The Use of Nuclear Magnetic Resonance as a Monitor in Optical Resolutions. II. The Synthesis and Resolution of *cis*- and *trans*-2-(*o*-Bromophenyl)cyclohexylamines[1a]

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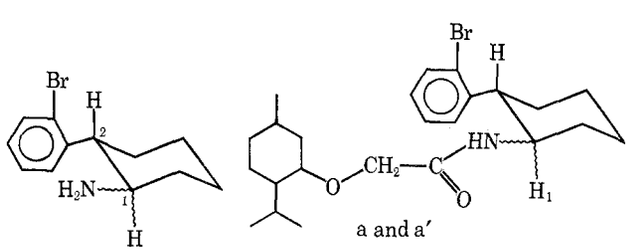
The use of nuclear magnetic resonance spectroscopy for the determination of optical purity of enantiomeric mixtures is well established. Several related approaches to this technique have been reported, all utilizing the magnetic nonequivalence of diastereotopic[2] nuclei obtained when enatiomeric compounds are either suitably derivatized with optically active reagents[3-5] or dissolved in chiral solvents.[6] In this paper we wish to report the use of the difference in the geminal nonequivalence of certain methylene hydrogens of diastereomeric (−)-menthoxyacetamides as a convenient monitor for the optical resolution of two amines. This technique was previously utilized to follow the resolution of the *cis*- and *trans*-2-*o*-tolylcyclohexanols through their (−)-menthoxyacetates[5] and we have now demonstrated this to be a useful method for (−)-methoxyacetamides as well. The attractiveness of this method is that the diastereotopic nuclei are on the resolving agent, thus allowing nmr to be used as a convenient monitor for following the separation of the diastereomers, and therefore the resolution of the enantiomers, without the need of intermediate chemical steps.

The enantiomers of *trans*- and *cis*-2-(*o*-bromophenyl)-cyclohexylamine (**1** and **2**) were resolved through their diastereomeric (−)-menthoxyacetamides. These amines were prepared by the stereospecific scheme described by Trager and Huitric[7] for the synthesis of other 2-arylcyclohexylamines and the (−)-menthoxyacetamides of **1** (**3** and **4**) and of **2** (**5** and **6**) were obtained



1, NH_2 equatorial; H axial
2, NH_2 axial; H equatorial

3 and **4**, H_1 axial
5 and **6**, H_1 equatorial

quantitatively from the reaction of the racemic amines with (−)-menthoxyacetyl chloride (**7**) in pyridine.

The trans diastereomers **3** and **4** were separated by repeated fractional crystallization and column chromatography while the cis amides **5** and **6** were separated simply by fractional crystallization. The details of the separations are described in the Experimental Section.

Figure 1 shows the nmr spectra of the methylene hydrogens (a and a′) on the acetamide portion of the diastereomeric (−)-menthoxyacetamides. Spectra A, B, D, and E are of the four diastereomeric amides **3**–**6**, while spectra C and F are of 50:50 mixtures of the two trans and the two cis amides, respectively. In both of the trans diastereomers, **3** and **4**, these methylene hydrogens are magnetically nonequivalent, and the signal of each hydrogen appears as a skewed doublet with geminal coupling of 15 Hz. However, the nonequivalence is not the same in the two diastereomers, being 0.15 ppm in **3** and 0.49 ppm in **4**.[8] Only one of the diastereomeric cis amides shows this geminal nonequivalence, the methylene protons of **5** having a difference in chemical shift of 0.41 ppm while those of **6** are equivalent, producing a sharp singlet. This large difference in nonequivalence allows the members of each diastereomeric pair to be readily distinguished by nmr spectroscopy, and thus by following the changing peaks intensities in the nmr spectra of these amides a complete assessment of the progress of the separation of diastereomers was possible. This was particularly useful in monitoring the separation of the trans diastereomers by column chromatography, since the individual fractions from the column could be readily analyzed by nmr.

The very large geminal nonequivalence seen in **4** and **5** is significantly greater than that observed for the corresponding hydrogens of diastereomeric (−)-menthoxyacetate esters of 2-arylcyclohexanols[5], which show a maximum geminal nonequivalence of 0.15–0.20 ppm. This large geminal nonequivalence in the amides is most reasonably accounted for by preferred time-average conformations in which the methylene hydrogens are dissymmetric about the amide function, but the anisotropy of the aromatic ring could also have an important effect.[4c] It is of interest that the nmr spectra of the acetamide methylene protons of these amides remain practically unchanged in a variety of solvents including chloroform, carbon tetrachloride, benzene, acetonitrile, pyridine, and trifluoroacetic acid (TFA), except that the pair of highly skewed doublets of **3** collapse to a broad singlet in TFA. This would indicate the preferred time-average conformations of these molecules about the amide function are essentially the same in these solvents.

