fraction, and k_i is the rate constant for reaction of this conformation. For the compounds of this study, $k_{gauche} = 0$; thus $k_{obsd} = n_{anti}k_{anti}$. However, it should be noted that reservations have been expressed concerning this approach; e.g., E. L. Eliel, and J. Biros, *J. Am. Chem. Soc.*, **88**, 3334 (1966). For this approach to be valid in the case of *erythro*-**2**, the low n_{anti} would require a compensatory effect in the form of a higher k_{anti}. This is possible if exceptional steric strains are present in the ground state that are relieved in the transition state. However, the observation of a (roughly) successful log k vs. E_s correlation in two cases[17] would demand an extremely fortuitous balancing of n and k factors.

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Notes

Determination of the Enantiomeric Purity of Isoquinoline Alkaloids by the Use of Chiral Lanthanide Nuclear Magnetic Resonance Shift Reagents

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Since the discovery[1] that lanthanide shift reagents[2] are capable of inducing simplification and enhancement of resolution in NMR spectra of various Lewis bases, many new developments and refinements have been introduced. Whitesides and coworkers[3-5] and others[6-10] have reported that chiral lanthanide shift reagents shift the resonances of many enantiomeric organic substances to different extents. This finding provides a simpler method for the determination of enantiomeric purity than others presently employed.[11-16] On the other hand, the usual procedure of adding the shift reagent incrementally to the substrate in amounts approximating an equimolar ratio to maximize the shifts results in problems. The principal ones are loss of resolution, precipitation, peak broadening, and complexity of the spectrum (especially in polyfunctional compounds) because of signal overlap due to large shifts. In addition, the significant amount of time consumed in such a method led us to investigate the reliability and reproducibility of a simpler procedure.

In essence, the method consists of the addition of the shift reagent in an approximately 1:15 molar ratio directly to the compound dissolved in a suitable solvent in an NMR tube. The procedure utilizes low-frequency NMR spectrometers, only about 25 mg of reagent, and requires less than 0.5 hr for the analysis. Because most of these alkaloids[17] are polyfunctional in nature,[18] it has been determined that, by the use of a relatively small amount of chiral shift reagent as mentioned above, the resolution of the enantiomeric signals is sufficient to permit complete analysis with a high degree of precision even at these low reagent concentrations (see Figure 1). Any signal that meets the requirement of being sufficiently separated from the others and which will respond to the chiral shift reagent is satisfactory. Thus, in one case, it was the methoxyl and/or the aromatic proton signal (glaucine, laudanosine, *N*-methylpavine, tetrahydropalmatine) and, in the other, the methyl signal (the C_1 methyl of salsolidine). For any specific application, the investigator can quickly determine the appropriate signal to be used.

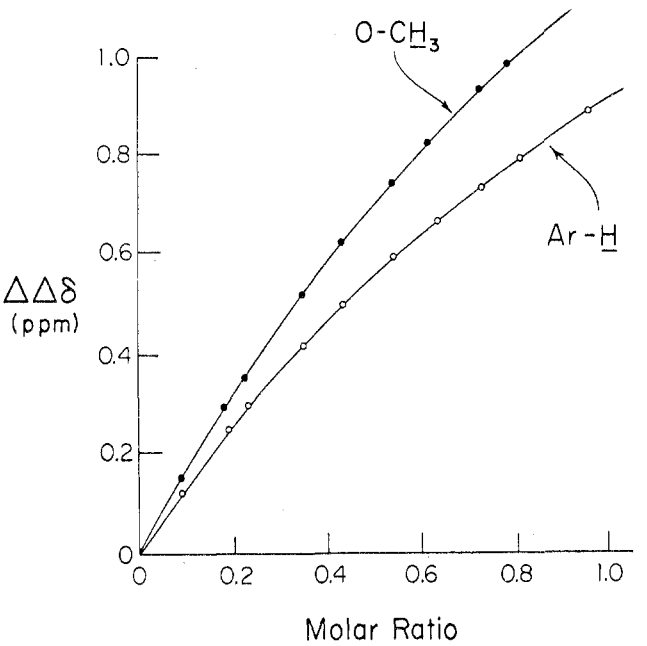

Figure 1. Plots of $\Delta\Delta\delta$ (parts per million) vs. molar ratio of Eu(facam)$_3$ chiral shift reagent to compound.

Five enantiomeric pairs were studied by this method with each representing a different class of isoquinoline alkaloids: (−)-(*S*)- and (+)-(*R*)-salsolidine (a simple tetrahydroisoquinoline alkaloid), (−)-(*R*)- and (+)-(*S*)-glaucine (an aporphine alkaloid), (−)-(*S*)- and (+)-(*R*)-tetrahydropalmatine (a protoberberine alkaloid), (−)-(*S,S*)- and (+)-(*R,R*)-*N*-methylpavine (a pavine alkaloid), and (−)-(*R*)- and (+)-(*S*)-laudanosine (a benzylisoquinoline alkaloid). Because both enantiomers were available to us for each compound, several mixtures (90:10, 80:20, 70:30, 60:40, and the racemic mixture of 50:50) were made up by weighing the two enantiomers in their respective proportions and then tested by the chiral NMR shift reagent procedure. These analyses agree very well with the expected results for the weighed mixtures of enantiomers. For the cases studied, the method accurately detects an enantiomeric mixture of 95:5.

