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* To whom inquiries should be directed.

NMR Determination of Enantiomers of 7-Chloro-3,3a-dihydro-2-methyl-2*H*,9*H*-isoxazolo[3,2-*b*][1,3]benzoxazin-9-one Using Chiral Shift Reagent, Tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III)

PHILIP REISBERG*, IAN A. BRENNER, and JEROME I. BODIN

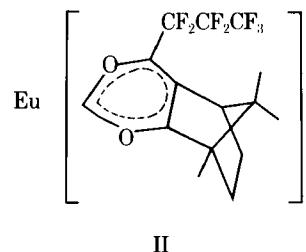
Abstract □ A simple NMR method was developed for the determination of the enantiomers of 7-chloro-3,3a-dihydro-2-methyl-2*H*,9*H*-isoxazolo[3,2-*b*][1,3]benzoxazin-9-one. Chiral shift reagent, tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III), causes the doublet assigned to the protons of the 2-methyl group, which normally appears at about 1.5 ppm, to split into two pairs of doublets and to shift downfield to about 2.0–3.5 ppm. The downfield pair of doublets represents the two enantiomers present in one racemate, designated as the β -form, while the upfield pair represents the enantiomers of the racemate designated as the α -form. From the integration of the area under the doublets, the relative concentration of all four enantiomers was determined.

Keyphrases □ NMR spectroscopy—determination, enantiomers of 7-chloro-3,3a-dihydro-2-methyl-2*H*,9*H*-isoxazolo[3,2-*b*][1,3]benzoxazin-9-one using europium chiral shift reagent □ Europium—chiral shift reagent, use in NMR determination of enantiomers of substituted isoxazolo[3,2-*b*][1,3]benzoxazin-9-one □ Enantiomers—substituted isoxazolo[3,2-*b*][1,3]benzoxazin-9-one, NMR determination using europium chiral shift reagent □ Chiral shift reagent, europium—use in NMR determination of enantiomers of substituted isoxazolo[3,2-*b*][1,3]benzoxazin-9-one

The use of deuterated tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium(III) shift reagent to determine the ratio of the diastereoisomers of 7-chloro-3,3a-dihydro-2-methyl-2*H*,9*H*-isoxazolo[3,2-*b*][1,3]benzoxazin-9-one¹ (I) was reported previously (1). An extension of this method to determine the enantiomers of each isomeric pair by use of the chiral shift reagent tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III) (II) has been successfully accomplished.

DISCUSSION

The use of lanthanide shift reagents in NMR spectroscopy in the last few years has been of great help in elucidating the struc-



tures of many organic compounds (2). With the introduction of the new optically active shift reagents (3), a new dimension was added to this approach. The chiral shift reagent can discriminate between enantiotropic groups and can separate peaks arising from the corresponding protons of a racemate. When the reagent is added to a chiral sample, pseudocontact shift differences are observed in the NMR spectrum.

The successful determination of the optical purity of different types of compounds has been reported (4, 5). Chiral shift reagents also have been used to distinguish *meso*- from *dextro*- or *levo*-diastereoisomers of dimethyl 2,3-diaminosuccinate (6). As with the nonchiral lanthanide shift reagents, the europium chiral complexes produced a downfield shift while the praseodymium chiral complexes did the reverse.

Since I has two optically active centers, it can exist as four different stereoisomers. In this work the presence of the four stereoisomers was investigated by use of the chiral shift reagent.

EXPERIMENTAL

Apparatus—Spectra were obtained at 60 MHz using an analytical spectrophotometer². A sweep time of 250 sec and a sweep width of 500 Hz were used, unless otherwise indicated; the δ -scale was used throughout. Tetramethylsilane (III), 1% (v/v) in deuterated chloroform³, was used as the internal reference from which chemical shifts were measured.

Reagents and Chemicals—Compound I, α - and β -forms, was used (1). For the chiral shift reagent, a 0.3 M solution of II was

¹ Previously referred to in the literature as W-2395.

² Varian T-60.

³ Norell Chemical Co., Landing, N.J.