The enantiomeric amines obtained upon acidic hydrolysis of the trans amides **3** and **4** gave optical rotations of equal magnitudes and opposite signs as did their crystalline hydrochloride salts. A similar hydrolysis of the two cis amides **5** and **6** afforded the enantiomeric cis amines, also having rotations of equal magnitudes and opposite signs.

An improved procedure for the synthesis of (−)-menthoxyacetic acid, in which the lithium salt of (−)-menthol is formed in THF rather than the sodium salt in toluene,[9] leads to a more facile procedure of higher

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(2) For a discussion of this terminology, see M. Raban and K. Mislow, *Top. Stereochem.*, **1**, 19 (1967).

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yield. The details are described in the Experimental Section.

Experimental Section[10]

trans-*o*-β-**Nitrostyrene.**—In the manner described by Gairaud and Lappin[11] a solution of 30 g (0.16 mol) of *o*-bromobenzaldehyde, 19.5 g (0.32 mol) of nitromethane, and 12.5 g (0.16 mol) of ammonium acetate in 100 ml of glacial acetic acid was heated in a 100° oil bath for 2 hr and then poured onto 2 l. of crushed ice. The resulting orange precipitate was collected and recrystallized from 95% EtOH to give 21 g (57%) of dark yellow crystals, mp 86–87° (lit.[12] 86°). Steam distillation of the neutralized aqueous filtrate afforded an additional 3 g (8%) of the styrene.

trans-**4-Nitro-5-(*o*-bromophenyl)cyclohexene.**—Employing the method of Wildman and Wildman,[13] a mixture of 29 g (0.128 mol) of *trans*-*o*-bromo-β-nitrostyrene, 30 g (0.56 mol) of condensed butadiene, and 100 mg of hydroquinone in 100-ml of dry toluene was heated at 108° in a heavy steel bomb for 7 days. Evaporation of the toluene yielded a brown oil which was crystallized from isopropyl alcohol to give 30 g (82%) of colorless crystals, mp 90–90.8°.

Anal. Calcd for $C_{12}H_{12}NO_2Br$: C, 51.09; H, 4.09; N, 4.96. Found: C, 51.26; H, 4.38; N, 4.75.

trans-**2-(*o*-Bromophenyl)nitrocyclohexane.**—Catalytic hydrogenation of *trans*-4-nitro-5-(*o*-bromophenyl)cyclohexene over 10% palladium on carbon in ethyl acetate at 30 psi for 1 hr afforded an oil which was crystallized from an isopropyl alcohol–hexane mixture to give colorless crystals, mp 82–83°.

Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.61; H, 5.02; N, 4.74.

cis-**2-(*o*-Bromophenyl)nitrocyclohexane.**—Using the method described by Zimmerman and Nevins,[14] a solution of 6 g (0.0216 mol) of *trans*-2-(*o*-bromophenyl)nitrocyclohexane and 25 ml of 10% ethanolic KOH in an additional 15 ml of ethanol was stirred for 30 min and then added to 600 ml of a buffer solution of the following composition: 600 ml of 95% EtOH, 45 g of sodium acetate trihydrate, and 5 ml of glacial acetic acid. After standing for 15 min the solution was diluted with 2 l. of water and extracted with three 300-ml portions of ether. The ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give an oil which was crystallized from hexane affording 5 g (83%) of blocky crystals, mp 82–83° (sublimes).

Anal. Calcd for $C_{12}H_{14}NO_2Br$: C, 50.72; H, 4.97; N, 4.93. Found: C, 51.16, H, 4.92; N, 4.67.

