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PHOSGENE —A VERSATILE REAGENT FOR ENANTIOMER SEPARATION BY CAPILLARY GAS CHROMATOGRAPHY

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SUMMARY

Phosgene has been used to form cyclic derivatives of chiral diols, α-hydroxy acids, N-methylamino acids and other di- and trifunctional compounds and the enantiomers then separated by gas chromatography on the chiral polysiloxane phase XE-60–L-valine–(*R*)-α-phenylethylamide. In this way phosgene can supplement the isocyanates as a versatile reagent for enantiomer separation.

INTRODUCTION

Numerous investigations on enantioselective molecular interactions in chromatographic systems have indicated that enantiomer separation is related to the structural properties of the chiral stationary phase and of the interacting chiral substrate. Amide functions as sites for hydrogen bond formation seem to contribute more to chiral recognition than most other functional groups[1,2]. Isocyanates have therefore become very useful reagents to introduce amide, N- and O-carbamoyl residues into chiral molecules[3]. In this way, new methods for enantiomer separation of chiral alcohols[4], α- and β-hydroxy acids[5,6], amines[5], amino acids and N-methylamino acids[6] have been elaborated.

More recently we have used phosgene as a reagent to form cyclic oxazolidin-2-ones from chiral amino alcohols of pharmaceutical relevance[7]. We now report on further investigations with phosgene as a reagent for enantiomer separation of chiral diols, hydroxy acids, dihydroxy acids, hydroxy amino acids, mercapto amino acids and N-methylamino acids.

EXPERIMENTAL

Gas chromatography (GC)

Carlo Erba Model 2101 and 2900 gas chromatographs with split injectors and flame ionization detectors were used. The chiral capillary columns were prepared as described[8,9].

Formation of derivatives

Cyclic carbonates of 1,2- and 1,3-diols were prepared in screw-cap vials by

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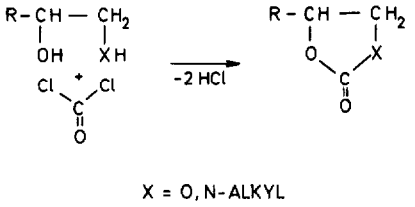
addition of 50 µl of a 20% solution of phosgene in toluene to 0.5–1 mg of sample in 200 µl of dichloromethane. After 1 h at room temperature the reaction mixture was taken to dryness in a stream of ntirogen. The residue was dissolved in 200 µl of dichloromethane and used for GC investigation. α-Hydroxy acids were derivatized in 200 µl of dioxane instead of dichloromethane. For derivatization of N-methylamino acids, 50 µl of a 0.5 *M* aqueous solution of sodium hydroxide were added to the dichloromethane prior to the addition of the phosgene solution. After 1 h at room temperature with occasional shaking of the reaction mixture, the organic solution was separated from the aqueous layer and transferred to a new vial. The sample was dried by repeated addition of 200 µl of dichloromethane and drying in a stream of nitrogen. Tartaric acid and trifunctional amino acids were esterified in a 1.5 *M* solution of hydrogen chloride in isopropanol at 100°C for 1 h. After removal of the isopropanol in a stream of nitrogen, the cyclic derivatives were formed according to the procedure used for N-methylamino acids.

RESULTS AND DISCUSSION

Diols

Analogous to the formation of oxazolidin-2-ones by the reaction of phosgene with N-alkylated α-amino alcohols[7], cyclic carbonates of chiral 1,2- and 1,3-diols are formed in a facile reaction with good yields in inert solvents[10] (Scheme 1). These derivatives can be separated into enantiomers on fused-silica capillaries with the chiral stationary phase XE-60–L-valine–(*R*)-α-phenylethylamide as illustrated in Figs. 1 and 2 and Table I. The formation of the derivatives proceeds without racemization as shown by the analysis of pure enantiomers, which were obtained by reduction of pure enantiomers of α-hydroxy acids with $LiAlH_4$. In all cases where pure enantiomers were available, the isomer with (*S*)-configuration was eluted prior to the (*R*)-enantiomer. Particularly high separation factors are found for alicyclic *trans*-1,2-diols (Table I and Fig. 2). Cyclic 1,3-diols however do not form cyclic carbonates, probably for sterical reasons.