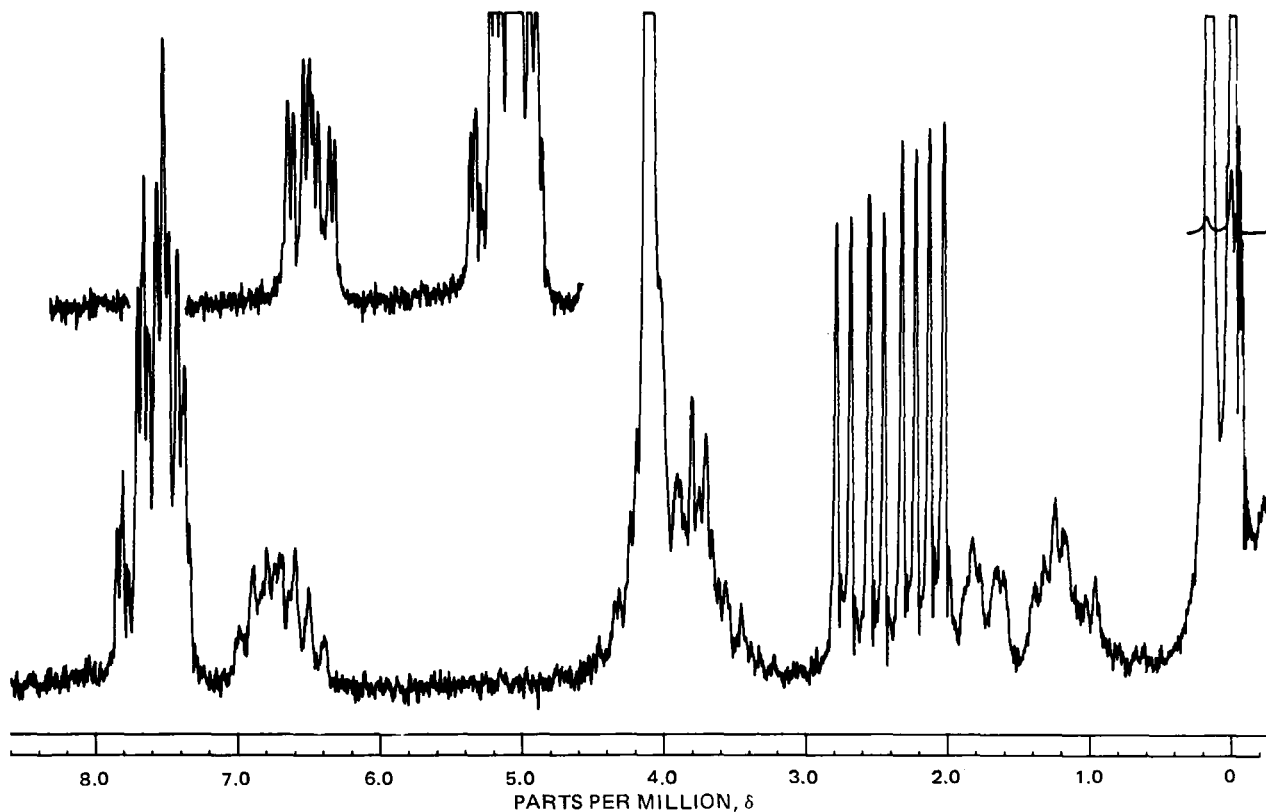


Figure 1—NMR spectrum of prepared mixture of I [α -form- β -form (1:1)] using chiral shift reagent (II) dissolved in deuteriochloroform as the solvent.

prepared using deuterated chloroform containing 1% of III as the solvent.

Procedure—Method A—A solution of 25 mg of the α -form and 25 mg of the β -form was prepared by dissolving them in 0.4 ml of

the chiral shift reagent. Then the NMR spectrum was obtained (Fig. 1).