This compound could be recoverted to its trans isomer by refluxing in 95% EtOH with a catalytic amount of Na_2CO_3, as reported by Zimmerman.[14]

trans-**2-(*o*-Bromophenyl)cyclohexylamine** (1).—In the manner outlined by Kornblum and coworkers,[15] finely powdered hydrogen reduced iron (18 g, 0.32 g-atom) was washed with 25 ml of 5% HCl, rinsed with 25 ml of glacial acetic acid, and then added to a stirred solution of 9 g (0.032 mol) of *trans*-2-(*o*-bromophenyl)-nitrocyclohexane in 100 ml of glacial acetic acid. This mixture was stirred at gentle reflux for 5 hr and then filtered while hot through a sintered glass funnel. The solid was rinsed with 50 ml of hot acetic acid and the combined acidic filtrates were made strongly basic by the careful addition of 50% NaOH, while cooling in an ice bath, and then diluted with water to a volume of 1 l. and extracted with 1 l. of ether in three portions. The ethereal solution was washed with water, dried (Na_2SO_4), concentrated, and distilled to give 6.3 g (78%) of colorless oil: bp 98–100° (0.1 mm); ir (neat) 2.97 and 3.03 μ (N–H). The hydrochloride salt was prepared by bubbling HCl gas through an absolute EtOH solution of **1**, evaporating the solution to dryness, and recrystallizing the solid from ethyl acetate–1,2-dichlorethane (10:1), mp 199–201°.

(10) Melting points were determined on a Kofler micro hot stage and are corrected. Specific rotations were measured at ambient temperature with a Rudolph polarimeter using a sodium lamp and a 2-dm tube. Infrared spectra were obtained on a Beckman IR-5-A spectrophotometer and nmr spectra on a Varian A-60 spectrometer using TMS as an internal reference. Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo.

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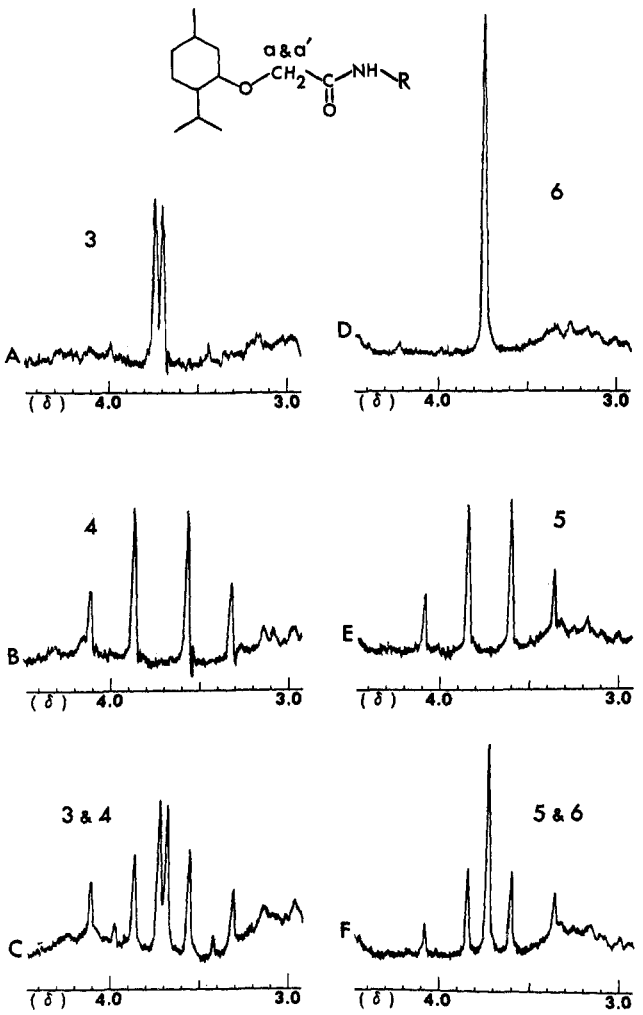

Figure 1.—Portions of the 60-MHz nmr spectra of the diastereomeric (−)-menthoxyacetamides measured in chloroform at 37°.

Anal. Calcd for $C_{12}H_{17}NBrCl$: C, 49.59; H, 5.90; N, 4.82. Found: C, 49.81; H, 6.05; N, 4.83.

cis-**2-(*o*-Bromophenyl)cyclohexylamine** (2).—This compound was prepared in a 66% yield from *cis*-2-(*o*-bromophenyl)nitrocyclohexane by the method described for obtaining **1**: bp 106° (0.2 mm); ir (neat) 2.98 and 3.05 μ (N–H). The hydrochloride salt was crystallized from isopropyl alcohol–hexane (2:1), mp 254–256°, sublimes.

Anal. Calcd for $C_{12}H_{17}NBrCl$: C, 49.59; H, 5.90; N, 4.82. Found: C, 49.63; H, 5.77; N, 4.78.

