Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.13; H, 6.58.

Hydrolysis of II (300 mg) using a 1:1 mixture of concentrated hydrochloric acid (10 ml) and water (10 ml) was effected by heating on a steam bath for 6 hr. The water and hydrochloric acid were removed *in vacuo* and the crude acid (solid) was dissolved in diethyl ether–methanol and methylated with excess diazomethane in ether. An nmr spectrum of the crude methyl ester (~250 mg) was identical with the solid IV obtained by alkaline hydrolysis. Also the nmr spectrum of the crude methyl ester showed the absence of *cis,anti,trans*-1,3-dimethyl-1,2,3,4-tetracarbomethoxycyclobutane, 3–5% of which could easily be detected in the nmr spectrum of a mixture of the two esters.

Epimerization of *cis,anti,cis*-1,3-Dimethyl-1,2,3,4-tetracarbomethoxycyclobutane (IV).—IV (100 mg) was hydrolyzed, according to the method of Schenck, and methylated with diazomethane. The nmr spectrum of the mixture of esters with peaks at δ 3.79, 3.75, 3.72, 3.42, 1.73, 1.62, and 1.52 corresponded to a mixture of IV and the unsymmetrical ester. Thin layer chromatography of the mixture on silica gel plates using ether–hexane gave two spots corresponding to the two esters.

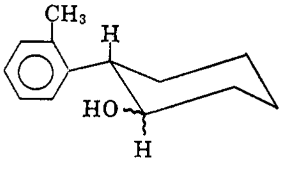
The Use of Nuclear Magnetic Resonance as a Monitor in Optical Resolutions[1a]

DONALD R. GALPIN[1b] AND ALAIN C. HUITRIC

College of Pharmacy, University of Washington,
Seattle, Washington 98105

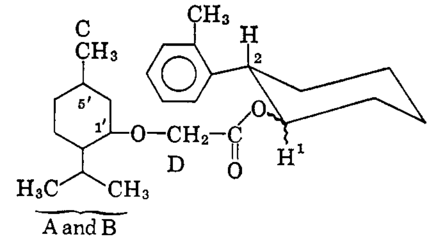
Received August 21, 1967

There are a number of examples in the literature of the magnetic nonequivalence of geminal hydrogens and geminal methyl groups in the vicinity of an asymmetric center[2–5] and also of magnetic nonequivalence of corresponding hydrogens in diastereomers.[6,7] Observed chemical shift differences are most notable when there is a group in the molecule which possesses a large inherent magnetic anisotropy, such as phenyl,[3,4,6,7] carboxyl,[2,4,5,7] or nitrile[5] groups. Recently, Raban and Mislow[7] have demonstrated the applicability of nmr spectroscopy to the analysis of mixtures of diastereoisomers as a method of determining optical purity. We have successfully utilized this method to follow the resolution of *trans*-2-*o*-tolylcyclohexanol (1) and *cis*-2-*o*-tolylcyclohexanol (2) through their (−)-menthoxyacetate esters by taking advantage of the nonequivalence of the methylene hydrogens of the acetate portion (hydrogens D) and the isopropyl methyl groups (A and B) of the menthol moiety and of the fact that these nonequivalences are different for members of a pair of diastereoisomeric esters. The signals of the methylene hydrogens were the most useful in following the progress of separation of the diastereomers. Basic hydrolysis of the diastereomers, reported elsewhere,[8] yielded the optically active alcohols. The assignment of the absolute configurations of these optically active alcohols is reported in another communication.[8]



1, OH equatorial; H axial
2, OH axial; H equatorial

Compound **1** was prepared from cyclohexene oxide and the lithium derivative of *o*-bromotoluene following the method of McKusick.[9] The *cis* alcohol **2** was obtained by a stereospecific reduction of 2-*o*-tolylcyclohexanone (**3**) with triisobutylaluminum[10] yielding predominantly the axial isomer. The (−)-menthoxyacetate esters of **1** (**6** and **7**) and **2** (**8** and **9**) were synthesized following the procedures outlined by Ingersoll.[11] The esters **6** and **7** were solids, whereas **8** and **9** were thick viscous liquids. The details of their separation are described in the Experimental Section.



