the β-keto-2-oxazoline. The latter, on standing in air, crystallized and the total yield of crystalline material was 2.91 g (85%). This material was identical with that obtained by hydrolysis of **16b**.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.86; H, 8.42; N, 9.23.

Dimerization of 2-Ethyl-4,4-dimethyl-2-oxazoline (18) to 19. A solution of 5.6 g (44 mmol) of **18** in 30 ml of tetrahydrofuran was treated with *n*-BuLi (30 ml, 1.59 *M*) at −78° and then allowed to warm to room temperature. Work-up, as in the case of **16b**, gave an oil which could not be distilled owing to heat sensitivity. Elution through silica gel with ether gave an oil, 5.0 g (92%), ir (film) 1645, 3230 cm^{-1}.

Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.39; H, 10.58; N, 11.10.

Acknowledgment. The authors are grateful to the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a**, 1772-43-6; **1a** picrate, 51869-42-2; **3** (R = $PhCH_2$), 13608-28-1; **5** (R = $PhCH_2$; R′ = Me), 103-25-3; **5** (R = $PhCH_2$; R′ = Et), 2021-28-5; **5** (R = $PhCH_2$; R = *i*-Pr), 22767-95-9; **5** (R = $PhCH_2$; R′ = *sec*-Bu), 51869-23-9; **6** (R = $PhCH_2$; R″ = Me), 51869-24-0; **8** (R = $PhCH_2$; R″ = Me), 34666-01-8; **16b**, 51911-66-1; **17**, 51869-25-1; **18**, 5146-88-3; **19**, 51869-26-2; **20**, 4271-19-6; **21**, 51869-27-3; **22**, 51869-28-4; **23**, 39008-00-9; **27** (R = *n*-Pr), 10297-62-8; **28**, 51869-17-1; **29** (α,β), 51869-18-2; **29** (β,γ), 51869-19-3; acetic acid, 64-19-7; 2-amino-2-methyl-1-propanol, 124-68-5; butyric acid, 107-92-6; 2-(2-hydroxy-2-propylpentyl)-4,4-dimethyl-2-oxazoline, 51869-20-6; $\Delta^{17,20}$-allopregn-21-oic acid, 51869-29-5; androstan-17-one, 963-74-6; β-ionone, 14901-07-6;

4,4-dimethyl-2-oxazoline–β-ionone adduct, 51869-21-7; ethyl β-ionylideneacetate, 5452-61-9; ethyl *retro*-β-ionylideneacetate, 51869-22-8; 2-(2-ketopropyl)-4,4-dimethyloxazolidine, 32385-89-0.

References and Notes

(1) Postdoctoral Fellow, Louisiana State University, 1969–1970.
(2) Postdoctoral Fellow, Wayne State University, 1970–1972.
(3) P. L. Creger, *J. Amer. Chem. Soc.*, **89,** 2500 (1967); **92,** 1396 (1970); *J. Org. Chem.*, **37,** 1907 (1972).
(4) H. C. Brown and M. M. Rogic, *J. Amer. Chem. Soc.*, **91,** 2146 (1969); J. Hooz and D. M. Gunn, *ibid.*, **91,** 6195 (1969); H. C. Brown, M. M. Midland, and A. B. Levy, *ibid.*, **94,** 3662 (1972).
(5) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93,** 2318 (1971).
(6) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35,** 262 (1970); *Tetrahedron Lett.*, 699 (1970).
(7) I. Kuwajima and Y. Doi, *Tetrahedron Lett.*, 1163 (1972).
(8) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).
(9) (a) A. I. Meyers and D. L. Temple, *J. Amer. Chem. Soc.*, **92,** 6644, 6646 (1970); (b) A. I. Meyers, E. D. Mihelich, and R. L. Nolen, *J. Org. Chem.*, **39,** 2783 (1974).
(10) P. Allen and J. Ginos, *J. Org. Chem.*, **28,** 2759 (1963).
(11) D. Haidukewych and A. I. Meyers, *Tetrahedron Lett.*, 3031 (1972); C. U. Pittman, S. P. McManus, and J. W. Larson, *Chem. Rev.*, **72,** 357 (1972).
(12) (a) For more recent methods of preparation *cf.* E. Ghera and S. Shoua, *J. Chem. Soc., Chem. Commun.*, 639 (1972); R. A. Wohl and J. Cannie, *J. Org. Chem.*, **37,** 1787 (1972); (b) A. I. Meyers, D. L. Temple, D. Haidukewych and E. D. Mihelich, *J. Org. Chem.*, **39,** 2787 (1974).
(13) (a) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38,** 36 (1973); (b) A. I. Meyers, M. S. Ao, and E. M. Smith, *ibid.*, **38,** 2129 (1973); C. Lion and J. E. Dubois, *Tetrahedron*, **29,** 3417 (1973).
(14) An alternative mechanism leading to **16** may be invoked which allows **12** to add to the C=N link of trace amounts of unmetalated 2-methyloxazoline. This route has been observed in the dimerization of lithiomethyl thiazoles: G. Knaus and A. I. Meyers, *J. Org. Chem.*, **39** 1189 (1974).
(15) For other recent syntheses of β-hydroxy esters and acids see E. Negishi and T. Hoshida, *J. Amer. Chem. Soc.*, **95,** 6837 (1973); S. Watanabe, *Chem. Ind. (London)*, 1811 (1969); G. Read, *et al.*, *J. Chem. Soc. C*, 2799 (1969); P. E. Pfeffer, E. Kinsel, and L. S. Silbert, *J. Org. Chem.*, **37,** 1256 (1972); G. W. Moersch and A. R. Burkett, *ibid.*, **36,** 1149 (1971); M. W. Rathke, *J. Amer. Chem. Soc.*, **92,** 3222 (1970).
(16) W. Adam, J. Baeza, and J.-C. Liu, *J. Amer. Chem. Soc.*, **94,** 2000 (1972), and previous references cited therein.
(17) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, **41,** 1662 (1963).
(18) Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind., and Galbraith Laboratories, Knoxville, Tenn.
(19) S. M. McElvain and L. R. Morris, *J. Amer. Chem. Soc.*, **74,** 2657 (1952).
(20) Prepared by treating the bromoacetal [H. Brederèck, *et al.*, *Chem. Ber.*, **97,** 827 (1964)] with 5.0 equiv of sodium iodide in acetone and heating for 48 hr, bp 32° (0.25 mm), 66% yield.
(21) R. E. Marker, H. M. Crooks, R. B. Wagner, A. C. Shabica, E. M. Jones, and E. L. Wittbecken, *J. Amer. Chem. Soc.*, **64,** 822 (1942).
(22) See Table II, footnote *e*.

