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Note

Resolution of enantiomeric drugs of some β-amino alcohols as their urea derivatives by high-performance liquid chromatography on a chiral stationary phase

QING YANG*, ZENG-PEI SUN and DA-KUI LING
National Institute for the Control of Pharmaceutical and Biological Products, Beijing (China)
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Compounds with a β-amino alcohol functional group are widely used as therapeutic agents. According to their pharmacological action, they may be divided into three main categories: (1) vasoconstrictors (*e.g.*, ephedrine); (2) hypertensive agents (*e.g.*, methoxamine, epinephrine); and (3) β-receptor blocking agents (*e.g.*, propranolol, alprenolol). All of them contain chiral centers. Their optical isomers may have different biological activities.

The enantiomeric separation of β-amino alcohol compounds with a commercially available (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine chiral stationary phase (Pirkle-type DNBPG column) were reported by Wainer and co-workers, also condensed the amino alcohols either with β-naphthaldehyde to form oxazolidine derivatives[1,2] or with phosgene to form oxazolidone derivatives[3–5]. Both derivatization reactions require the reaction mixture to be cooled and stirred or refluxed for a long period.

We have previously reported the enantiomeric separation of derivatives of amines and alcohols with α-naphthyl isocyanate on a DNBPG column[6]. In this paper, we report the synthesis and direct resolution of a series of urea derivatives of β-amino alcohols using the same reagent.

EXPERIMENTAL

Apparatus

High-performance liquid chromatography (HPLC) was carried out with a Series 3B liquid chromatograph pump (Perkin-Elmer, Norwalk, CT, U.S.A.), an SPD-1 variable-wavelength UV–VIS detector (Shimadzu, Kyoto, Japan) set at 254 nm and sensitivity 0.04 a.u.f.s., a Perkin-Elmer 023 recorder set at a chart speed of 2.5 mm/min and a Model 7105 injector (Rheodyne, Cotati, CA, U.S.A.).

The covalently bonded Pirkle-type 1-A column (21 cm × 4 mm I.D.) was packed with 5-μm spherical particles of γ-aminopropylsilica modified with DNBPG prepared as described elsewhere[7]. The flow-rate of the mobile phase [*n*-hexane–isopropanol–acetonitrile (90:10:2)] was 2 ml/min.

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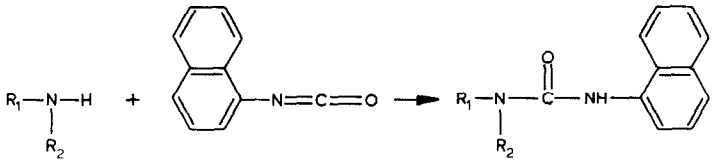
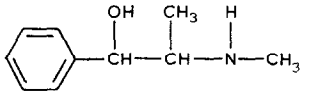
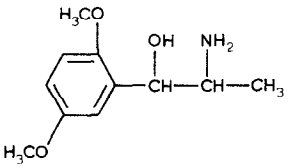
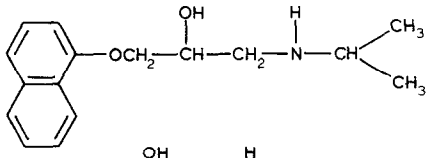
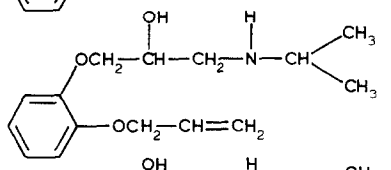
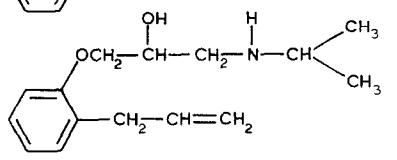
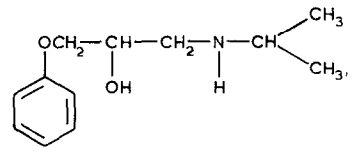
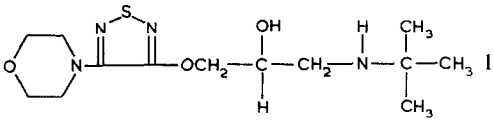
TABLE I

SEPARATION OF α-NAPHTHYL ISOCYANATE DERIVATIVES OF β-AMINO ALCOHOLS ON A PIRKLE-TYPE DNBPG COLUMN



Compound	*Structure*	k'_1*	α	R_s	*First-eluted enantiomer***
Ephedrine		23.26	1.03	0.76	*d*
Methoxamine		28.53	1.11	1.14	
Propranolol		19.76	1.25	1.61	
Oxprenolol		7.65	1.19	2.0	
Alprenolol		7.84	1.19	2.09	
Metroprolol***		20.64	1.14	1.54	
Timolol§		15.0	1.13	1.08	*l*

* Capacity factor of the first-eluted enantiomer.

** Configuration of the α-naphthyl isocyanate derivative moiety of β-amino alcohol.

*** Mobile phase, *n*-hexane–isopropanol–acetonitrile (90:10:1); flow-rate, 2.5 ml/min.

§ Mobile phase, *n*-hexane–isopropanol–acetonitrile (95:5:3.5); flow-rate, 2.5 ml/min.

Chemicals and reagents

The *l*- and *d*-ephedrine, *l*- and *d*-timolol and racemic methoxamine, propranolol, alprenolol, metroprolol and oxprenolol should be in the free base form; if not, they must be converted from the salts to the free bases by adding aqueous ammonia and then extracting with chloroform.

α-Naphthyl isocyanate (analytical-reagent grade) was purchased from BDH (Poole, U.K.). Acetonitrile (HPLC-grade; State Huang Yan Chemical Experimental Factory, China), isopropanol (analytical-reagent grade; Beijing Chemical Plant, China), which was treated with Linde type 5 Å molecular sieves and filtered, and *n*-hexane (analytical-reagent grade, Beijing 52952 Chemical Plant, China) were purchased.

Preparation of derivatives

Each β-amino alcohol was dissolved in toluene and a 10% excess of α-naphthyl isocyanate reagent was added. The mixture was shaken and kept at room temperature for 15–20 min. Finally, it was diluted with the mobile phase and chromatographed.

Order of enantiomeric elution

The *l*- and *d*-isomers were identified by comparing the chromatograms for the *l*-isomer and the racemic mixture.

RESULTS AND DISCUSSION

Björkqvist[8] has reported that phenyl isocyanate can react with amines, alcohols, water, phenols and carboxylic acids, amines showing the fastest reaction rate at room temperature. A reaction time of 5–15 min is usually sufficient for complete reaction. A single and stable derivative is obtained even with primary amines. Phenyl isocyanate has proved to be an excellent derivatizing reagent for compounds with active hydrogen atoms. These characteristics also apply to α-naphthyl isocyanate. The isocyanate group reacts rapidly and selectively with primary and secondary amines under mild conditions to form the corresponding urea derivatives[6]. As ephedrine, propranolol and related β-adrenegic antagonists are, in general, secondary amines, it appeared worthwhile examining the applicability of α-naphthyl isocyanate to the resolution of the enantiomers of these drugs. The results are given in Table I.

All of the enantiomers in Table I were well resolved when they were converted into the corresponding urea derivatives. Details of the isolation and identification of some of these derivatives have been given elsewhere[9].

The results demonstrate that the procedure has several advantages, such as simple operation, rapid derivatization, good resolution and few by-products. It is concluded that the derivatization of β-amino alcohols with α-naphthyl isocyanate is a useful technique for the separation of their enantiomers by HPLC on a Pirkle-type DNBPG column.

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