The NMR spectrum of glaucine is well known[19-22] and serves as an example of the analysis (Figure 2a). Two characteristic signals were used for the determination of its enantiomeric composition: (a) the methoxyl singlet resonance at 3.68 ppm (upfield from the three remaining methoxyl singlets) and (b) the strongly deshielded C_{11} aromatic proton at 8.11 ppm. Addition of Eu(facam)$_3$ to a solution of

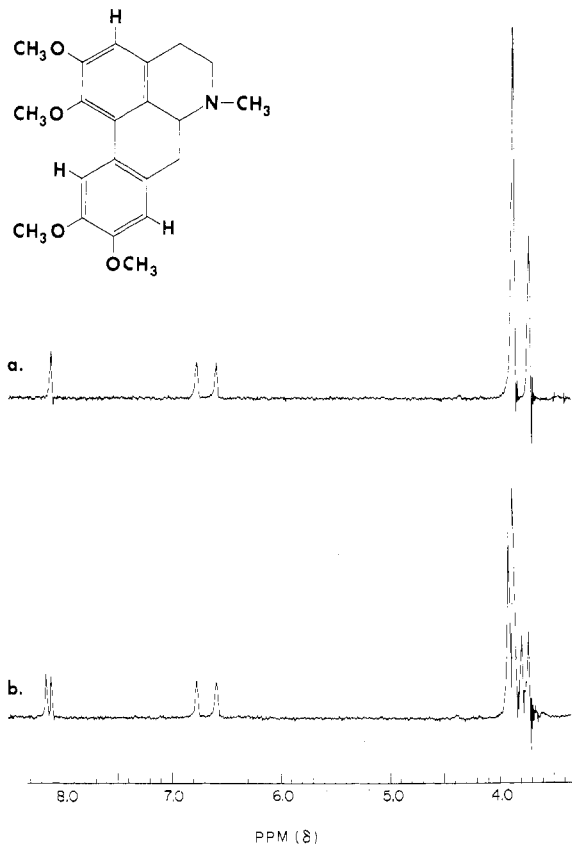

Figure 2. (a) The NMR spectrum of a 0.5 *M* solution of (±)-(*S*)-glaucine in $CDCl_3$ using an A-60D Varian Associates NMR spectrometer; (b) the NMR spectrum after the addition of a 0.033 *M* solution of Eu(facam)$_3$ in $CDCl_3$.[28]

(±)-glaucine in $CDCl_3$ caused both of the singlet resonances for the C_{11} aromatic and the C_1 methoxyl protons to be split into two equal signals (Figure 2b), with the *S* enantiomer shifting 0.05 ppm in each case. Several integrations, as well as actual weighings of the tracings of the expanded area below the signals, showed the expected 50:50 ratio of the enantiomers.

The determination of enantiomeric purity is a concern of all natural product chemists but has been exceptionally useful to us in following the progress of resolutions of racemic mixtures and/or the racemization of enantiomers frequently used in our laboratories. Since the method does not require the possession of both, or even one, of the enantiomers in pure form, direct determination of the relative enantiomeric concentrations is thus possible with a single scan NMR spectrum of any aliquot without resorting to the tedious procedures of separation and identification.

It is our hope that this report will demonstrate the remarkable simplicity and reliability inherent in the use of small amounts of chiral lanthanide NMR shift reagents for the determination of the enantiomeric purity of many optically active isoquinoline and related alkaloids.

Experimental Section

The NMR spectra were determined on a Varian A-60D spectrometer. Several mixtures were made up by weighing the two enantiomers in their respective proportions (50:50, 60:40, 70:30, 80:20, and 90:10) and dissolving them in $CDCl_3$ to form a 0.5 *M* solution. The shift reagent, Eu(facam)$_3$,[23] was weighed and added to the enantiomeric mixture to give a reagent concentration of 0.033 *M*. This ratio of substrate to reagent (15:1) effected the desired separation of signals in almost all cases. Occasionally, in specific areas, this ratio was altered slightly to achieve the best separation. Several machine integrations of the area below each separated enantiomeric peak are adequate for a reasonably precise analysis. Other integration procedures have been performed and are recommended for more accurate analyses (e.g., weighing of the tracings of the expanded area below the signals, use of a compensating polar planimeter, etc.), although the simpler method usually supplies the experimentally needed information.

All of the enantiomers tested by this procedure are known compounds, a few of which were commercially available. Synthesis, spectral, and analytical data for the others are reported elsewhere.[24]

Salsolidine. The (±) form was obtained by the Bischler–Napieralski cyclization of *N*-acetylhomoveratrylamide and resolution with the appropriate *O,O*-dibenzoyltartaric acids via the bitartrates provided the required enantiomers.[24a]

Glaucine. The (+) form was obtained from Pierce Chemical Co. The (−) form was obtained by racemizing the (+) form under catalytic hydrogenation conditions described by Kametani et al.[25] and applied by Genenah.[24a] Resolution by bitartrate formation using L-tartaric acid provided the (−) isomer.

Tetrahydropalmatine. Both enantiomers of this base were available as the hydrochlorides from Pierce Chemical Co.

***N*-Methylpavine.** The racemic form was prepared by the method of Battersby and Binks[26] and the enantiomeric forms were obtained by the use of the enantiomeric tartaric acids to provide the appropriate bitartrates.

Laudanosine. The method of Mirza[27] was used to obtain the racemic form from papaverine methiodide. The enantiomers were obtained through bitartrate formation with the appropriate *O,O*-dibenzoyltartaric acids.[24a]

Registry No.—(−)-(*S*)-Salsolidine, 493-48-1; (+)-(*R*)-salsolidine, 54193-08-7; (−)-(*R*)-glaucine, 38325-02-9; (+)-(*S*)-glaucine, 475-81-0; (−)-(*S*)-tetrahydropalmatine, 483-14-7; (+)-(*R*)-tetrahydropalmatine, 3520-14-7; (−)-(*S,S*)-*N*-methylpavine, 6901-16-2; (+)-(*R,R,*)-*N*-methylpavine, 16584-62-6; (−)-(*R*)-laudanosine, 85-63-2; (+)-(*S*)-laudanosine, 2688-77-9.

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