Oxazolines. X. Synthesis of γ-Butyrolactones

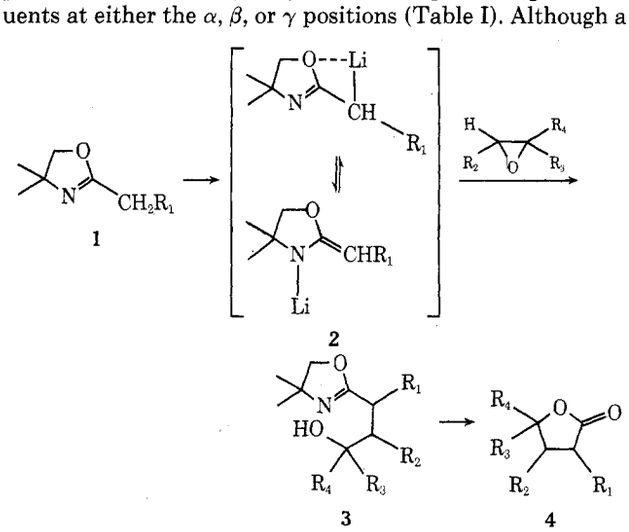
A. I. Meyers,* Edward D. Mihelich, and Robert L. Nolen

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521

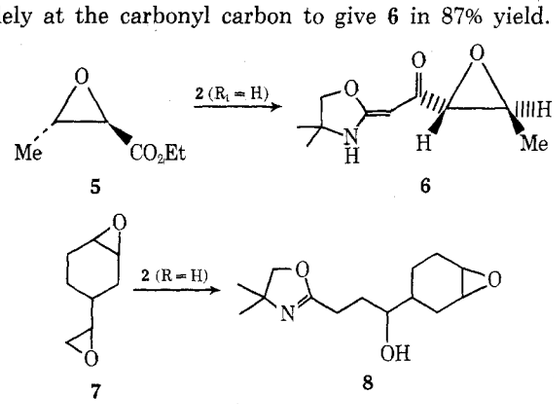
Received April 16, 1974

A variety of butyrolactones (4), substituted in the α, β, and/or γ positions with alkyl groups, is described. The approach originates from the lithio salt of 2,4,4-trimethyl-2-oxazoline (1, R = H) and higher 2-alkyl homologs (1, R = alkyl) which readily reacts with epoxides at low temperature to produce the 2-(β-hydroxyalkyl)oxazolines 3. Hydrolysis of the latter leads to the butyrolactones 4 in good overall yields. Several examples in which the epoxide is part of a polyfunctional molecule are given to indicate the selectivity of the lithio oxazoline.

In the previous article[1] a series of homologated acetic acids were prepared by treating the lithio salt of 2-substituted 4,4-dimethyl-2-oxazolines **2** with a variety of alkyl halides and carbonyl compounds. Further work on this useful heterocyclic system (**1**) has revealed that its lithio salt **2** may also react with epoxides at low temperature, resulting in the hydroxypropyloxazolines **3**. Hydrolysis of the latter produces a variety of γ-butyrolactones **4** possessing substituents at either the α, β, or γ positions (Table I). Although a



number of epoxides gave good yields of lactones, others proved to be resistant to alkylation. For example, 1,2-disubstituted epoxides (entries 13, 14, and 15) gave little or no ring-opened products except for cyclohexene and cyclopentene oxides. For the latter case, the lactone (entry 12) was poorly formed, since this would necessitate a trans-fused product which involves considerable strain. However, the trans hydroxy acid was the major product formed. The extent to which 1,2 disubstitution prevents epoxide ring opening was clearly seen when the epoxy ester **5** was treated at −78° with the lithio oxazoline. Reaction occurred solely at the carbonyl carbon to give **6** in 87% yield. Al-



though tautomers were expected, the product was found to be entirely **6**, which appeared as a crystalline material. Other organometallics were reported to react with **5** to give ring-opened products[2] with varying degrees of selectivity. On the other hand, α-cyano epoxides were found to react with organolithium reagents exclusively at the cyano group.[3,4] When the bis epoxide **7** was subjected to the lithio oxazoline at −60°, the adduct **8** was isolated in 70% yield.