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GAS CHROMATOGRAPHIC ENANTIOMER SEPARATION OF CHIRAL ALCOHOLS

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SUMMARY

A micro-scale procedure for the gas chromatographic enantiomer separation of chiral aliphatic, aromatic and monoterpene alcohols on glass capillary columns coated with XE-60–*S*-valine-*S*-α-phenylethylamide is described. By the formation of stable isopropyl urethanes in a facile derivatization step, the polarity of alcohols and their enantioselective intermolecular interaction with the chiral stationary phase is sufficiently enhanced to result in enantiomer separation with moderate retention times.

INTRODUCTION

The gas chromatographic separation of enantiomers has been achieved by the use of chiral stationary phases employing high stereoselectivity towards many polar compounds. After the fundamental work of Gil-Av and his associates[1], many groups have contributed to the improvement of the technique and to the understanding of stereoselective molecular interactions. Our recent investigations with novel monomeric and polymeric chiral stationary phases have dealt with the enantiomer separation of hydroxy acids[2–4], amino alcohols[4–6] and carbohydrates[4,6–8]. Few examples of the direct enantiomer separation of alcohols have been demonstrated. Ôi and coworkers[9,10] have used various low-molecular-weight chiral stationary phases which clearly show stereoselectivity for alcohols, but the retention times are very long.

We report here a more general procedure for the enantiomer separation of alcohols using isopropyl urethane derivatives and XE-60–*S*-valine-*S*-α-phenylethylamide as a very temperature stable polymeric stationary phase of outstanding enantioselectivity.

EXPERIMENTAL

Formation of derivatives

Some of the alcohols were kindly supplied by E. Ziegler (Aromachemie, Aufsess, G.F.R.). Samples of 0.5 mg or less of racemic mixtures of alcohols were dissolved in 200 μl of dichloromethane and 100 μl of isopropyl isocyanate (Fluka, Neu-

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Ulm, G.F.R.) were added. The mixture was heated in a screw-capped vial at 100°C for 20 min. Excess of reagent was removed with a stream of dry nitrogen and the derivatives were dissolved in 0.5 ml of dichloromethane for gas chromatography.

Gas chromatography

Glass capillary columns were drawn from Pyrex glass tubes with a Hupe & