Absolute Configuration of *cis*- and *trans*-2-(*o*-Bromophenyl)cyclohexylamine and Related Compounds[1a]

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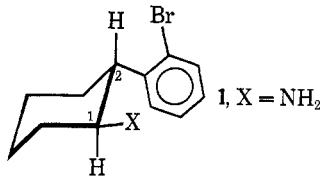
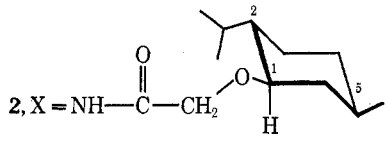
In connection with our investigation of the chiroptical properties of 2-arylcyclohexanols and 2-arylcyclohexylamines, we have observed significant differences in the CD spectra of chiral *cis*-2-(*o*-bromophenyl)cyclohexylamine when measured in methanol and in isooctane but no such differences were found with the trans isomer.[2] These observations made it important to obtain unequivocal proof of the absolute configuration of these compounds. This was accomplished by single-crystal x-ray diffraction analysis of **2**, the menthoxyacetamide of (+)-*trans*-2-(*o*-bromophenyl)cyclohexylamine (**1**), and by relating the absolute con-



1, X = NH_2

(1*S*,2*R*)



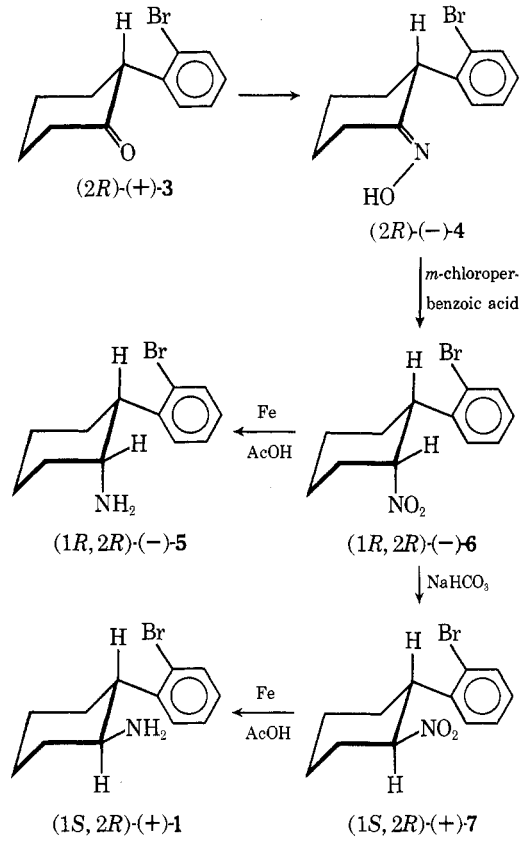
2, X = NH—C(=O)—CH_2

(1*R*, 2*S*,5*R*)

figuration of (−)-*cis*-2-(*o*-bromophenyl)cyclohexylamine (**5**) chemically to that of **1** by the method described in Scheme I.

The resolution of the amines via their menthoxyacetamides has been reported previously.[3] The crystalline menthoxyacetamide **2**, which yields the (+) amine **1** upon hydrolysis,[3] proved ideally suited for single-crystal x-ray diffraction analysis since it allowed the determination of the absolute configuration both from the anomalous dispersion of the bromine and from the known configuration of the (−)-menthol moiety.[4] The crystal structure analysis of **2** unequivocally shows that the absolute configuration of the (+) amine **1** is (1*S*,2*R*). Since (1*S*,2*R*)-(+)-**1** and the (−)-cis amine **5** are both obtained from (+)-2-(*o*-bromophenyl)cyclohexanone (**3**) by the reactions outlined in Scheme I, the absolute configuration of the (−)-cis amine **5** is established as (1*R*,2*R*) and that of the (+) ketone **3** as (*R*). This also establishes the absolute configurations of the nitro intermediates (1*R*,2*R*)-(−)-*cis*-**6** and (1*S*,2*R*)-(+)-*trans*-**7**, and it confirms the original assignment of the absolute configurations of (1*S*,2*S*)-(+)-*cis*-2-(*o*-bromophenyl)cyclohexanol, (1*S*,2*S*)-(+)-*cis*-2-(*o*-bromophenyl)cyclohexylamine,

Scheme I



(1*S*,2*S*)-(+)-*cis*-2-(*o*-bromophenyl)-1-azidocyclohexane, and (1*R*,2*S*)-(−)-*trans*-2-(*o*-bromophenyl)cyclohexanol, which were made on the basis of the CD spectrum of the common precursor (*S*)-(−)-2-(*o*-bromophenyl)cyclohexanone,[5] the enantiomer of **3**.

The menthoxyacetamide **2** crystallizes in the monoclinic space group $P2_1$ with two independent molecules in the asymmetric unit. Perspective drawings[6] of the two crystallographically independent molecules of **2** are shown in Figure 1. The two conformations adopted by this molecule in the crystalline state are similar but not identical. In both conformations, the cyclohexane rings of the amine and menthol moieties are in the chair form with all substituents equatorial. In addition, the N–C–C–O grouping of the menthoxyacetamide moiety is syn planar in both conformations (torsion angles of −10.5 and −3.9° in molecules A and B, respectively). The major conformational differences in the two crystallographically independent molecules appear in the rotational orientations of the aromatic and menthoxyacetamide groups with respect to the cyclohexylamine ring. Thus, in conformation B the aromatic ring is nearly perpendicular (94°) to the mean plane of the cyclohexane ring of the amine, while in conformation A the aromatic ring is tilted 26° from perpendicular (64° from the mean plane of the cyclohexane ring); see Figure 2. The *o*-bromo substituent is on the axial side of C2 in both conformations and in conformation A, where the rings are highly skewed, this substituent is directed away from the amide group on C1. The torsion angle about the C–N bond of the C2–C1–N–

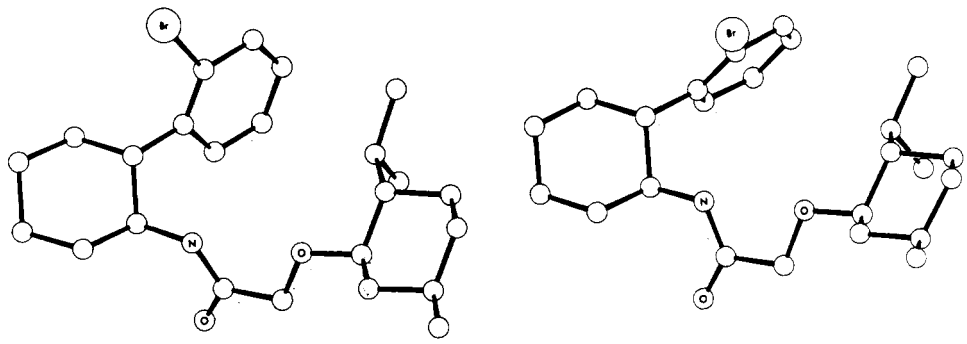


Figure 1. Perspective drawings of the two crystallographically independent molecules of **2** from the x-ray data.

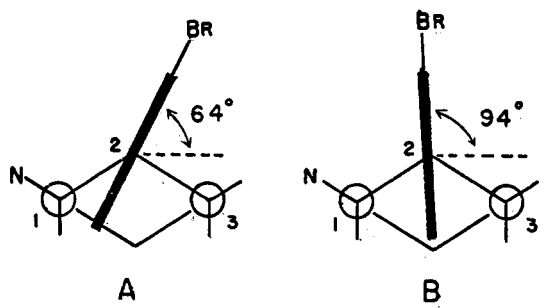


Figure 2. Conformations of the phenyl ring in the crystallographically independent molecules of **2** (projection down the phenyl–C_2 bond).

C=O grouping is 141° in conformation A and 169° in conformation B. This results in the menthoxyacetamide group being tilted further away from the aromatic ring in conformation B than in conformation A. All other differences in torsion angle are less than 10°.