Method B—A solution of 50 mg of I was obtained by dissolving it in 0.4 ml of the chiral shift reagent. The NMR spectrum was ob-

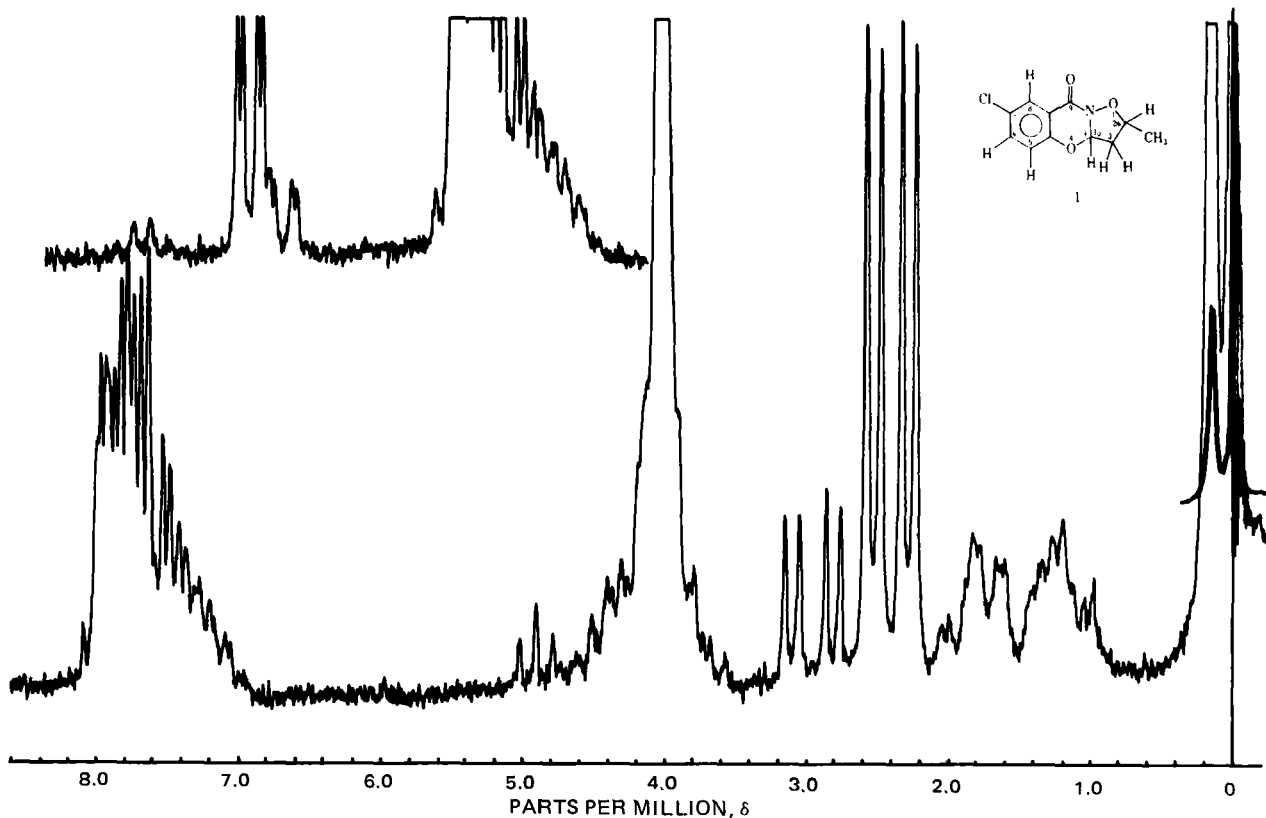


Figure 2—NMR spectrum of I using chiral shift reagent (II) dissolved in deuteriochloroform as the solvent.