Scheme 1. Reaction of phosgene with diols and α-amino alcohols.

Chiral diols are important as starting compounds in the synthesis of complicated natural compounds[11,12]. Several procedures for asymmetric synthesis of chiral diols have been described in the literature[13,14]. This necessitates the development of sensitive analytical procedures to determine the degree of enantiomeric excess. For stereochemical studies of chiral diols, the formation of diastereoisomeric derivatives monitored by use of chiral shift reagents in ^{1}HNMR, ^{13}CNMR or high-performance liquid chromatography (HPLC) has been suggested[15,16].

Direct GC enantiomer separation of several aryl-substituted diols on Chira-

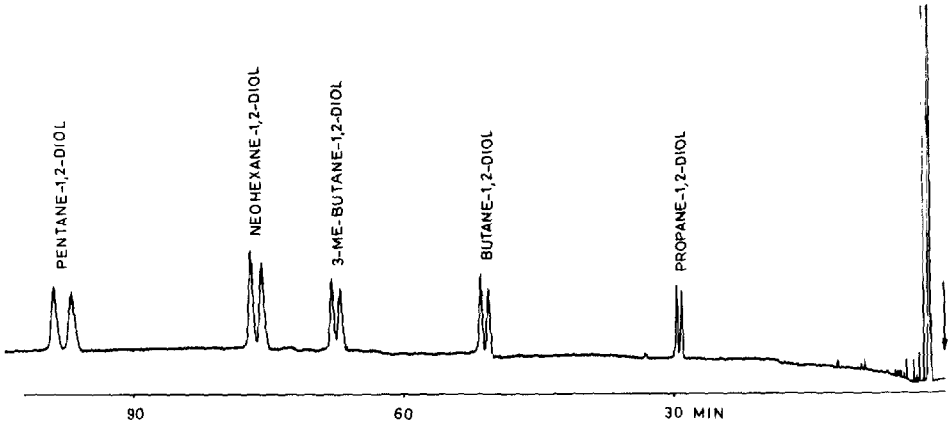


Fig. 1. Enantiomer separation of cyclic carbonates of 1,2- and 1,3-diols. Columns: 35-m fused-silica capillary with XE-60–L-valine–(*R*)-α-phenylethylamide (Chrompack). Column temperature: 80°C; 1 bar H_2. *S*-Enantiomers are eluted before *R*-enantiomers.

sil-Val has been reported by Bayer[17]. In this case, perfluoroacylated derivatives were used, however, this procedure fails with aliphatic and alicyclic diols. Diols with additional functional groups such as tartaric acid can also be converted into cyclic carbonates after esterification of the carboxylic groups. In this case the separation is possible on XE-60–L-valine–(*S*)-α-phenylethylamide (Fig. 3). Difficulties in the formation of suitable derivatives of tartaric acid enantiomers were recently reported by Frank *et al.*[18].

α-Hydroxy acids

As shown in Scheme 2, α-hydroxy acids form 1,3-dioxolane-2,4-diones on reaction with phosgene[19]. Again these cyclic derivatives are readily separated on