6 and **7** H-1, axial
8 and **9** H-1, equatorial

The important chemical shifts of the four esters are given in Table I. The pertinent portions of the spectra of the optically pure esters of the *trans* alcohol, compounds **6** and **7**, are shown in Figure 1. The nonequivalence of the two methylene hydrogens D in a given ester is clearly demonstrated. The signals of these methylene hydrogens for each diastereomer ap-

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR THE (−)-MENTHOXYACETATE ESTERS OF *trans*- AND *cis*-2-*o*-TOLYLCYCLOHEXANOL[a]

	CH_2 (D)		CH_3 (C)[b]	Isopropyl CH_3
Compd	τ, ppm	J_{gem}, Hz	τ, ppm	(A and B)[c] τ, ppm
6	6.16	16.0	9.15	9.15
	6.34			9.30
7	6.16	16.0	9.15	9.15
	6.36			9.28
8	6.08[d]		9.13	9.11
				9.21
9	5.98	16.0	9.10	9.14
	6.18			9.30

[a] The spectra were obtained in chloroform or chloroform-*d* at 60 MHz and 37°. The chemical shifts of the D hydrogens represent the calculated centers of gravity of the signals of the AB systems. The centers of gravity are approximated for the doublets of the methyl hydrogens because the uncertainty of the chemical shifts of the coupled methine hydrogens precludes accurate calculations. [b] The two components of the doublets were not always discernible because of overlapping of signals. [c] Doublets with separation of 7.0 Hz due to coupling with the isopropyl methine hydrogen. [d] Identical chemical shifts, single peak.

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[1] (a) This investigation was supported in part by Research Grant MH 11942-01 from the National Institute of Mental Health, U. S. Public Health Service. (b) To whom all correspondence should be addressed at the College of Pharmacy, Washington State University, Pullman, Wash. 99163.

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[3] G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964).

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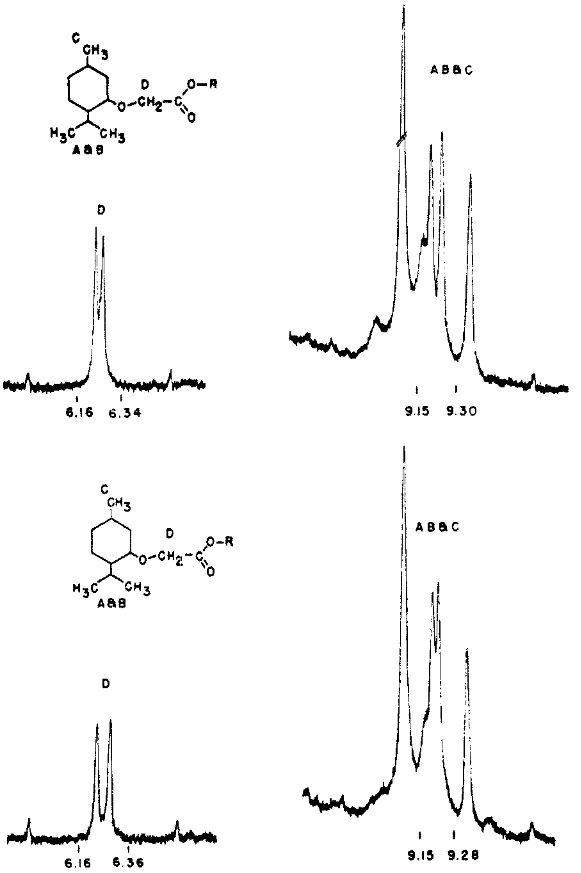

Figure 1.—Portions of 60-MHz nmr spectra (250-Hz sweep width) of (+)-*trans*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate (**6**) (upper curves) and (−)-*trans*-2-*o*-tolylcyclohexyl (−)-menthoxyacetate (**7**) (lower curves) measured in chloroform-*d* at 37°.

pear as highly skewed doublets with geminal coupling of 16 Hz but the nonequivalence is not the same in the two diastereoisomeric esters. In the spectrum of the initial 50:50 mixture of the esters there is overlapping of the lower field doublet from each ester and the combined signals give a complex of three main peaks in which the lower field component has twice the intensity of the other two. These signals provide a very convenient and efficient method of following the progress of separation of the two esters. An examination of the ethyl region reveals that in each ester the isopropyl methyl groups A and B are also nonequivalent, a condition also present in menthol itself,[12] and the degree of nonequivalence is not the same in the two esters. The signals of all three methyl groups in the menthol moiety appear as doublets. Because the signals of the protons with which these groups are coupled are not distinguishable (they fall under the broad envelope of the other ring hydrogens) exact chemical shifts cannot be calculated for A, B, and C. They are estimated and are accurate to within 0.02 τ units. In both isomers the signal of one isopropyl methyl group and that of the C methyl at C-5′ are overlapping at τ 9.15. The signals of the other isopropyl methyl group appear at τ 9.30 and 9.28 in **6** and **7**, respectively. In a mixture of these esters the methyl region exhibits a six-peak complex in which the signals of the latter methyl groups are not exactly superimposed.

In one of the esters of the *cis* alcohol, compound **8**, the methylene hydrogens D have essentially identical chemical shifts giving a sharp singlet at τ 6.08. In **9** these hydrogens are nonequivalent giving rise to a set of highly skewed doublets centered at τ 5.98 and 6.18 (J_{gem} = 16 Hz). Since this pair of doublets is centered at τ 6.08, in a mixture of **8** and **9** the signal for these hydrogens is essentially a three-peak complex in which the center component is attributable to the methylene group of **8**. The spectrum of the methyl region of these esters is analogous to that of the *trans* esters **6** and **7**, except that all three methyl groups in each ester are nonequivalent.

If the spectrum of a mixture of **8** and **9** is obtained in carbon tetrachloride, the signal of the methylene hydrogens is a sharp singlet. The methyl region, however, still maintains a sufficient degree of nonequivalence that the presence of the two isomers can be recognized.

By following the changing peak intensities in the nmr spectra of these esters a complete assessment of the progress of the separation was possible. The *trans* alcohol **1** was totally resolved. The enantiomers recovered from the hydrolysis of **6** and **7** gave rotations equal in magnitude, but opposite in sign.[8] For the *cis* esters **8** and **9** only the latter appears to have been isolated in relatively pure form; the most pure sample of **8** isolated is approximately 75% optically pure.

The sensitivity of the nmr analysis depends considerably on the differences in chemical shifts of the diagnostic signals in the two diastereomeric esters. Although we have not made a systematic analysis of sensitivity, we estimate that in our systems it is possible to estimate close to 95% purity of one diastereomer by nmr.

Experimental Section

Melting points indicated as Kofler were determined on a Kofler micro hot stage melting point apparatus and are corrected; melting points indicated as Fisher-Johns were determined on a Fisher-Johns hot plate melting point apparatus and are uncorrected.

Optical rotations were determined in a Rudolf polarimeter in the solvents specified at ambient temperature using a 1-dm tube.

The nmr spectra were determined at 60 MHz on a Varian Associates A-60 spectrometer in chloroform or deuteriochloroform at 37°, using TMS as an internal reference.

***trans*-2-*o*-Tolylcyclohexanol (1).**—This compound, prepared by the method of McKusick[9] for 2-*m*-tolylcyclohexanol, has been reported by Huitric, *et al.*[13,14] The yield from the synthesis of 1 mole of this alcohol was 86% after distillation, bp 90–92° (0.45 mm) (lit.[13] bp 103–104° (~1 mm)).

2-*o*-Tolylcyclohexanone (3).—Following the method outlined by Holum[15] a slurry of 200 g (2.0 moles) of chromium trioxide in 1400 ml of dry cold pyridine was prepared. To this mixture 114 g (0.6 mole) of **1** in 200 ml of pyridine was added and the reaction allowed to proceed at room temperature for 20 hr with stirring at a moderate rate. The reaction mixture was then diluted with about 6 l. of water and extracted several times with ether. The combined ether extracts were washed several times with 10% hydrochloric acid solution, followed by a single wash with 10% sodium carbonate and one wash with water, and dried over Drierite. Following filtration and solvent removal, the crude product crystallized (101 g, 89%) and was recrystallized

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[12] High Resolution NMR Spectra Catalog, Vol. 1, Varian Associates, Palo Alto, Calif., Spectrum 281.

[13] A. C. Huitric, T. C. West, R. A. Durbin, and G. H. Bryan, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 131 (1959).