(−)-**Menthoxyacetic Acid.**—To a solution of 156 g (1 mol) of menthol, $[\alpha]_D$ −50° (*c* 10, 95% EtOH), in 500 ml of anhydrous THF under nitrogen was added 8 g (1.15 g-atoms) of lithium metal ribbon cut into small pieces and this mixture was stirred at gentle reflux for 4 hr. The unreacted lithium was mechanically removed, a solution of 42.5 g (0.45 mol) of dry monochloroacetic acid in 125 ml of anhydrous THF was slowly added, and the resulting solution was stirred at gentle reflux for 20 hr. Following the addition of 300 ml of water the THF and menthol were steam distilled from the yellow aqueous suspension, which was then cooled in an ice bath, and the solid lithium salt was collected on a Büchner funnel and washed with cold water. The free acid was liberated upon acidification of an ether suspension of the salt with 10% HCl and the resulting ethereal solution was washed with water, dried (Na_2SO_4), concentrated, and distilled to give 84 g (88%) of clear oil: bp 124–126° (0.4 mm); $[\alpha]_D$ −92.7° (*c* 10, 95% EtOH) [lit.[9] bp 134–137° (2 mm); $[\alpha]_D$ −91.5° (*c* 2, EtOH)].

The acid chloride was prepared in thionyl chloride as described by Ingersoll[9] and distilled, bp 85–87° (0.4 mm) [lit.[9] bp 132° (10 mm)].

Synthesis of the Mixture of Diastereomers 3 and 4.—To a solution of 4.2 g (0.0165 mol) of **1** in 15 ml of dry pyridine was added 4.0 g (0.017 mol) of freshly distilled (−)-menthoxyacetyl

chloride and the resulting mixture was allowed to stand at room temperature for 2 days and then diluted with 100 ml of ether. The ethereal solution was washed with water, 10% HCl, 10% Na_2CO_3, and water, dried (Na_2SO_4), and concentrated to give 7 g (96%) of a brown oil.

Isolation of (−)-*trans*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (3).—This amide was obtained by crystallization of the crude mixture of diastereomers from a concentrated hexane solution at Dry Ice–isopropyl alcohol bath temperature. The amide was collected by filtration and washed with cold hexane but melted upon warming to room temperature. This material was recrystallized six times at refrigerator temperature to give a viscous oil (at room temperature): $[\alpha]_D$ −14° (*c* 5, chloroform); ir (neat) 2.92 (N–H), 6.00 μ (C=O). The nmr spectrum indicated the presence of only one diastereomer.

Isolation of (+)-*trans*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (4).—This diastereomer was isolated by column chromatography of the residual amide mixture remaining after the isolation of **3**. Typically, 4 g of the oil mixture was chromatographed on 125 g of neutral alumina (Merck), eluting with petroleum ether followed by increasing concentrations of benzene–petroleum ether mixtures. The eluted oil was collected in approximately 200-mg portions and analyzed by nmr spectroscopy. The desired diastereomer **4** eluted first and the pure fractions from several columns were combined and crystallized from hexane to give colorless crystals: mp 70.5–71.5°; $[\alpha]_D$ −73° (*c* 5, chloroform). The nmr spectrum indicated the presence of only one diastereomer.

Anal. Calcd for $C_{24}H_{36}NO_2Br$: C, 63.99; H, 8.06; H, 3.11. Found: C, 63.72; H, 8.03; N, 3.15.

Synthesis of the Mixture of Diastereomers 5 and 6.—The mixture of diastereomeric amides was obtained as an oil in a 98% yield from the reaction of **2** with (−)-menthoxyacetyl chloride in pyridine as described for the synthesis of **3** and **4**.

Isolation of (+)-*cis*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (5).—This diastereomer was obtained by fractional crystallization of the crude amide mixture in hexane at refrigerator temperature to give colorless crystals: mp 121–122.5°; $[\alpha]_D$ +86° (*c* 5, methanol); ir (Nujol) 2.94 (N-H), 5.99 μ (C=O). The nmr spectrum indicated the presence of only one diastereomer.

Anal. Calcd for $C_{24}H_{36}NO_2Br$: C, 63.99; H, 8.06; N, 3.11. Found: C, 64.06; H, 8.08; N, 3.08.

