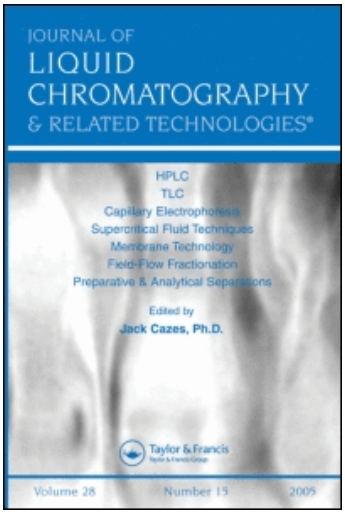

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SEPARATION OF R(+)-AND S(-)-BENZYL-3-TETRAHYDROFUROATES USING TWO DIFFERENT CHIRAL COLUMNS

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ABSTRACT

A chiral separation of R(+)-and S(-)-benzyl-3-tetrahydrofuroate (I) and p-nitrobenzyl-3-tetrahydrofuroate (II) using a Chiralcel OB® (cellulose tribenzoate) column with a hexane/2-propanol (60:40 v/v) mobile phase is described. Enantiomeric purity of R(+)-I was evaluated using the same chromatographic conditions. I was also separated using a Chiralspher® (polyamides bonded to silica gel) column with an ethanol/distilled water (50:50 v/v) mobile phase.

INTRODUCTION

The synthesis (1) and resolution of 3-tetrahydrofuroic acid via its quinine salt have been previously reported (2).

The present note describes an HPLC method for the chiral separation of the enantiomers of benzyl-3-tetrahydrofuroate using

two different analytical chiral columns. P-nitrobenzyl-3-tetrahydrofuroate and enantiomerically enriched benzyl-3-tetrahydrofuroate were also evaluated using a cellulose tribenzoate column.

MATERIALS AND METHODS

Chromatographic System

The HPLC system consisted of a Waters Model 6000A high pressure pump, 440 UV absorbance detector with a 254 nm filter, and WISP® automatic injection system (Milford, MA). The chiral columns used were 10 μm Chiralcel OB® (cellulose tribenzoate) packed in a 25 cm by 0.46 (id) cm column from J. T. Baker (Phillipsburg, NJ) and a 5 μm Chiralspher® (polyamides bonded to silica gel) packed in a 25 cm by 0.4 (id) cm column from Curtin-Matheson Scientific (Elk Grove Village, IL).

Chemicals

HPLC grade hexane and 2-propanol were purchased from Curtin-Matheson Scientific (Elk Grove Village, IL). Water was triple distilled using a milli-Q-reagent water system from Continental Water System (El Paso, TX). The 95% ethanol was purchased from U.S. Industrial Chemical Co., (Houston, TX). The 3-tetrahydrofuroic acid was prepared by catalytic reduction of 3-furoic acid (1) and subsequently esterified to obtain the benzyl and the p-nitrobenzyl derivatives. Resolution of 3-tetrahydrofuroic acid via its quinine salt yielded acid with the same value for a rotation as that obtained by Hill and Schearer (2).

Chromatographic Conditions

Hexane/2-propanol (60:40 v/v) at a flow rate of 1 mL/min and a Chiralcel OB® column were used to analyze racemic p-nitro-

benzyl-3-tetrahydrofuroate as well as racemic and R(+)- benzyl-3-tetrahydrofuroate.

When the Chiralspher® column was used, the mobile phase was changed to ethanol/distilled water (50:50 v/v) at a flow rate of 0.5 mL/min. All samples were prepared in the respective mobile phase.

RESULTS

The structures of benzyl-3-tetrahydrofuroate and p-nitrobenzyl-3-tetrahydrofuroate are shown in (Figure 1). Using the chromatographic conditions described in the Methods section, the Chiralcel OB® column separated the enantiomers of benzyl-3-tetrahydrofuroate (Figure 2A) and p-nitrobenzyl-3-tetrahydrofuroate (Figure 2B). The R(+)- and S(-)- enantiomers of benzyl-3-tetrahydrofuroate eluted at 9 and 11 minutes, respectively using a mobile phase of hexane/2-propanol (60:40 v/v). With the same mobile phase, the R(+)- and S(-)- enantiomers for p-nitrobenzyl-3-tetrahydrofuroate eluted at 32 and 39 minutes, respectively. An enriched sample of R(+)- benzyl-3-tetrahydrofuroate, prepared from R(+)- furoic acid resolved by multiple recrystallization of the quinine salt, was separated as shown in (Figure 3). In addition, enantiomeric separation of racemic benzyl-3-tetrahydrofuroate was also achieved using a Chiralspher®

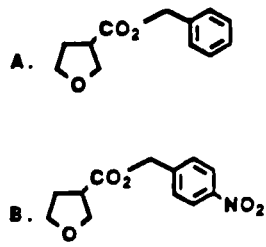

Figure 1. Structures of benzyl-3-tetrahydrofuroate (A) and p-nitrobenzyl-3-tetrahydrofuroate (B).

