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NEW PROCEDURE FOR GAS CHROMATOGRAPHIC ENANTIOMER SEPARATION

APPLICATION TO CHIRAL AMINES AND HYDROXY ACIDS

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SUMMARY

By reaction with isopropyl isocyanate, chiral amines can be converted into urea derivatives. With the same reagent, urethane derivatives of chiral α-hydroxy acid esters are formed. The enantiomers of both types of derivatives are separated on XE-60–*S*-valine–*S*-α-phenylethylamide with high separation factors.

INTRODUCTION

In our investigations of enantioselective chiral stationary phases we have synthesized several chiral derivatives of the polysiloxanes XE-60 and OV-225[1–3]. The properties of these phases are similar to Chirasil-val, a polymer chiral stationary phase introduced by Frank *et al.*[4,5]. On XE-60–*S*-valine–*S*(*R*)-α-phenylethylamide and on the corresponding OV-225 derivatives we have achieved good enantiomer separations of amino acids[1], amino alcohols[1,2], amines[1,2] and carbohydrates[1,6,7]. Enantiomer separation is not only effected by the enantioselectivity of the stationary phase but also strongly influenced by the type of volatile derivatives employed. This could be demonstrated by our recent separations of chiral alcohols as their urethane derivatives[8]. In this work we describe the formation of corresponding derivatives of α-hydroxy acid esters and amines and their separation on glass capillary columns with XE-60–*S*-valine–*S*-α-phenylethylamide*.

EXPERIMENTAL

Formation of derivatives

Samples consisting of 0.5 mg of racemic mixtures of chiral amines were dissolved in 200 μl of dichloromethane and 100 μl of isopropyl isocyanate (Fluka, Neu Ulm, G.F.R.) in a screw-cap vial. After 10 min at room temperature the excess of

* Fused-silica columns with this stationary phase and the corresponding phase with *R*-α-phenylethylamide are available from Chrompack (Middelburg, The Netherlands).

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reagent was removed with a steady stream of dry nitrogen. The residue was dissolved in 0.5 ml of dichloromethane for gas chromatographic investigation.

Samples, each of 0.1–0.5 mg, of chiral hydroxy acids were esterified in 1 ml of a 1.5 *N* solution of dry HCl gas in isopropanol for 30 min at 100°C. After removing the reagent with nitrogen, 200 μl of dichloromethane and 100 μl of isopropyl isocyanate were added and the sample was heated for 20 min at 100°C. Methyl esters and methyl and *tert.*-butyl urethanes were prepared similarly. Again the reagent was removed with nitrogen and the derivative dissolved in 0.5 ml of dichloromethane for gas chromatography.

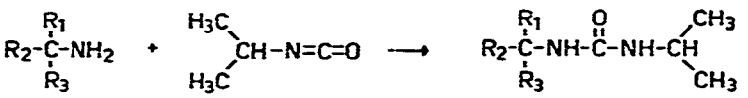
Gas chromatography

The preparation of the stationary phase and of the glass capillary columns has been described in previous communications[1,3,9]. For gas chromatographic investigations Carlo Erba Model 2101 gas chromatographs with flame-ionization detectors and hydrogen as carrier gas were used.

RESULTS AND DISCUSSION

Amines

The enantiomers of N-trifluoroacetylated 2-aminoalkanes have been separated on several monomer and polymer chiral stationary phases with α-values of between 1.01 and 1.02[1–3]. In this work we suggest the application of N-isopropylurea derivatives of chiral amines for enantiomer separation on XE-60–*S*-valine–*S*-α-phenylethylamide as shown in Scheme 1. Urea derivatives can easily be prepared on a



Scheme 1.

microgram scale with isopropyl isocyanate as reagent at room temperature in only 10 min and in excellent yields. (If the reaction is performed at 100°C the urea derivatives again may react with isopropyl isocyanate and derivatives of higher molecular weight are formed which were identified by gas chromatography–mass spectrometry.) These derivatives are less volatile than the trifluoroacetyl derivatives but their separation factors are significantly higher (1.02–1.034, see Table I and Fig. 1). For 2-aminopentane and α-phenylethylamine the *S*-enantiomers have longer retention times than the *R*-enantiomers; the other amines were only available as racemates.