Isolation of (−)-*cis*-2-(*o*-Bromophenyl)cyclohexyl (−)-Menthoxyacetamide (6).—The residual amide mixture remaining after the isolation of **5** was crystallized from hexane at Dry Ice–isopropyl alcohol bath temperature and the crude solid was recrystallized from hexane by slow evaporation of solvent at room temperature. The fine needle crystals which formed recrystallized from hexane: mp 104.5–105.5°; $[\alpha]_D$ −174° (*c* 4, methanol). The nmr spectrum indicated the presence of only one diastereomer.

(−)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine.—To a solution of 0.45 g of **3** in 8 ml of glacial acetic acid was added 5 ml of concentrated HCl and the resulting solution was heated in a 105° oil bath for 40 hr, cooled, and diluted with 30 ml of water. This solution was extracted with three 25-ml portions of ether and then carefully basified to pH 11 with 50% NaOH, while cooling in an ice bath. The resulting cloudy solution was extracted with 100 ml of ether in three portions and the ethereal solution was washed with water, dried (Na_2SO_4), and concentrated to give 0.23 g (91%) of a yellow oil, $[\alpha]_D$ −56° (*c* 2, methanol). The ir and nmr spectra were identical with those of **1**. The hydrochloride salt was prepared as for **1**: mp 217–219°; $[\alpha]_D$ −46° (*c* 5, methanol).

(+)-*trans*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained upon an identical acidic hydrolysis of **4**, $[\alpha]_D$ +56° (*c* 2, methanol). The hydrochloride salt was prepared as for **1**: mp 217–219°; $[\alpha]_D$ +46° (*c* 4, methanol).

(+)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained as an oil upon an acidic hydrolysis of **5**, as previously described for the hydrolysis of **3**, $[\alpha]_D$ +109° (*c* 3, methanol). The ir and nmr spectra were identical with those of **2**. The hydrochloride salt was prepared as for **2**: mp 240–242°, sublimes extensively; $[\alpha]_D$ +123° (*c* 4, methanol).

(−)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine.—This compound was obtained as an oil upon the acidic hydrolysis of **6**, $[\alpha]_D$ −110° (*c* 2, methanol). The hydrochloride salt was prepared as for **2**: mp 240–242°, sublimes extensively; $[\alpha]_D$ −122° (*c* 4, methanol).

Registry No.—**1**, 30808-81-2; **1** HCl, 30808-95-8; **2**, 30808-82-3; **2** HCl, 30808-96-9; **3**, 30808-83-4; **4**, 30808-84-5; **5**, 30808-85-6; **6**, 30808-86-7; *trans*-4-nitro-5-(*o*-bromophenyl)cyclohexene, 30808-87-8; *trans*-2-(*o*-bromophenyl)nitrocyclohexane, 30808-88-9; *cis*-2-(*o*-bromophenyl)nitrocyclohexane, 30896-88-9; (−)-*trans*-2-(*o*-bromophenyl)cyclohexylamine, 30808-89-0, 30808-93-6 (HCl); (+)-*trans*-2-(*o*-bromophenyl)cyclohexylamine, 30808-90-3, 30808-97-0 (HCl); (+)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, 30808-91-4, 30808-98-1 (HCl); (−)-*cis*-2-(*o*-bromophenyl)cyclohexylamine, 30808-92-5, 30808-94-7 (HCl).

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The Mechanism of the Base-Catalyzed Conversion of Nitriles to Amides by Hydrogen Peroxide

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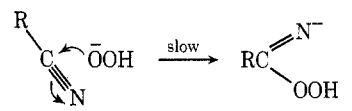
The conversion of nitriles to amides by alkaline solutions of hydrogen peroxide is a well-known preparative procedure.[1] Wiberg[2] has investigated the mechanism of this reaction in the pH range 7–8. Our interest in the nucleophilic reactivity of peroxy anions[3] and the α effect[4] led us to a reinvestigation of this reaction. Wiberg's mechanism,[2] eq 2–4, involves rate-

$$RC{\equiv}N + 2\,H_2O_2 \xrightarrow{HO^-} RC(=O)NH_2 + O_2 + H_2O \qquad (1)$$



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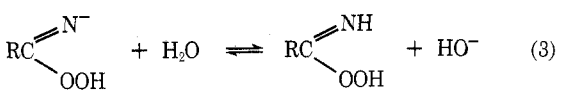

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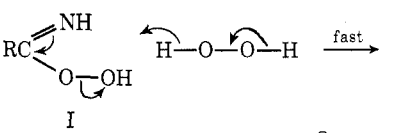

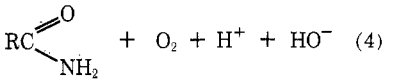

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