over sodium sulfate. Removal of the solvent gave 0.165 g of dark oil which was chromatographed on deactivated silica gel (6% H_2O), using chloroform in hexane as eluting solvent (chloroform was increased from 5 to 20%), to yield 0.036 g (27%) of colorless solid: mp 69.5–70 °C (mp of racemic[3] is 82–83 °C); $[\alpha]D$ −71° (c 6, chloroform); NMR (CCl_4) δ 5.00 (m, 1, $W_{1/2}$ = 9.5 Hz, H-1), 3.37 (td, 1, $J_{2,3a} \sim 13$, $J_{2,1} \sim J_{2,3e} \sim 3.5$ Hz, H-2). The ir and NMR spectra are identical with those of racemic **6**.[3] In the absence of hydroquinone the yield of **6** was less than 15%. The above conditions, in the absence of hydroquinone, yielded about 90% of *cis*-2-phenylnitrocyclohexane from 2-phenylcyclohexanone oxime.

(1*S*,2*R*)-(+)-*trans*-2-(*o*-Bromophenyl)nitrocyclohexane (7). Isomerization of **6** by refluxing in methanol with a catalytic amount of sodium bicarbonate yielded **7**: mp 81–81.5 °C (mp of racemic[3] is 82–83 °C); $[\alpha]D$ +48° (c 5, chloroform); NMR (CCl_4) δ 4.80 (dt, 1, $J_{1,2} \sim J_{1,6a} \sim 11.2$, $J_{1,6e} \sim 4.2$ Hz, H-1), 3.70 (dt, 1, $J_{2,1} \sim J_{2,3a} \sim 11.2$, $J_{2,3a} \sim 4$ Hz, H-2). The ir and NMR spectra are identical with those of racemic **7**.[3]

(1*R*,2*R*)-(−)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine (5). This compound was obtained by the reduction of **6** with iron in acetic acid as described for the racemic compound,[3] $[\alpha]D$ −76° (c 3, methanol) (69% optical purity compared to resolved amine[3]). The ir and NMR spectra are identical with those of racemic **5**.[3]

(1*S*,2*R*)-(+)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine (1). This compound was obtained by the reduction of **7** with iron in acetic acid as described for the racemic compound,[3] $[\alpha]D$ +37° (c 2, methanol) (66% optical purity compared to resolved amine[3]). The ir and NMR spectra are identical with those of racemic **1**.[3]

The optical purity of **1** and **5** obtained by Scheme I, compared to **1** and **5** obtained by resolution via the menthoxyacetamides,[3] indicates that the oxime **4** and the nitro compounds **6** and **7** also have optical purities of about 67% and that the (+) oxime, $[\alpha]D$ +39°, is essentially optically pure.

Registry No.—**1**, 30808-90-3; **2**, 30808-84-5; **3**, 58342-33-9; **4**, 58298-49-0; **5**, 3080-92-5; **6**, 58342-34-0; **7**, 58342-35-1; (*S*)-(+)-2-(*o*-bromophenyl)cyclohexanone oxime, 58298-50-3; (*S*)-(−)-2-(*o*-bromophenyl)cyclohexanone, 31916-20-8; hydroxylamine hydrochloride, 5470-11-1.

Supplementary Material Available. A listing of the fractional atomic coordinates and thermal parameters for the (−)-methoxyacetamide of (1*S*,2*R*)-(+)-*trans*-2-(*o*-bromophenyl)cyclohexylamine (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Supported in part by Grants NS-08329 and GM-13366 from the National Institutes of Health. Presented in part by A.C. at the American Crystallographic Association Summer Meeting, Ottawa, Canada, August 16–21, 1970. (b) NIH Predoctoral Fellow 1-FI-GM-41,752, 1968–1970.

(2) The CD spectra of the cis isomer give Cotton effects of opposite signs in the $1L_b$ region (270-nm region) when measured in methanol and in isooctane. This phenomenon will be discussed in a future publication treating the chiroptical properties of a series of 2-arylcyclohexanols and cyclohexylamines.