2-Hydroxy acids

In previous publications we have shown that the enantiomers of several 2-(O-trifluoroacetoxy)carboxylic acid isopropyl esters can be separated on chiral stationary phases derived from 2-hydroxy acids[10,11]. These phases lack thermal stability because of their low molecular weight. The α values achieved with 40-m Pyrex glass capillary columns were between 1.01 and 1.02. Unfortunately the enantioselectivity of these phases for hydroxy acids cannot easily be transferred to polymer phases. Frank *et al.*[4] have reported that the cyclohexyl amide derivative of lactic acid is well separated on Chirasil-val. As has been already demonstrated for chiral al-

TABLE I

SEPARATION FACTORS (α) AND OPERATING TEMPERATURES FOR ENANTIOMER SEPARATION OF CHIRAL AMINES AS ISOPROPYL UREA DERIVATIVES

Column: 40-m Pyrex glass capillary coated with XE-60–*S*-valine–*S*-α-phenylethylamide.

Racemate	*α Value*	*Column temperature (°C)*
2-Aminopentane	1.021	170
2-Amino-3-methyl-pentane (diastereoisomers)	1.027 1.024	170
2-Aminohexane	1.025	170
2-Amino-5-methylhexane	1.033	170
2-Aminoheptane	1.030	170
2-Amino-6-methylheptane	1.033	170
2-Aminooctane	1.034	170
2-Phenylethylamine	1.058	200

cohols[8], urethane derivatives can be prepared by reaction of hydroxy groups with isopropyl isocyanate. This reaction can also be applied to hydroxy groups of 2-hydroxy acid esters. Again excellent enantiomer separations are obtained, as demonstrated in Figs. 2 and 3. The α values are given in Table II. The best separations were obtained for 2-hydroxy acid isopropyl esters as isopropyl urethanes. Methyl or isopropyl esters as methyl or *tert.*-butyl urethane derivatives display lower α values.

The order of elution of the enantiomers is consistent: the L-enantiomers have longer retention times than the D-enantiomers.

We have also applied this method to some β-hydroxy acids. The best results were obtained with *tert.*-butyl urethanes of the isopropyl esters, but the separation

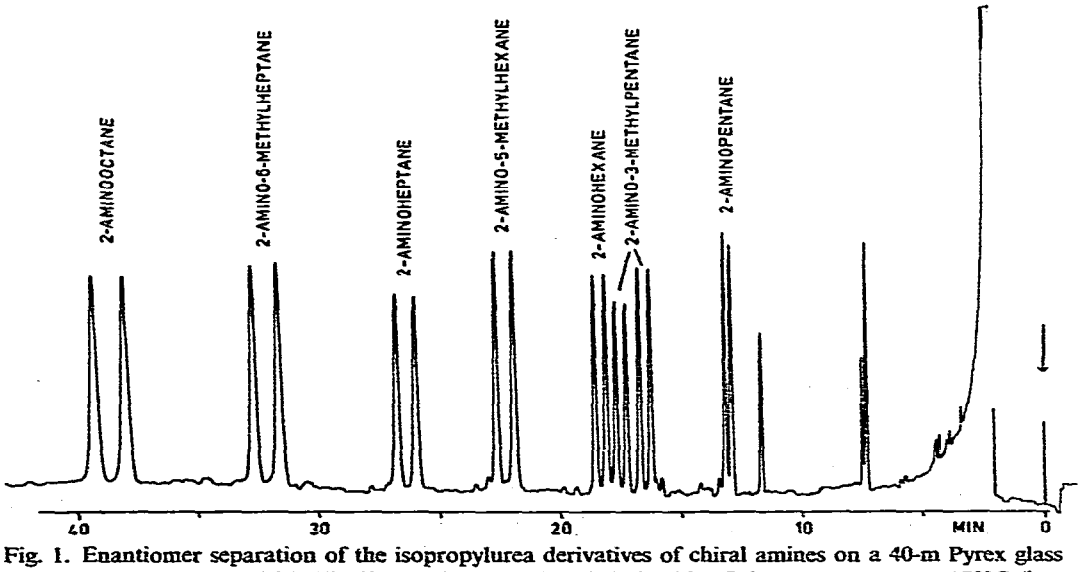


Fig. 1. Enantiomer separation of the isopropylurea derivatives of chiral amines on a 40-m Pyrex glass capillary column coated with XE-60–*S*-valine–*S*-α-phenylethylamide. Column temperature: 170°C (isothermal).

