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Note

Improved gas chromatographic enantiomer separation of pharmaceutically relevant amino alcohols as oxazolidinones

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The increasing therapeutical application of β-blocking agents[1] has resulted in an increasing demand for specific and sensitive methods for the analysis of these drugs. Liquid[2,3] and gas chromatographic[4–7] techniques were developed for monitoring and separating β-blockers. Among several procedures for stereochemical analysis of β-blockers, the formation and separation of diastereomers by liquid[8,9] and gas chromatography (GC)[8,10] as well as direct enantiomer separation using chiral stationary phases have been applied. Only recently we have demonstrated the use of a chiral polysiloxane XE-60-L-valine-(*R*)-α-phenylethylamide[11] for enantiomer separation of N,O-heptafluorobutyryl derivatives by capillary GC[12]. In this communication we describe an improved and more convenient procedure for direct enantiomer separation of β-blocking and related drugs.

EXPERIMENTAL

Gas chromatography

A Carlo Erba Model 2101 gas chromatograph with split inlet and a flame ionization detector was used.

Preparation of chiral capillary columns

The procedure was described in ref. 12.

Formation of oxazolidin-2-one derivatives[6,13]

Amounts of about 1 mg of amino alcohol were dissolved or suspended in 400 μl of diethyl ether in a screw-cap vial and 50 μl of a 0.5 *N* aqueous solution of sodium hydroxide were added. The mixture was shaken and 30 μl of a 20% solution of phosgene in toluene were added to the mixture with a syringe. The mixture was shaken occasionally and the ether layer was transferred to a new vial after 1 h of reaction time at room temperature. After evaporation to dryness in a stream of nitrogen, 400 μl of dichloromethane were added. After removal of the solvent together with traces of water in a stream of dry nitrogen, the sample was dissolved in 200 μl of dichloromethane. About 0.2 μl of this solution were sufficient for one GC injection.

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RESULTS AND DISCUSSION

Although phosgene has only occasionally been used as a derivatizing agent in GC[14], it was shown to form stable oxazolidin-2-ones (2-oxazolidones) with α-amino alcohols even in aqueous media[6]. In a recent communication of Wainer *et al.*[13] the chemistry of the formation of oxazolidin-2-ones and the cleavage of the derivatives of chiral norephedrine were studied in detail. It could be demonstrated by comparing the optical rotation before and after derivatization and regeneration that no racemization occurs during these reactions, a very important fact when small amounts of enantiomeric impurities are to be studied. The separation of the oxazolidin-2-one derivatives of norephedrine enantiomers by high-performance liquid chromatography on a chiral support[13] also demonstrates the presence of enantioselective molecular interaction with these derivatives.

We prepared the oxazolidin-2-one derivatives of ephedrine, pseudoephedrine and norephedrine by a reaction of phosgene with the amino alcohols in ether solution with the addition of a small amount of aqueous sodium hydroxide. Excellent yields of the derivatives are obtained at room temperature in short reaction times and without noticeable racemization. The enantiomers could be completely separated on a short pyrex glass capillary column with the chiral stationary phase XE-60-L-valine-(*R*)-α-phenylethylamide (Fig. 1). The same procedure was applied to the β-block-

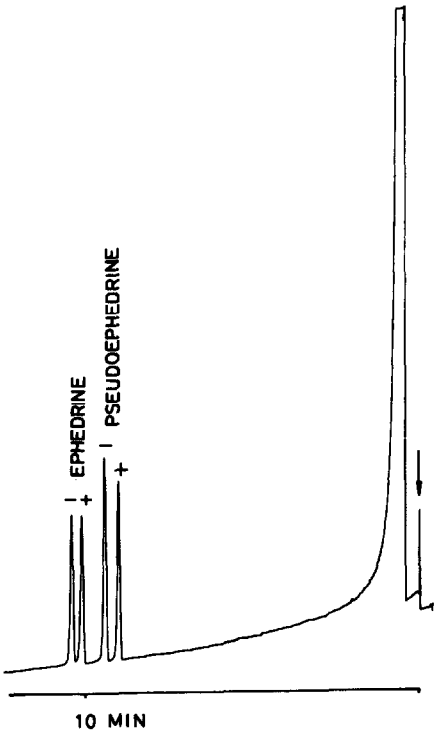

Fig. 1. Separation of the enantiomers of pseudoephedrine and ephedrine as oxazolidin-2-one derivatives. 18-m pyrex glass capillary column with XE-60-L-valine-(*R*)-α-phenylethylamide. Column temp. 165°C; 0.8 bar H_2.