(3) T. G. Cochran and A. C. Huitric, *J. Org. Chem.*, **36**, 3046 (1971).

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(8) Scattering factors for bromine were those of D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965), and those for oxygen, nitrogen, and carbon were from J. Berghuis, I. J. Haanappell, M. Potters, B. O. Loopstra, C. A. MacGillavry, and A. L. Veenendaal, *Acta Crystallogr.*, **8**, 478 (1955).

(9) The anomalous dispersion corrections $\Delta f'$ and $\Delta f''$ were from "International Tables for X-Ray Crystallography", Vol. III, K. Lonsdale, C. H. MacGillavry, and G. A. Reich, Ed., Kynoch Press, Birmingham, England, 1962, p 216.

(10) The *R* factor ratio of 1.04 is significant at the 99.5% confidence level for the 505 parameters (positional and anisotropic thermal parameters for 56 atoms) and the 3816 observed reflections, as discussed by W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(11) (a) R. J. Sundberg and P. A. Bukowich, *J. Org. Chem.*, **33**, 4098 (1968); (b) W. D. Emmonds and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

Reaction of Lactones and Thiolactones with 2-Amino-2-methyl-1-propanol. Synthesis of 2-Substituted 2-Oxazolines

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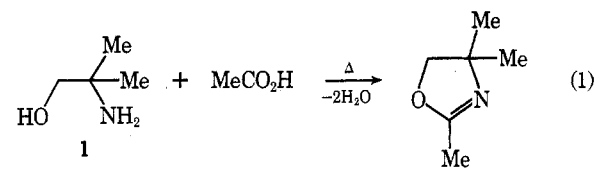
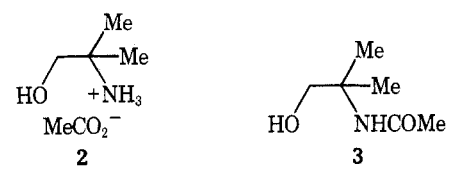
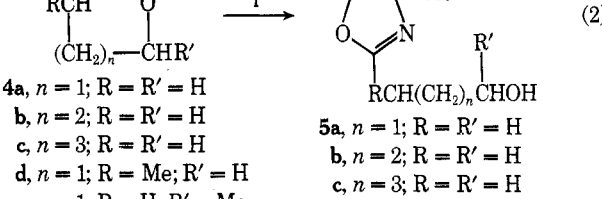
One of the simplest and least expensive preparative procedures for 2-oxazolines involves the reaction of an amino alcohol with a carboxylic acid[2,3] as exemplified in eq 1 with acetic acid and 2-amino-2-methyl-1-propanol (**1**). The reaction is assumed to proceed through successive steps involving the salt **2** and the amide **3**.



(1)



We describe a process similar to that shown in eq 1 which uses a lactone instead of the carboxylic acid. The product is a functionalized 2-oxazoline derivative. Thus, γ-butyrolactone (**4a**), δ-valerolactone (**4b**), and ε-caprolactone (**4c**), and the methylated derivatives of γ-butyrolactone **4d** and **4e** react with **1** to give the respective 2-substituted 4,4-dimethyl-2-oxazoline derivatives, **5a–e**. ε-Caprolactone reacted quantitatively, as determined by GC analysis, and gave a 60% yield of analytically pure product. Yields from the other lactones ranged from 11 to 65%.[4]



(2)

4a, $n = 1$; R = R′ = H
b, $n = 2$; R = R′ = H
c, $n = 3$; R = R′ = H
d, $n = 1$; R = Me; R′ = H
e, $n = 1$; R = H; R′ = Me

5a, $n = 1$; R = R′ = H
b, $n = 2$; R = R′ = H
c, $n = 3$; R = R′ = H
d, $n = 1$; R = Me; R′ = H
e, $n = 1$; R = H; R′ = Me

Steric factors in the lactone slowed the conversion rates measureably. The α- or γ-methyl-substituted lactones **4d** and **4e** reacted about half as fast as γ-butyrolactone. More severe steric factors made reaction progress very slow. Thus, 2,2-diphenylbutyrolactone was recovered unchanged after 8 days at reflux with the amino alcohol in xylene.

