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Note

Resolution of norephedrine as its 2-oxazolidone derivative: enantiomeric separation on a chiral high-performance liquid chromatographic stationary phase and preparative regeneration of the resolved isomers

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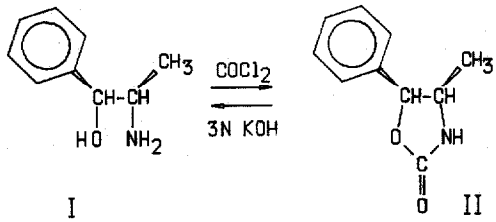
Norephedrine (I, phenylpropanolamine, Fig. 1) is a sympathomimetic agent widely used as a nasal decongestant, bronchodilator and anorexic. More than 125 commercial preparations containing this substance are available in the U.S.A. Norephedrine is also a useful starting point for stereospecific syntheses. For example, the resolved enantiomers have been utilized in the synthesis of α-aminopropiophenones[1] and of α-substituted carboxylic acid derivatives[2]. Because of the broad applicability of norephedrine, the analytical and preparative resolution of its enantiomers has received a great deal of attention.

Analytical methods using indirect (diastereomers) and direct (chiral stationary phases, CSPs) approaches have been reported. Beckett and Testa[3] and Kruse *et al.*[4] used gas chromatography (GC) to resolve norephedrine as diastereomeric amides. Saeed *et al.* [5], König and Benecke[6] and Benecke *et al.*[7] used GC CSPs to resolve norephedrine as enantiomeric amides. Although these methods readily determine the enantiomeric composition of norephedrine, they are difficult to adapt to large scale preparation of the resolved enantiomers.

Preparative resolutions of norephedrine have been reported by several investigators. Berrang *et al.*[1] resolved norephedrine by recrystallization of diastereomeric salts using *o,o*-dibenzoyl-D-tartaric acid as the counter ion. Prelog *et al.*[8] and Domon *et al.*[9] separated the enantiomers by partitioning between two liquid phases. These



I II

Fig. 1. The reaction of norephedrine (I) with phosgene to form 4-methyl-5-phenyl-2-oxazolidone (II).

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preparative methods are not readily useful as analytical probes of enantiomeric purity, however.

We report here the development of a direct enantiomeric high-performance liquid chromatographic (HPLC) resolution of norephedrine which can be used as both an analytical probe of enantiomeric purity and as a preparative method. Our approach involves condensation of norephedrine with phosgene to form the enantiomeric 4-methyl-5-phenyl-2-oxazolidones, followed by resolution of the isomers by HPLC on a commercially available CSP. The resolved norephedrine can then be regenerated for preparative purposes by alkaline hydrolysis of the derivative, with complete retention of configuration.

EXPERIMENTAL

Apparatus

The chromatography was performed with a Spectra-Physics (Santa Clara, CA, U.S.A.) Model 8000 liquid chromatograph equipped with an SP 8000 data system and a Spectra-Physics Model 8310 UV–visible detector. The column was a stainless-steel Regis-packed Pirkle covalent phenylglycine preparative column (25 cm × 10 mm I.D.) with a silica packing of 5-μm spherical particles which were first derivatized with γ-aminopropyl groups; the terminal amine was then linked to (*R*)-N-(3,5-dinitrobenzoyl)phenylglycine via amide linkages (Regis Chemical, Morton Grove, IL, U.S.A.). ^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a 200 MHz Fourier transform NMR spectrometer (Varian XL-200; Varian Associates, Instrument Group, Palo Alto, CA, U.S.A.). Optical rotations were measured with a Model 241MC Polarimeter (Perkin-Elmer, Norwalk, CT, U.S.A.). Mass spectra were obtained with a double-focusing, electron-impact mass spectrometer (Varian MAT 311A, Finnigan MAT, San Jose, CA, U.S.A.).

Materials

The (+)-enantiomer of norephedrine and racemic norephedrine were obtained as the hydrochloride salts from Aldrich (Milwaukee, WI, U.S.A.). Phosgene, 12.5% in toluene, was purchased from MCB (Gibbstown, NJ, U.S.A.). The HPLC solvents were purchased from Burdick E Jackson (Muskegon, MI, U.S.A.). The remaining chemicals and solvents were reagent grade and were used as purchased.