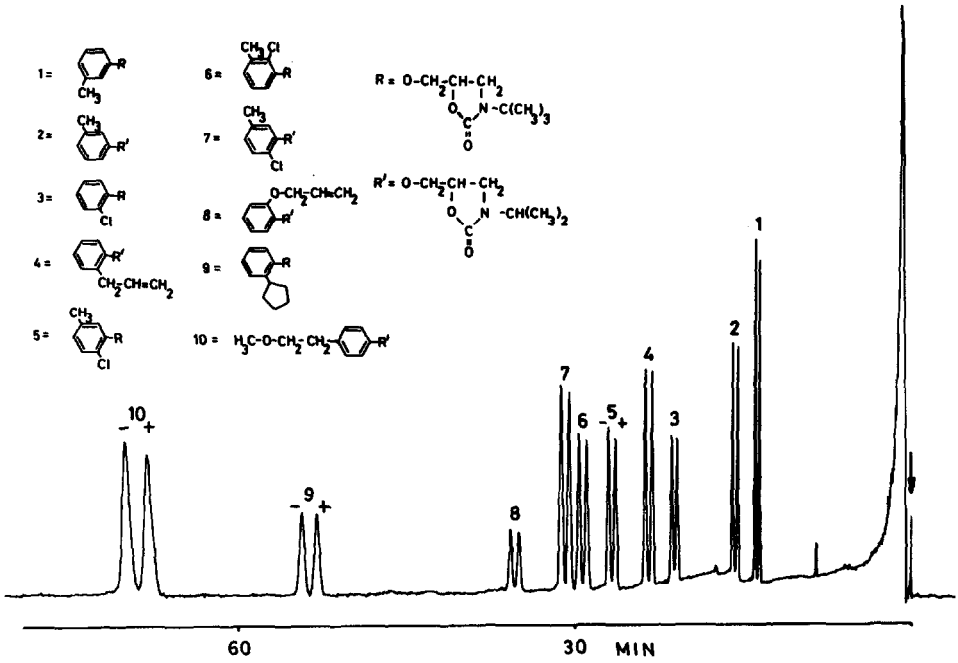

Fig. 2. Separation of the enantiomers of β-adrenergic drugs as oxazolidin-2-one derivatives. 18-m pyrex glass capillary column with XE-60-L-valine-(*R*)-α-phenylethylamide. Column temp. 195°C; 0.8 bar H_2. Peaks: 1 = dechlorobupranolol, 2 = toliprolol, 3 = demethylbupranolol, 4 = alprenolol, 5 = bupranolol, 6 = 2-chlorobupranolol, 7 = isopropylbupranolol, 8 = oxprenolol, 9 = penbutolol, 10 = metoprolol.

TABLE I

SEPARATION FACTORS (α) AND COLUMN TEMPERATURES FOR ENANTIOMER SEPARATION OF α-AMINO ALCOHOLS AS OXAZOLIDIN-2-ONE DERIVATIVES

Separation was carried out on an 18-m pyrex glass capillary column coated with XE-60-L-valine-(*R*)-α-phenylethylamide.

Racemate	*α-value*	*Column temp. (°C)*
Ephedrine*	1.040	165
Pseudoephedrine*	1.047	165
Norephedrine	1.026	195
Dechlorobupranolol	1.028	195
Toliprolol	1.029	195
Demethylbupranolol	1.021	195
Alprenolol	1.029	195
Bupranolol*	1.025	195
2-Chlorobupranolol	1.023	195
Isopropylbupranolol	1.022	195
Oxprenolol	1.023	195
Penbutolol*	1.025	195
Metoprolol*	1.031	195
Propranolol	1.031	195
Bunitrolol	1.018	195
Metipranolol	1.034	195

* (−) enantiomer elutes after (+) enantiomer.

ing drugs listed in Table I. For the first time a complete separation of the N-*tert.*-butyl-substituted β-blockers such as bupranolol and penbutolol was achieved. The type of N-substituent does not seem to influence the formation and separation of the oxazolidin-2-one derivatives. In all cases where pure enantiomers were available the (*S*) (−)-isomers were eluted after the (*R*) (+)-isomers (Fig. 2). Derivatization and chromatography of pure enantiomers gave only one peak and no indication for racemization. Although the volatility of the oxazolidin-2-one derivatives is somewhat lower than that of the heptafluorobutyryl derivatives, the oxazolidin-2-ones seem to be much more stable. They could also be eluted from commercial fused-silica capillaries (Chrompack) without any difficulty and they were stable in dichloromethane solution for a period of weeks, in contrast to the perfluoroacyl derivatives, which are highly sensitive to active sites in the chromatographic system and to humidity[15].

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