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twice from *n*-hexane, Fisher-Johns mp 54-55° (lit.[16] mp 55.5-56.5°).

cis-**2-*o*-Tolylcyclohexanol (2).**—This alcohol was obtained by the reduction of **3** with triisobutylaluminum (K & K) in a modification of a procedure outlined by Haubenstock and Davidson[10] for the reduction of dihydroisophorone. To a stirred solution of 37.6 g of triisobutylaluminum in 200 ml of dry benzene under nitrogen a solution of 37.6 g (0.20 mole) of **3** in 120 ml of dry benzene was slowly added, maintaining the temperature below 40° by cooling in an ice bath. Stirring was continued for 15 min following the completion of the addition and then the reaction mixture was decomposed by slowly adding 100 ml of water. After acidification with hydrochloric acid, the benzene layer was separated and the aqueous layer extracted with benzene. The combined benzene solutions were washed once with 10% hydrochloric acid, then with water and dried over Drierite. Analysis of the crude reaction work-up by vpc on a Carbowax 20M column at 195° indicated three peaks in the ratio of 16:2:1, corresponding to **2**, **1**, and **3**, respectively, emerging from the column in that order. Following filtration and solvent removal, the crude product was distilled, bp 89-91° (0.35 mm). Recovery of materials was essentially quantitative (97%).

The *cis* alcohol **2** was separated from the other reaction products by column chromatography. The mixture was chromatographed over neutral alumina using benzene as the eluent; **3** and **2** eluted first. The mixtures of **3** and **2** obtained from these columns were rechromatographed over silica gel using petroleum ether (30-60°) and petroleum ether-benzene mixtures as eluents; **2** elutes first. Columns were generally prepared with 180 g of adsorbent effecting separation on 5 g of applied mixtures. Fraction analysis was carried out on a carbowax 20M column at 190°. The *cis* alcohol **2** isolated by this procedure was distilled at bp 82-84° (0.23 mm) (lit.[14] bp 76-78° (0.15-0.17 mm)).

(−)-Menthoxyacetic Acid (4) and (−)-Menthoxyacetyl Chloride (5).—The synthesis of these compounds is described.[11,17] The synthesis of **4** by a procedure slightly modified from that of Ingersoll[11] yielded a product with bp 114-116° (0.35 mm) and $[\alpha]^{25}_{D}$ −92.5 (*c* 10, 95% ethanol) (lit. bp 134-137° (2 mm),[17] $[\alpha]^{25}_{D}$ −91.5 (*c* 2, 95% ethanol[11])). The acid did not crystallize. The acid halide **5** was prepared using thionyl chloride as described by Ingersoll.[11] The excess thionyl chloride was removed under reduced pressure (water pump) and the product distilled *in vacuo*, bp 82-84° (0.4 mm) (lit.[11] bp 132° (10 mm)).

(±)-*trans*-2-*o*-Tolylcyclohexyl (−)-Menthoxyacetate (6 and 7).—This mixture of diastereomeric esters was prepared in 96% yield from **1** and **5** by the pyridine method as described by Ingersoll[11] for the synthesis of (±)-menthyl (−)-menthoxyacetate. The crude product was crystallized once from *n*-hexane: Fisher-Johns mp 63-66°; $[\alpha]^{26}_{D}$ −50.1 (*c* 5, chloroform).

(±)-*cis*-2-*o*-Tolylcyclohexyl (−)-Menthoxyacetate (8 and 9).—This mixture of diastereomeric esters was prepared from **2** and **5** by the pyridine method as described above for the synthesis of **6** and **7**. The solvent was removed *in vacuo*, $[\alpha]^{26}_{D}$ −47.5 (*c* 10, chloroform). All attempts to induce crystallization of this mixture of esters failed.

Separation of (+)-*trans*-2-*o*-Tolylcyclohexyl (−)-Menthoxyacetate (6).—Following the method of semisystematic recrystallization outlined by Ingersoll[11] for the resolution of (±)-menthyl (−)-menthoxyacetate, the separation of **6** was accomplished. The most suitable solvent was acetonitrile; differential solubility of the isomers in petroleum ether, *n*-hexane, carbon tetrachloride, chloroform, and dioxane was insufficient to produce significant separation. Progress of the separation was followed by melting point determination and nmr spectroscopy. After several recrystallizations, a few milligrams of seed crystals were obtained. The following is a typical separation. Approximately a 10% solution of the 50:50 mixture of esters in hot acetonitrile was allowed to cool to room temperature and seeded, and after several hours a first crop of crystals was collected by filtration and washed with cold acetonitrile. The filtrate, now somewhat diluted, was cooled to 10° and a second crop obtained. Under these conditions approximately 10% of the mixture was recovered as essentially pure **6**; the melting point was generally in the vicinity of 92-96°. Further attempts to secure more of this isomer in a relatively pure state by chilling the mother liquors proved fruitless. The solvent was removed and the residues saved for the elution chromatography procedure described below.