The reaction was extended to preparation of the ketooxazoline **5f** and the mercaptooxazoline **5g** by the utilization of α-angelicalactone (**4f**) and of γ-thiobutyrolactone (**4g**). The yields and the spectral and physical properties of all of the oxazolines are shown in Tables I and II.

Table I. Yields, Physical Constants, and Analytical Data for Oxazolines

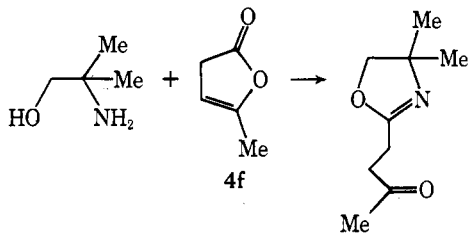
2 substituent	Conversion,[a] %	Yield,[b] %	Bp, °C (mmHg)	n^{25}D	Elemental anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
3-Hydroxy-1-propyl (5a)	65–80	65	77–78 (0.5)	1.4583	58.40	9.00	8.97	58.26	8.87	8.78
4-Hydroxy-1-butyl (5b)	75–92	25[c]	102–104 (0.5)	1.4620	63.13	10.01	*d*	63.10	9.95	*d*
5-Hydroxy-1-pentyl (5c)	100[e]	60	100–103 (1.5)	1.4630	64.83	10.34	*d*	64.90	10.36	*d*
4-Hydroxy-2-butyl (5d)	47–58	34	74–75 (0.19)	(158–159)[f]	45.00[f]	5.04	*d*	45.00	5.13	*d*
3-Hydroxy-1-butyl (5e)	45–57	11[c]	74–75 (0.25)	1.4530[g]	59.97	10.07	7.77	60.29	10.05	7.65
3-Oxo-1-butyl (5f)	100[e]	20	90–95 (3)	1.4580	63.88	8.93	8.28	63.74	9.09	8.42
3-Mercapto-1-propyl (5g)	50–62	46	74–77 (3)	1.4880	55.45	8.73	8.09	55.53	8.74	7.95

[a] Based on GC and ir analysis of the lactone remaining in the crude product mixture; conversion range is for amino alcohol:lactone ratios from 1:1 to 2:1 and a 48-h reaction period. [b] Yield of analytically pure distilled product. [c] Yield of purified product is low owing to competitive polymerization of the lactone. [d] Not determined. [e] Amino alcohol:lactone ratio was 1:1. [f] Picrate melting point and combustion analysis. [g] The purified liquid contained water as indicated by the combustion analysis and other analytical indicators. The combustion analyses compared best with a composition involving 2 mol of oxazoline to 1 mol of water; hence the calculated values are for $C_9H_{17}NO \cdot 1/2\ H_2O$. The picrate was an oil.

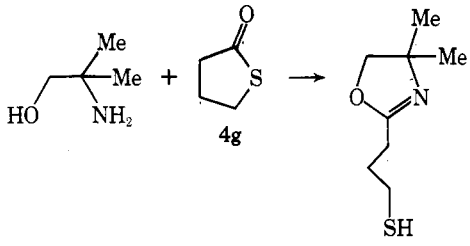
Table II. Ir and NMR Data on Oxazoline Products