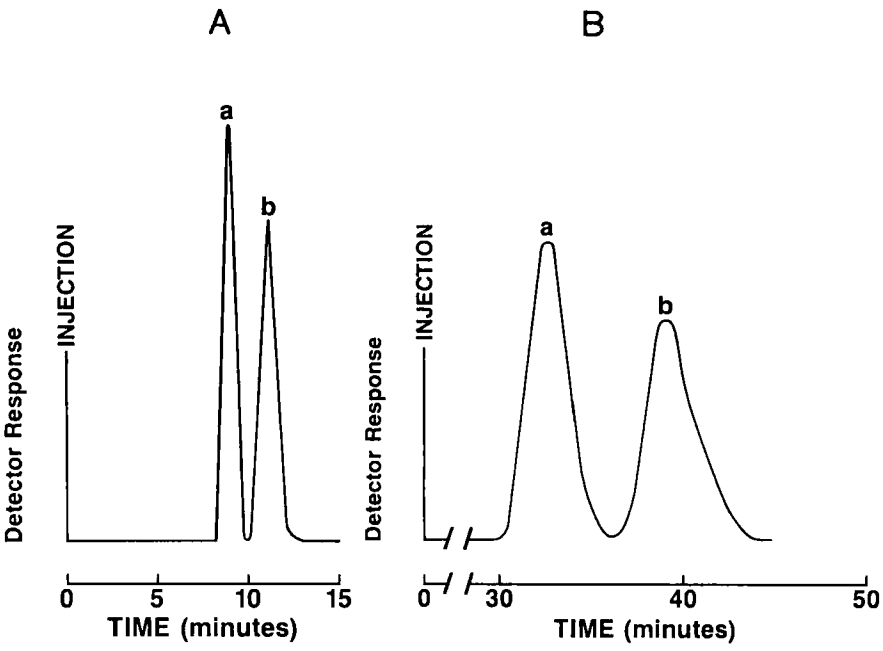

Figure 2. HPLC separation of racemic benzyl-3-tetrahydrofuroate (2A) and p-nitrobenzyl-3-tetrahydrofuroate (2B) using a Chiralcel OB® column.

(polyamides bonded to silica gel) column (Figure 4). The retention of the R(+)- and S(-)- enantiomers for benzyl-3-tetrahydrofuroate using a mobile phase of ethanol/distilled water (50:50 v/v) was 8 and 10.5 minutes, respectively.

DISCUSSION

The separation mechanisms of the Chiralspher® and Chiralcel OB® columns are different. The Chiralspher® column uses direct diastereomeric interaction between the asymmetric atom of the compound and individual optically active residues of the chiral packing, and the inclusion of the enantiomers into

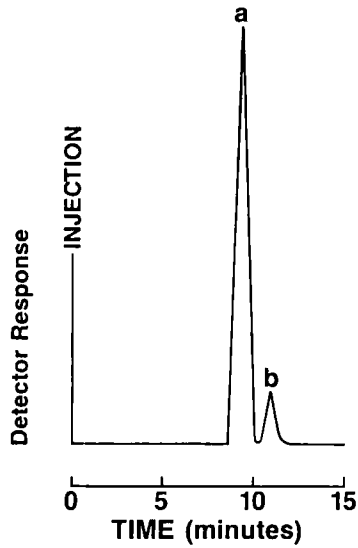

Figure 3. Chromatography of enantiomerically enriched R(+)-enantiomer of benzyl-3-tetrahydrofuroate.

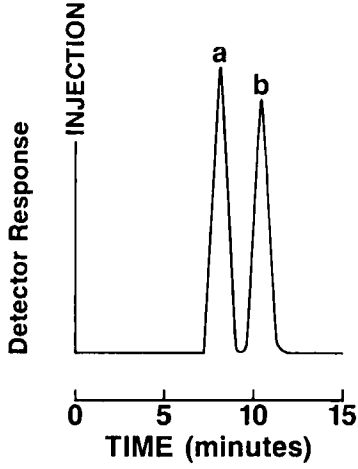

Figure 4. HPLC separation of racemic benzyl-3-tetrahydrofuroates into its two enantiomers using a Chiralspher® chiral column.

asymmetric cavities of the polymer structure. The main absorbing force is hydrogen bonding between polar groups of the enantiomers and the amide groups of the polymer (3).

In contrast, the Chiralcel OB® column's separation is based on a multi-mode mechanism of hydrogen bonding, pi-pi electron interactions, dipole stacking and/or inclusion complexes (3). Although the separation mechanism for the two columns are different, a baseline separation for the enantiomers of benzyl-3-tetrahydrofuroates was achieved within 15 minutes for both columns using different chromatographic conditions. The addition of the p-nitro group to the benzyl ring dramatically increased the retention of the enantiomers using Chiralcel OB® column and the same mobile phase conditions. This indicates that small changes in structure dramatically affect retention in the multi-mode separation mechanism of the Chiralcel OB® column.

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