Recrystallization of the ester, mp 92-95°, twice from acetonitrile and once from *n*-hexane produced no change in melting point or specific rotation over the latter two recrystallizations: Kofler mp 95.2-96.4°; $[\alpha]^{27}_{D}$ −32.5 (*c* 10, chloroform). The nmr spectrum indicated only a single isomer.

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.48; H, 9.93.

Separation of (−)-*trans*-2-*o*-Tolylcyclohexyl (−)-Menthoxyacetate (7).—The separation of **7** was accomplished by column chromatography over neutral alumina of the residues from the above recrystallization process, using petroleum ether and petroleum ether-benzene mixtures 95:5. From 5 g of applied mixture to 180 g of adsorbent approximately 600-800 mg of essentially pure **7** was obtained. Analysis of fraction composition was by nmr spectroscopy. When contamination with the other ester **6** occurred, the column was immediately stripped (benzene and ethanol). The residues from the stripping of several columns were combined and the cycle of separation repeated starting with fractional recrystallization from acetonitrile.

The essentially pure **7** obtained by this process was recrystallized successively from acetonitrile, *n*-hexane, and acetonitrile with no change in melting point or specific rotation from the last two recrystallizations Kofler mp 79.0-80.0°; $[\alpha]^{28}_{D}$ −67.9 (*c* 10, chloroform). The nmr spectrum indicated a single isomer present.

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.35; H, 9.65.

Separation of (±)-*cis*-2-*o*-Tolylcyclohexyl (−)-Menthoxyacetate (8 and 9).—The separation of this mixture of esters was accomplished by column chromatography over neutral alumina as described for the isolation of **7**. In this case, however, the elution process was extended until the separation of both isomers was evident. The (−)-*cis* ester **9** elutes first. Fractions were analyzed by nmr spectroscopy.

Isolation of (−)-*cis*-2-*o*-Tolylcyclohexyl (−)-Menthoxyacetate (9).—This ester, which eluted first from the columns, was obtained in larger quantities and in purer state than its diastereomer **8**. The purest sample of **9** isolated was a viscous liquid, judged from its nmr spectrum to be at least 95% pure, $[\alpha]^{28}_{D}$ −143.5 (*c* 10, chloroform). The presence of **8** in the nmr spectrum of this sample was undiscernible.

Isolation of (+)-*cis*-2-*o*-Tolycyclohexyl (−)-Menthoxyacetate (8).—This ester was never isolated in pure state. The purest sample isolated, estimated from its nmr spectrum and specific rotation to be about 75% **8**, was a viscous liquid, $[\alpha]^{28}_{D}$ +3.22 (*c* 10, chloroform).

The hydrolysis of the separated esters is reported in another publication.[8] Hydrolysis of **6** gave (+)-*trans*-2-*o*-tolylcyclohexanol, $[\alpha]^{25}_{D}$ +70.6° (*c* 10, chloroform) and hydrolysis of **7** gave the levo enantiomer, $[\alpha]^{25}_{D}$ −70.6 (*c* 10, chloroform). Hydrolysis of a sample of **9** considered to be about 85% pure gave (−)-*cis*-2-*o*-tolylcyclohexanol, $[\alpha]^{25}_{D}$ −102° (*c* 0.128, methanol).[8] Ester **8** was not hydrolyzed.

Registry No.—**1**, 6125-71-9; **2**, 15315-32-9; **6**, 15315-33-0; **7**, 15315-34-1; **8**, 15352-72-4; **9**, 15315-35-2.

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The Palladium-Catalyzed Decarbonylation of β-Phenylisovaleraldehyde. A Notable Diminution of the Neophyl Rearrangement

JAMES W. WILT AND VICTOR P. ABEGG

Department of Chemistry, Loyola University,
Chicago, Illinois 60626

Received October 2, 1967

Recently Newman and Gill[1] described the preparation of neopentylbenzene by the decarbonylation of 3,3-dimethyl-4-phenylbutanal (1) (eq 1). They used a method earlier employed by Newman and Zahm[2]

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