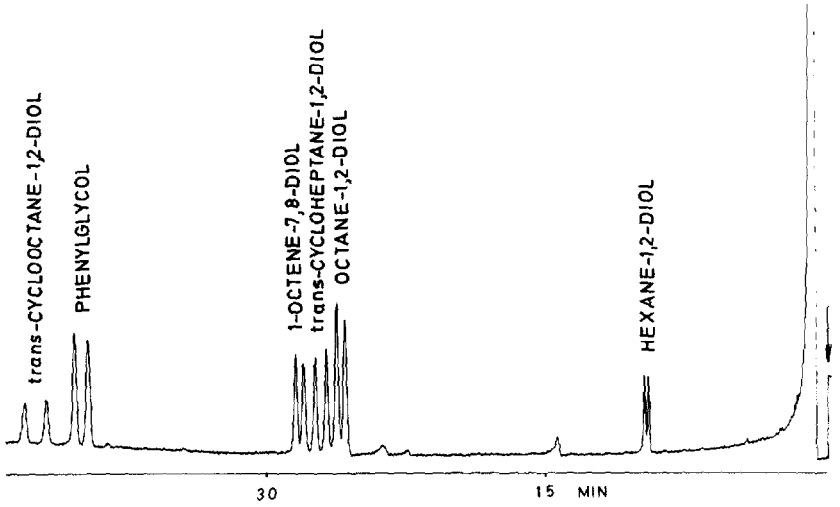


Fig. 2. Enantiomer separation of cyclic carbonates of some 1,2-diols. Column: 25-m fused-silica capillary with XE-60–L-valine–(*R*)-α-phenylethylamide. Column temperature: 110°C, 10 min isothermal, then programmed at 1°C/min; 0.8 bar H_2.

TABLE I

SEPARATION FACTORS (α), COLUMN LENGTHS, COLUMN TEMPERATURES AND ORDER OF ELUTION IN ENANTIOMER SEPARATIONS OF CHIRAL DIOLS, α-HYDROXY ACIDS, N-METHYLAMINO ACIDS AND TRIFUNCTIONAL ACIDS

Racemate	α	*Column length (m)/ temperature (°C)*	*First enantiomer eluted*
Propane-1,2-diol	1.021	35/80	*S*
Butane-1,2-diol	1.017	35/80	*S*
Pentane-1,2-diol	1.021	35/80	*S*
3-Methylbutane-1,2-diol	1.013	35/80	–*
Neohexane-1,2-diol	1.016	35/80	–
Hexane-1,2-diol	1.026	25/100	*S*
4-Methylpentane-1,2-diol	1.013	35/110	–
Octane-1,2-diol	1.026	25/120	–
1-Octene-7,8-diol	1.025	25/120	–
Phenylglycol	1.031	25/120	*S*
2-Ethylhexane-1,3-diol	1.025 1.018	25/120	–
Butane-1,3-diol	1.018	35/140	*S*
trans-Cycloheptane-1,2-diol	1.031	25/140	–
trans-Cyclooctane-1,2-diol	1.044	25/140	–
trans-Cyclodecane-1,2-diol	1.031	25/140	–
Tartaric acid $(Oip)_2$**	1.020	35/145	L
Lactic acid	1.015	35/110	L
2-Hydroxybutyric acid	1.017	35/110	–
2-Hydroxypentanoic acid	1.022	35/110	–
2-Hydroxyisopentanoic acid	1.016	35/110	–
2-Hydroxyhexanoic acid	1.019	35/110	–
2-Hydroxyisohexanoic acid	1.020	35/120	L
2-Hydroxy-3-methylpentanoic acid	1.014	35/120	L
2-Hydroxyoctanoic acid	1.035	35/126	–
N-Methylalanine	1.020	25/100	L
N-Methyl-α-aminobutyric acid	1.025	25/100	L
N-Methylvaline	1.038	25/110	L
N-Methylisoleucine	1.031	25/110	L
N-Methylalloisoleucine	1.028	25/110	L
N-Methylleucine	1.034	25/110	L
Proline	1.038	25/140	D
N-Methylthreonine (Oip)	1.049	25/120	L
N-Methylallothreonine (Oip)	1.028	25/120	L
Threonine (Oip)	1.077	18/170	L
allo-Threonine (Oip)	1.094	18/170	L
Serine (Oip)	1.086	18/170	L
Cysteine (Oip)	1.079	18/170	L
Penicillamine (Oip)	1.085	18/170	L

* Order of elution was not determined.