Compd	$\nu_{C=N}$,[a] cm-1	ν_{O-H},[a] cm-1	Chemical shift, ppm[b] C-4 Me	C-5 H	OH	C-2 α-H	C-2 β-H	C-2 γ-H	C-2 δ-H	Other
5a	1667	3310	1.29 (6, s)	3.92 (2, s)	4.91 (1, s)	2.39 (2, t, 6.8)	1.88 (2, m)	3.64 (2, t, 6.1)		
5b	1663	3330	1.12 (6, s)	3.88 (2, s)	4.69 (1, s)	2.25 (2, t, 6.7)	1.44–1.89	1.89 (4, m)	3.56 (2, t, 6.1)	
5c	1660	3325	1.12 (6, s)	3.86 (2, s)	4.71 (1, s)	2.22 (2, t, 7.0)	1.30–1.90 (6, m)			3.53 (2, t, 5.8)[c]
5d	1658	3340	1.23 (6, s)	3.88 (2, s)	4.60 (1, s)	2.63 (1, m)	1.75 (2, m)	3.59 (2, t, 6.0)		1.16 (3, d, 7.0)[d]
5e	1665	3380	1.23 (6, s)	3.88 (2, s)	4.19 (1, s)	2.34 (2, t, 7.7)	1.75 (2, m)	3.77 (1, m)	1.15 (3, d, 6.5)	
5f	1670	(1718)[e]	1.17 (6, s)	3.93 (2, s)		2.72 (2, t, 7.8)	2.39 (2, t, 7.8)		2.09 (3, s)	
5g	1670	(2560)[f]	1.13 (6, s)	3.87 (2, s)		2.35 (2, t, 7.0)	1.93 (2, m)	2.57 (2, m)		

[a] Spectra taken as neat liquids; more detailed information is available, cf. W. J. Patterson, Ph.D. Dissertation, University of Alabama, 1974, and P. J. Kelly, M. S. Thesis, University of Alabama in Huntsville, 1976. [b] Values in parentheses indicate number of protons, multiplicity, and coupling constant in hertz; s = singlet, d = doublet, t = triplet, m = multiplet. [c] C-2 ε protons. [d] C-2 α-Me. [e] C=O stretching. [f] S–H stretching.



(3)



(4)

The recent work of Meyers and Mihelich[5] suggests the possible use of this procedure in the conversion of lactones to their alkylated forms and possibly in the preparation of asymmetric derivatives. For this purpose other amino alcohols may be of interest.[6]

Experimental Section

Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected. Ir spectra were recorded on a Beckman IR-10 spectrometer and NMR were recorded as 10–20% solutions in $CDCl_3$ at 90 MHz with a tetramethylsilane internal reference on a Bruker HFX-90 instrument.

All starting compounds and solvents were obtained from Aldrich Chemical Co. and were used without further purification.

The procedure below is typical. All reactions were monitored by infrared or by GC to determine the extent of reaction based on consumed lactone. Reactions were typically run for 48 h or until the volume of the aqueous layer in the Dean-Stark trap reached a maximum.

It was determined that the amino alcohol **1** was slowly distilling (bp 165 °C) as the reaction proceeded. This obviously could affect the percent conversion values (see Table I) when a 1:1 ratio of the amino alcohol:lactone is used. Actually, the effect was negligible with **4c** and **4f** owing to the high reactivity of the lactones. With the other lactones, even at an amino alcohol:lactone ratio of 2:1, the reactivities of the lactones were such that amino alcohol distillation affected percent conversion (Table I) as determined by the amount of lactone remaining (GC and quantitative ir measurements). This can be dealt with in two ways. In the case of γ-butyrolactone, with toluene as the solvent a successful reaction was achieved but at the expense of reaction time. On the other hand, the use of xylene allows a faster reaction (1–4 days for the range of lactones evaluated) and leads to no real losses since the amino alcohol, lactone, and xylene can be recycled by fractionation. Hence we prefer the latter method although one might want to explore the options for optimum conditions for an amino alcohol-lactone pair. We have not optimized conditions for any compounds reported here. A typical run for a 2:1 amino alcohol:lactone ratio is given below.

2-(3-Hydroxypropyl)-4,4-dimethyl-2-oxazoline (5a). To a 500-ml single-necked flask fitted with a magnetic stirrer, Dean-Stark trap, and condenser were added γ-butyrolactone (24.1 g, 0.29 mol), 2-amino-2-methyl-1-propanol (50.0 g, 0.56 mol), and xylene (100 ml). The mixture was stirred and refluxed gently, just allowing the xylene–water azeotrope to distill. The volume of the aqueous layer in the Dean-Stark trap with time was 5.5 ml at 5.75 h, 7.3 ml at 7.75 h, 12.3 ml at 15 h, 16.2 ml at 22 h, and 21 ml at 45 h. The reaction was stopped at 45 h. Analysis by GC indicated 80% conversion of the lactone. The xylene was removed on a rotary evaporator and the residue was distilled to yield 2-(3-hydroxypropyl)-4,4-dimethyl-2-oxazoline, bp 74–78 °C (0.5 mm), which still contained some lactone (GC). Distillation on an adiabatic spinning band column with a reflux ratio of 10/1 yielded 2-(3-hydroxypropyl)-4,4-dimethyl-2-oxazoline (65% yield based on conversion of lactone): bp 77–78 °C (0.5 mm); purity (GLC) 99.6%; ir (NaCl plates) 3310 (O–H), 2960, 2875, 1667 (C=N), 1460, 1363, 1164, 1065, 1038, 945, 819, and 775 cm^{-1}. Other analytical data are shown in Tables I and II.