The conformations adopted by molecules in solution are of significant importance to their chiroptical properties. While the conformational parameters observed for a molecule in the crystalline state are a complicated function of inter- and intramolecular forces, they do represent energy minima, and thus are conformations which are likely to be of importance in solution. It is therefore of interest that one of the major conformational differences in the two crystallographically independent molecules of **2** is the rotational orientation of the aromatic ring with respect to the cyclohexylamine ring. Solvent-induced changes in the relative populations of this type of rotamer are not unexpected and could account for the solvent inversion of the sign of the Cotton effect observed in the CD spectra of the cis amine **5**.

Experimental Section

The amide **2**, $C_{24}H_{36}NO_2Br$, $[\alpha]D$ −73° ($CHCl_3$),[3] crystallizes from *n*-hexane in space group $P2_1$ with the following crystal data: a = 13.748 ± 0.004 Å; b = 18.739 ± 0.004 Å; c = 9.876 ± 0.002 Å; β = 110.74 ± 0.02°; D_m = 1.27 g/cm³ (flotation in CsCl solution); D_{calcd} = 1.26 g/cm³ (Z = 4 molecules/unit cell). Systematic absences were observed for $0k0$ with $k = 2n + 1$. The alternate space group choice $P2_1/m$ was rejected by the known chiral asymmetry of the molecule. X-ray intensities were measured on a Picker FACS-1 four-circle diffractometer using the $\omega/2\theta$ scan technique and Nb-filtered Mo radiation (γ = 0.71069 Å). Intensities to 2θ = 50°, corresponding to an interplanar spacing of 0.83 Å, were recorded from a crystal which had been cut to cubic shape with edges approximately 0.33 mm. A total of 4592 independent reflections were measured, of which 3816 had intensities greater than twice the standard deviation of their measurement. No absorption corrections were applied, and structure amplitudes were obtained from the intensities in the usual manner. A sharpened, origin-removed three-dimensional Patterson synthesis enabled the positions of the two unique bromine atoms to be located and the coordinates of the 54 other nonhydrogen atoms comprising the two molecules in the asymmetric unit were determined from subsequent electron-density maps based on phases calculated from the bromine positions. The positional and anisotropic thermal parameters of all the atoms were refined using a full-matrix least-squares procedure with weights taken as $\sqrt{\omega} = 1/\sigma_F$[7] until a discrepancy factor, R, of 0.064 was achieved.[8] Up to this point, the normal bromine scattering curve, $f°_{Br}$, was used with no correction for anomalous scattering of the x rays by the bromine atoms. At this stage, the absolute configuration of the molecule was determined by applying the true bromine scattering curve including anomalous scattering effects, $f_{Br} = f°_{Br} + \Delta f'_{Br} + i\Delta f''_{Br}$. Structure factors were calculated[9] for molecules with atom coordinates x, y, z and for molecules with atom coordinates $-x, -y, -z$; that is, structure factors were calculated for both possible optical isomers. The conventional discrepancy factor R was 0.070 for one structure and 0.073 for its enantiomer. This difference is highly significant[10] and the absolute configuration for this molecule is unambiguously established as the one giving the lower R. An independent verification for this assignment of absolute configuration is that the absolute configuration of the (−)-menthol moiety of the structure producing the lower R is in agreement with the known absolute configuration of (−)-menthol.[4]

Although the positions of all 72 hydrogen atoms in the asymmetric unit could be either located in a difference Fourier map or calculated from the positions of the carbon atoms, they have not been included in the calculations since the additional significance does not compensate for the added cost of refinement for a structure of this size. (See paragraph at end of paper regarding supplementary material.)

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Specific rotations were measured at ambient temperature with a Rudolph polarimeter using a sodium lamp. Infrared spectra were obtained with a Beckman IR-5A or IR-20 spectrometer and ^1H NMR spectra on a Varian A-60 or T-60 spectrometer using tetramethylsilane as internal reference.