** Separation on XE-60–L-valine–(*S*)-α-phenylethylamide; Oip = isopropyl ester.

fused-silica capillaries with XE-60–L-valine–(*R*)-α-phenylethylamide (Fig. 4). Investigation of pure enantiomers showed that no racemization takes place during the reaction with phosgene. Compared to 2-carbamoyloxy carboxylic esters, the cyclic derivatives are formed in one reaction step and are more volatile. In all cases where

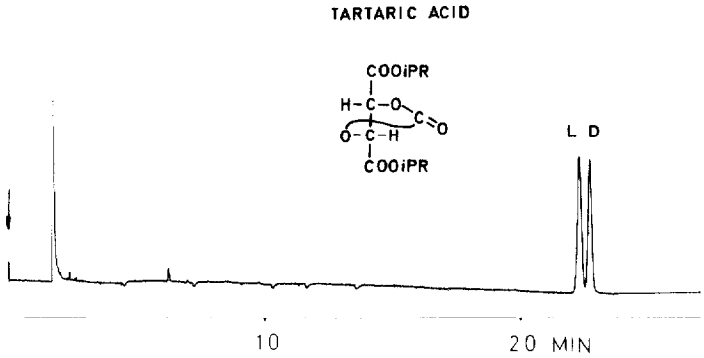
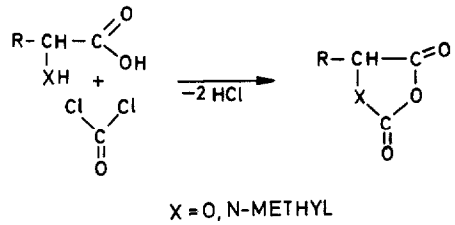


Fig. 3. Enantiomer separation of tartaric acid after esterification with isopropanol and formation of cyclic carbonate. Column: 35-m fused-silica capillary with XE-60–L-valine–(*S*)-α-phenylethylamide (Chrompack). Column temperature: 145°C; 0.9 bar H_2.



Scheme 2. Reaction of phosgene with α-hydroxy acids and N-methyl-α-amino acids.

pure enantiomers were available the L-enantiomers were shown to be eluted prior to the D-enantiomers.

N-methylamino acids

In Scheme 2 the reaction of phosgene with N-methylamino acids to give oxazolidine-2,4-diones is shown. These derivatives may be resolved on both XE-60–L-valine–(*S*)- or –(*R*)-α-phenylethylamide. Again the volatility of the cyclic derivatives

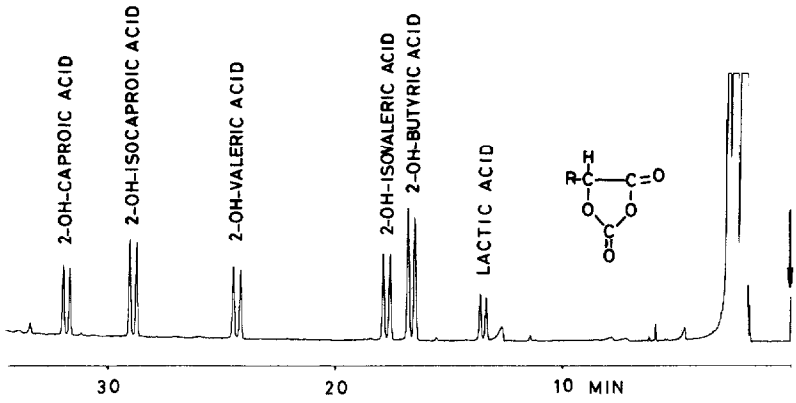


Fig. 4. Enantiomer separation of α-hydroxy acids as 1,3-dioxolane-2,4-diones. Column: 35-m fused-silica capillary with XE-60–L-valine–(*R*)-α-phenylethylamide (Chrompack). Column temperature: 100°C, 15 min isothermal, then raised at 2°C/min to 150°C; 0.9 bar H_2.