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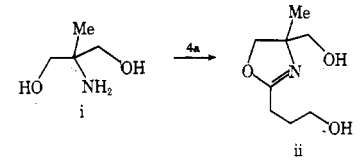
Registry No.—**1**, 124-68-5; **4a**, 96-48-0; **4b**, 542-28-9; **4c**, 502-44-3; **4d**, 1679-47-6; **4e**, 108-29-2; **4f**, 591-12-8; **4g**, 1003-10-7; **5a**, 51849-54-8; **5b**, 58241-39-7; **5c**, 58241-40-0; **5d**, 58241-41-1; **5e**, 51849-55-9; **5f**, 58241-42-2; **5g**, 58241-43-3.

References and Notes

(1) (a) The University of Alabama in Huntsville; (b) Oakwood College; (c) Marshall Space Flight Center; (d) University of Alabama.
(2) J. H. Billman and E. E. Parker, U.S. Patent 2 556 791 (1951); *Chem. Abstr.*, **46**, 525 (1952).
(3) For a review of oxazoline chemistry, see J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).
(4) Polymerization of the lactone invalidates some of the conversion figures in Table I. Also, some amino alcohol was distilled with the water to give a low conversion; allowances were not made for this in the reaction stoichiometry in all cases; see the Experimental Section.
(5) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 1186 (1975).
(6) 2-Amino-2-methyl-1,3-propanediol (i) has been successfully employed in making diols such as (ii) by the same procedure employed here: S. P.



McManus and M. Ortiz, unpublished results; cf. M. Ortiz, M.S. Thesis, The University of Alabama in Huntsville, May 1973.

Trifluoromethylthiocopper.[1] A Reagent for the Introduction of the Trifluoromethylthio Group into Aromatic Nuclei

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The trifluoromethylthio and trifluoromethylsulfonyl groups are important nuclear substituents in the preparation of potential new dyes,[2] medicinal agents,[3] and novel heterocyclic systems.[4] At present, there are two standard procedures for the introduction of a trifluoromethylthio group into an aromatic nucleus. The first method requires a photoinitiated chlorination of an aryl methyl sulfide side chain, followed by reaction with antimony trifluoride[5] (eq 1).

$$ArSCH_3 + Cl_2 \xrightarrow{h\nu} ArSCCl_3 \xrightarrow{SbF_3} ArSCF_3 \quad (1)$$

The second method uses trifluoromethanesulfenyl chloride in either one of two ways. In one procedure[6] (eq 2), reaction of an aryl Grignard reagent with trifluoromethanesulfenyl chloride gives the desired aryl trifluoromethyl sulfide, while in the other procedure[7] (eq 3), reaction of activated aromatic derivatives, such as anilines, with trifluoromethanesulfenyl chloride leads to para-substituted aryl trifluoromethyl sulfides. When higher temperatures and Lewis acid catalysts are used, less activated aryl derivatives undergo reaction, but mixtures of aryl trifluoromethyl sulfide isomers are obtained.

$$ArMgX + CF_3SCl \longrightarrow ArSCF_3 + (ArH + ArCl) \quad (2)$$

$$C_6H_5N(CH_3)_2 + CF_3SCl \longrightarrow CF_3S\text{-}C_6H_4\text{-}N(CH_3)_2 + C_6H_5N(CH_3)_2\cdot HCl \quad (3)$$