Oxazolidone synthesis

Racemic and enantiomerically pure 4-methyl-5-phenyl-2-oxazolidones were synthesized from the respective hydrochloride salts of norephedrine according to the procedure described by Hyne[10]. In a typical run using the racemate, a vigorously stirred mixture of norephedrine hydrochloride (0.740 g, 0.004 mole), 12 ml 10% sodium hydroxide solution and 20 ml diethyl ether was cooled to 0°C and 9.4 ml of 12.5% phosgene in toluene was added dropwise. The mixture was stirred for 1 h. The organic layer was then collected, dried over anhydrous sodium sulfate, and evaporated under reduced pressure, and the solid residue was recrystallized from absolute ethanol.

Regeneration of norephedrine

Norephedrine was regenerated via the hydrolysis of the 2-oxazolidone according to the procedure described by Teng and Bruce[11]. In a typical run, the oxazolidone (1.77 g, 0.01 mole) was added to a solution of 28 ml 3 *N* potassium hydroxide solution and 28 ml methanol; the mixture was then refluxed for 5 h. The methanol was then evaporated under reduced pressure and the remaining mixture was extracted with methylene chloride. The methylene chloride layer was collected, dried over sodium sulfate and evaporated. The solid residue was then dissolved in ethanol and hydrogen chloride gas was bubbled through the solution. After evaporation of the solvent, the norephedrine hydrochloride was recrystallized from a solution of ethanol and diethyl ether.

HPLC conditions

The mobile phase consisted of 97 parts hexane to which were added 3 parts of ethanol–acetonitrile (2:1). A flow-rate of 6 ml/min and a column temperature of 35°C were maintained throughout. The detector was set at 254 nm.

Thin-layer chromatographic conditions

(+)-Norephedrine hydrochloride and the corresponding 2-oxazolidone were spotted on 20 cm × 5 cm glass plates coated with a 250 μm layer of silica gel (Silica gel GF plates; Analtech, Newark, DE, U.S.A.). The plates were developed with a solution of methanol–chloroform–acetic acid (65:25:10), then air-dried. The (+)-norephedrine hydrochloride could be visualized with either ninhydrin spray or iodine vapor. The oxazolidone could only be visualized with iodine vapor.

RESULTS AND DISCUSSION

The reaction of both (+)-norephedrine and racemic norephedrine with phosgene proceeds smoothly and can be carried out using milligram or gram quantities. The mass spectra (molecular ion peak *m/z* 177, base peak *m/z* 107), infrared spectra (sharp peak at 1770 cm^{-1}), and NMR spectra of the recrystallized products from the reactions are identical and consistent with the formation of a single reaction product, 4-methyl-5-phenyl-2-oxazolidone (II). The oxazolidone obtained from (+)-norephedrine had a specific rotation of $[\alpha]_D = +126°$ and melted between 116 and 117°C. These properties are consistent with those of the corresponding (−)-isomer reported by Fodor *et al.*[12]: $[\alpha]_D = -158.4°$; mp 117.5–119°C.

Chromatography of the recrystallized product from the cyclization of racemic norephedrine on the CSP produced a chromatogram (Fig. 2a) with two prominent peaks in a 1:1 ratio. The peaks had capacity factors (k') of 9.16 and 9.57, a separation factor (α) of 1.04 and a resolution factor (R_s) of 0.96. The chromatogram of the 2-oxazolidone resulting from the cyclization of (+)-norephedrine contained a single peak with a k' value corresponding to that of compound B in Fig. 2. The enantiomeric elution order, *i.e.*, the elution of the enantiomeric 2-oxazolidone corresponding to (−)-norephedrine before the (+)-enantiomer, was confirmed through the cyclization and chromatography of a mixture of (+) and (−) norephedrine (90:10) (Fig. 2b).