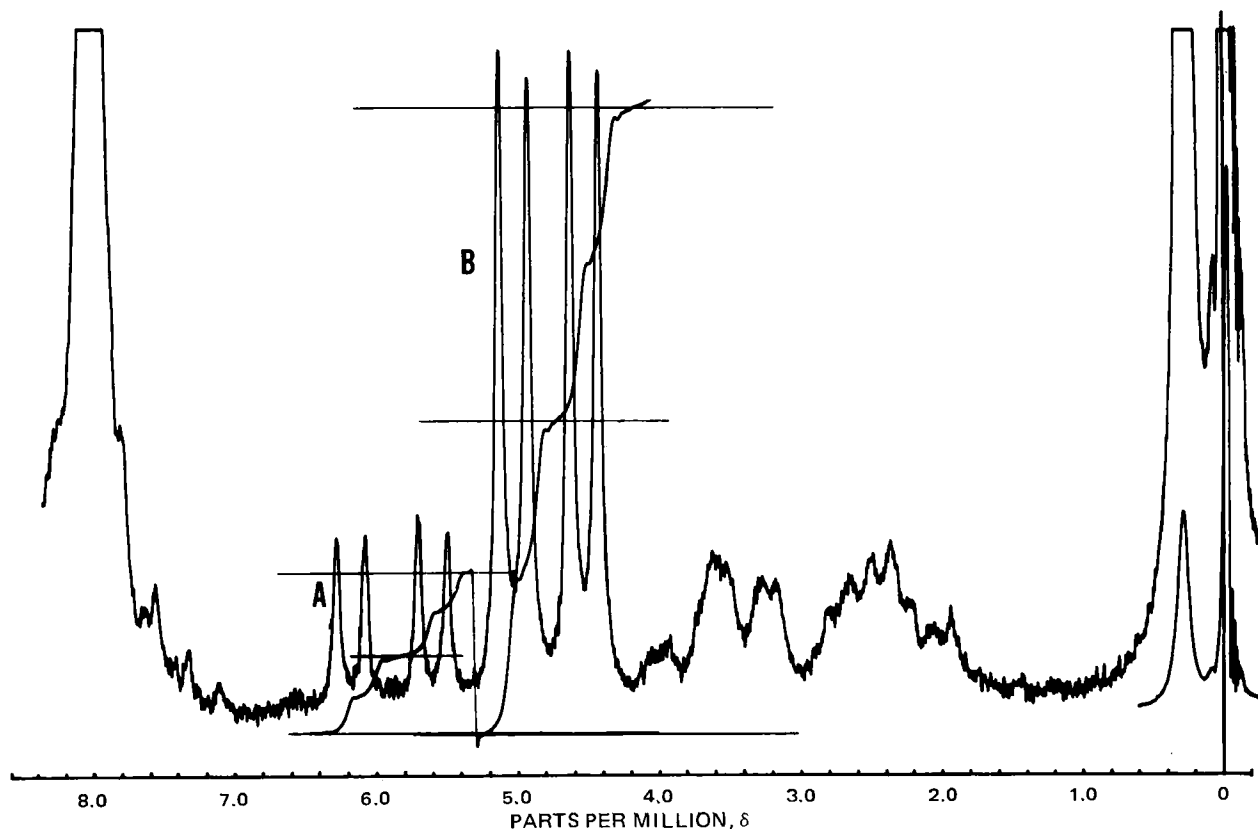


Figure 3—Expansion of Fig. 2 to 250-Hz sweep width. Key: A, average = 34.00; B, average = 129.64; α -form = 129.64 (79.2%); β -form = 34.00 (20.8%); and Compound I = 163.64 (100%).

tained at 500- and 250-Hz sweep widths (Figs. 2 and 3).

RESULTS

The NMR signal for the protons of the methyl group of the α - and β -forms of I appears as a pair of doublets in the 2.5–3.5-ppm region after addition of the lanthanide shift reagent (1). With the use of the chiral lanthanide shift reagent, the NMR signal for the protons of the methyl group of the α - and β -forms is further split into two pairs of doublets (Fig. 1). The two downfield doublets at about 2.5–3.0 ppm represent the two enantiomers present in the β -racemate, while two upfield doublets at about 2.0–2.5 ppm represent the two enantiomers present in the α -form.

The NMR signal for the protons of the methyl group in I in Figs. 2 and 3 also appears as two pairs of doublets; the two smaller downfield doublets correspond to the two enantiomers present in the β -form, while the two enantiomers of the α -form are found further upfield.

Integration of the area shows that I consists of a 79:21 mixture of the α - and β -racemates. The integrated values of the doublets of the α -form are equal to one another, and each represents 39.5% of the total area. The integrated values of the doublets of the β -form are also equal but only represent 10.5% of the total area. There is a slight difference in area for the enantiomers of the β -form, probably due to baseline elevation resulting in higher integral values.

By use of the chiral lanthanide shift reagent, the structure of I has been elucidated further.

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