Chiral *cis*- and *trans*-2-(*o*-bromophenyl)cyclohexylamines and their (−)-menthoxyacetamides have been reported previously.[3]

(*S*)-(+)-2-(*o*-Bromophenyl)cyclohexanone Oxime. A solution of 0.45 g (1.78 mmol) of (*S*)-(−)-2-(*o*-bromophenyl)cyclohexanone[5] ($[\alpha]D$ −15°), 0.25 g (3.56 mmol) of hydroxylamine hydrochloride, and 0.245 g (1.78 mmol) of potassium carbonate in 50 ml of methanol was heated to reflux for 2 h, cooled, and added to 125 ml of ice water. Filtration and recrystallization from 95% ethanol gave 0.39 g of colorless, crystalline product, mp 160–161 °C, $[\alpha]D$ +39° (*c* 2, methanol).

(*R*)-(−)-2-(*o*-Bromophenyl)cyclohexanone Oxime (4). In the preparation of **4** from **3** ($[\alpha]D$ +15°) 85% ethanol was used as solvent instead of methanol and the recovered oxime had about 67% of the specific rotation of the (+) enantiomer described above, $[\alpha]D$ −26° (*c* 1, methanol), mp 160–161 °C.

(1*R*,2*R*)-(−)-*cis*-2-(*o*-Bromophenyl)nitrocyclohexane (6). This compound was obtained by a modified version of the known methods for peracid oxidation of oximes.[11] A mixture of 0.125 g (0.47 mmol) of **4** ($[\alpha]D$ −26°), 0.025 g (0.42 mmol) of urea, 0.075 g (0.068 mmol) of hydroquinone, and 0.5 g of dibasic sodium phosphate in 25 ml of acetonitrile was heated to reflux and a solution of 0.61 g of *m*-chloroperbenzoic acid (about 80% purity) in 25 ml of acetonitrile was added to the refluxing mixture over a period of 90 min. Refluxing was continued for 4 h. The solvent was removed under reduced pressure, water was added, and the aqueous mixture was extracted with dichloromethane. The dichloromethane solution was washed successively with 10% sodium bisulfite solution, saturated sodium bicarbonate solution, and water, and dried

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).

(4) (a) A. Fredga, *Acta Chem. Scand.*, **1**, 371 (1947); (b) W. Huckel, *J. Prakt. Chem.*, **157**, 225 (1941); V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); (c) R. Parthasarathy, J. Ohrt, A. Horeau, J. P. Vigneron, and H. B. Kagan, *Tetrahedron*, **26**, 4705 (1970).

(5) T. G. Cochran, D. V. Wareham, and A. C. Huitric, *J. Pharm. Sci.*, **60**, 180 (1971).

(6) C. K. Johnson, ORTEP, Oak Ridge National Laboratory Report ORNL-3794, 1965.

(7) The term σ_F is the standard deviation in the structure factor, based on counting statistics: G. H. Stout and L. H. Jensen, "X-Ray Structure Determination", Macmillan, New York, N.Y., 1968, p 456.

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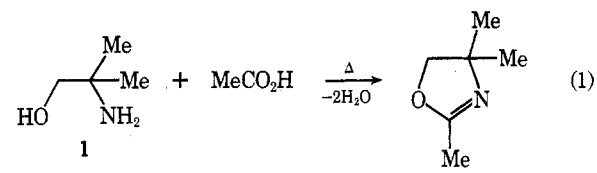
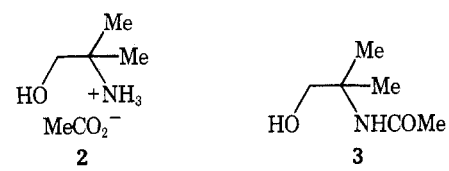
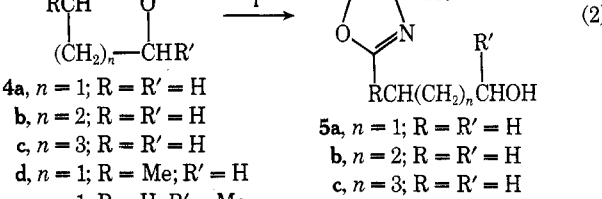
One of the simplest and least expensive preparative procedures for 2-oxazolines involves the reaction of an amino alcohol with a carboxylic acid[2,3] as exemplified in eq 1 with acetic acid and 2-amino-2-methyl-1-propanol (**1**). The reaction is assumed to proceed through successive steps involving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