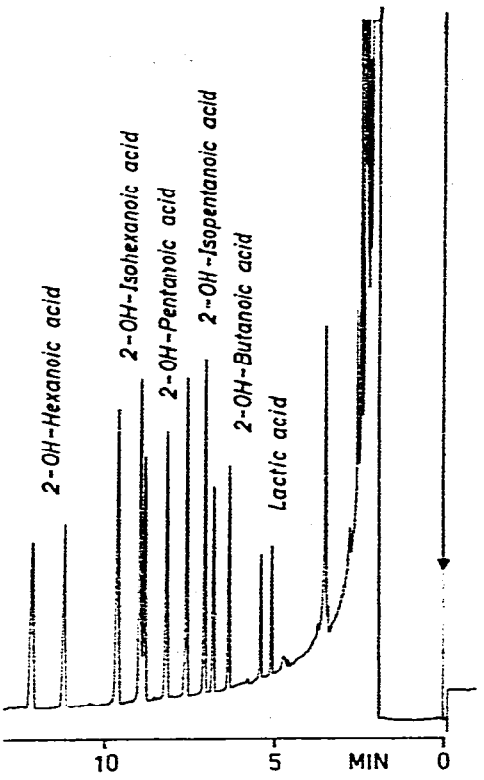


Fig. 2. Enantiomer separation of 2-hydroxy acid isopropyl esters as isopropylurethane derivatives. Column as in Fig. 1. Column temperature: 160°C (isothermal).

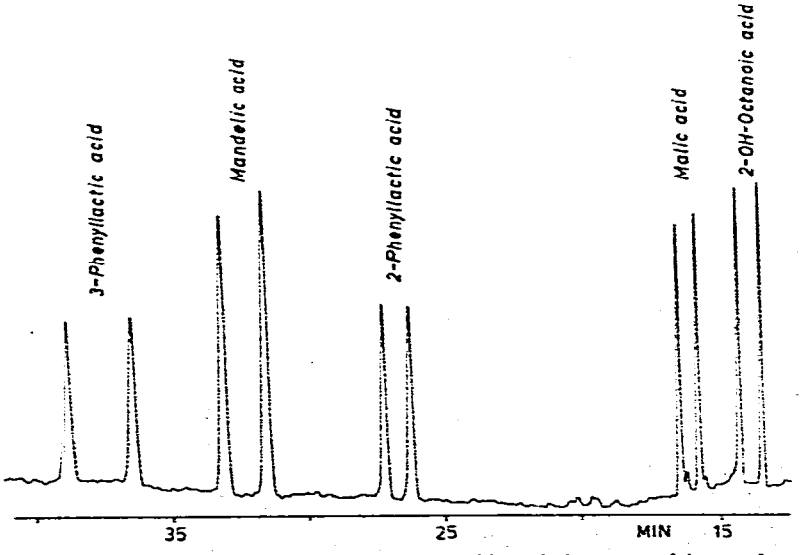


Fig. 3. Enantiomer separation of 2-hydroxy acid methyl esters as isopropylurethane derivatives. Column as in Fig. 1. Column temperature: 170°C (isothermal).

TABLE II

SEPARATION FACTORS (α) AND OPERATING TEMPERATURES FOR ENANTIOMER SEPARATION OF CHIRAL 2-HYDROXY ACID ISOPROPYL ESTERS AS ISOPROPYLURETHANES

Column: 40-m Pyrex glass capillary coated with XE-60–*S*-valine–*S*-α-phenylethylamide

Racemate	*α Value*	*Column temperature (°C)*
Lactic acid	1.095	140
2-Hydroxybutyric acid	1.065	160
2-Hydroxyisopentanoic acid	1.069	160
2-Hydroxypentanoic acid	1.071	160
2-Hydroxyisohexanoic acid	1.069	160
2-Hydroxyhexanoic acid	1.079	160
2-Hydroxyoctanoic acid	1.087	160
2-Hydroxydodecanoid acid	1.084	170
2-Hydroxytetradecanoic acid	1.055	200
2-Hydroxyhexadecanoic acid	1.056	200
Malic acid	1.065	160
Mandelic acid	1.071	160
2-Phenyllactic acid	1.037	170
3-Phenyllactic acid	1.092	160

values are comparably poor and only incomplete separations are achieved (for 3-hydroxybutyric acid, $\alpha = 1.013$ at 160°C).

CONCLUSIONS

Isopropyl isocyanate may be used as an almost universal reagent for the formation of urea or urethane derivatives of chiral compounds with amino or hydroxy groups. The derivatives of amines and 2-hydroxy acid esters can be separated with much larger separation factors than the corresponding trifluoroacetyl derivatives. This increase in enantioselectivity may be ascribed to the additional NH group in the urea and urethane derivatives as a site for hydrogen bonding or dipolar molecular interaction with the chiral sites of XE-60–*S*-valine–*S*-α-phenylethylamide.

ACKNOWLEDGEMENT

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