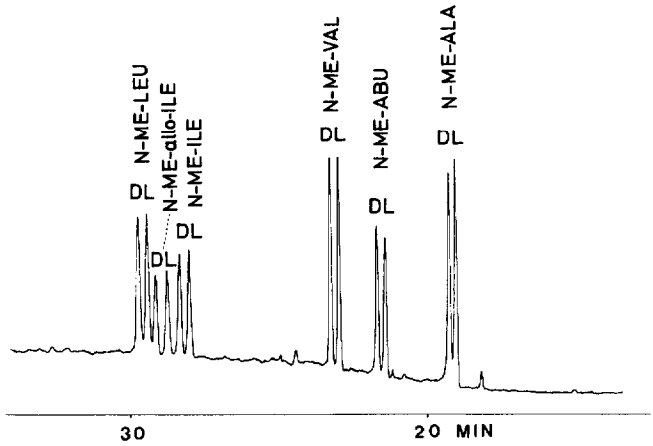


Fig. 5. Enantiomer separation of N-methylamino acids as oxazolidine-2,4-diones. Column: 40-m Pyrex glass capillary with XE-60–L-valine–(*S*)-α-(α-naphthyl)ethylamide. Column temperature: 110°C; programmed at 2°C/min to 150°C; 0.8 bar H_2.

is higher than that of the N-methyl-N-carbamoylamino acid amide derivatives used previously[6]. This procedure may also be applied to the separation of proline enantiomers. The best separation was obtained on a Pyrex glass capillary column with XE-60–L-valine–(*S*)-α-(α-naphthyl)ethylamide, a chiral stationary phase prepared in an analogous way to the phenylethylamide phases[8] (Fig. 5).

Trifunctional amino acids

In a similar way to tartaric acid, some trifunctional amino acids can be converted into cyclic derivatives with phosgene after esterification of the carboxylic

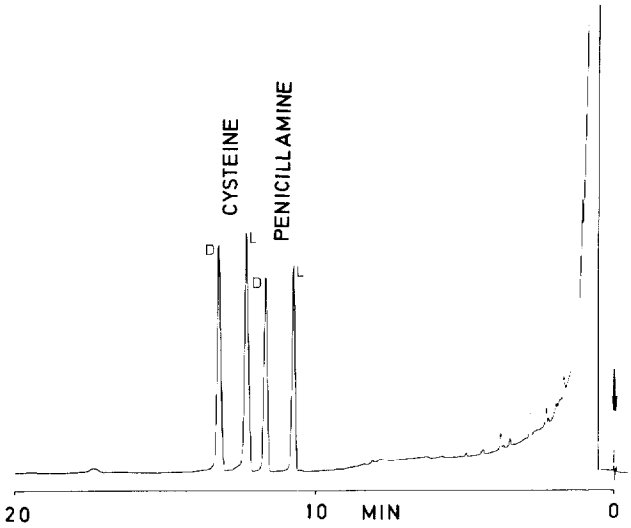


Fig. 6. Enantiomer separation of penicillamine and cysteine after esterifiction with isopropanol and formation of thiazolidin-2-ones with phosgene. Column: 18-m Pyrex glass capillary with XE-60–L-valine–(*R*)-α-phenylethylamide. Column temperature: 170°C; 0.8 bar H_2.

group. This method is applicable to α-amino-β-hydroxy acids or α-amino-β-mercapto acids (Fig. 6). The four stereoisomers of N-methylthreonine and N-methylallothreonine could also be separated according to this procedure. L-N-Methylallothreonine is a constituent of the peptide antibiotic herbicolin A[20].

CONCLUSIONS

With phosgene as a derivatizing reagent, cyclic derivatives of a great variety of di- and trifunctional chiral compounds are formed without racemization. The enantiomers can be separated on XE-60–L-valine–(*R*)- or –(*S*)-α-phenylethylamide. The derivatives of α-hydroxy acids and N-methylamino acids are more volatile than those formed with isocyanates. For the first time, the enantiomer separation of aliphatic diols is possible after formation of cyclic carbonates.

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