The average yield of the reaction was investigated by using three separate cyclizations of (+)-norephedrine. The 2-oxazolidone concentration of the reaction

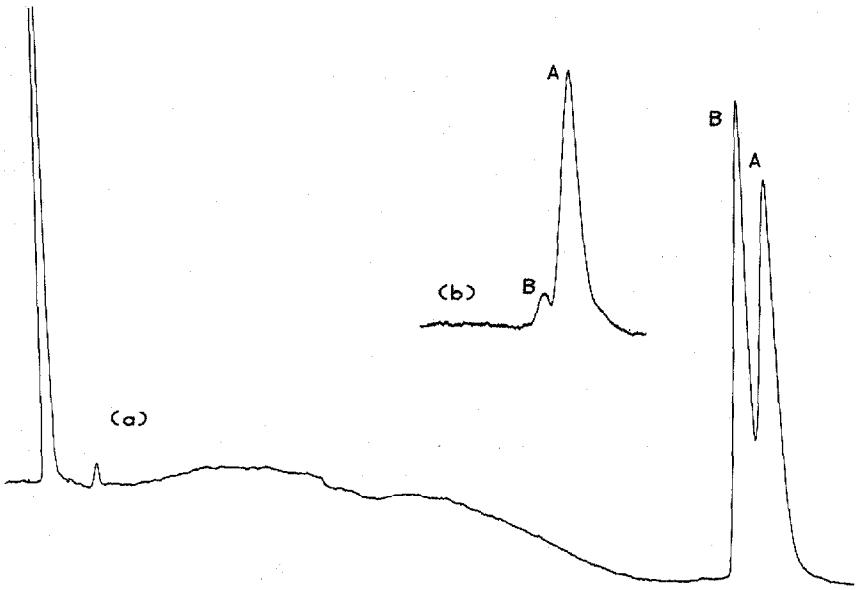

Fig. 2. The chromatograms of mixtures of enantiomeric oxazolidones: A = the oxazolidone derived from the cyclization of (−)-norephedrine; B = the oxalidone derived from the cyclization of (+)-norephedrine. Enantiomeric ratios before derivatization: (a): A:B = 50:50; (b): A:B = 10:90.

mixtures was determined by HPLC with the corresponding crystalline 2-oxazolidone as an external standard. The average yield of the reaction was determined to be 87.6%.

The specific rotation of a sample of (+)-norephedrine was measured and found to be $[\alpha]_D = +34.0°$. The sample was then converted to the 2-oxazolidone. After recrystallization, the 2-oxazolidone was hydrolyzed by refluxing in a mixture of 3 *N* potassium hydroxide solution–methanol (50:50). The resulting product was collected, converted into the hydrochloride salt and recrystallized. The specific rotation of the product was found to be $[\alpha]_D = +34.8°$.

In addition, the mass spectrum of the recrystallized material from the above experiment was identical to that of a sample of the starting material. TLC analysis of the hydrolyzed product, the starting (+)-norephedrine and the 2-oxazolidone yielded symmetrical spots with R_F values of 0.66, 0.66 and 0.85, respectively.

The regenerated material was then subjected to a second cyclization with phosgene and again produced the 2-oxazolidone, which exhibited a single peak with capacity factor identical to that of the 2-oxazolidone derived from (+)-norephedrine.

On the basis of these results, the material was identified as (+)-norephedrine and the sequence (+)-norephedrine to 2-oxazolidone to (+)-norephedrine was demonstrated to proceed with retention of configuration. The average yield of the hydrolysis is 68.5%; the yield of the whole process is 60%.

CONCLUSION

The reaction of racemic norephedrine with phosgene produces enantiomeric 2-oxazolidones which can be directly resolved by HPLC on a CSP. The cyclization and the subsequent hydrolysis of the resulting oxazolidone proceed without racemization. Since the reactions can be carried out in either milligram or gram quantities of norephedrine, this approach can be used both as a probe of the enantiomeric purity of norephedrine and as a method for the generation of the pure enantiomers.

Preliminary work with other molecules containing α,β-amino alcohol moieties suggests that this approach may be applicable to a number of biologically important molecules or their synthetic precursors.

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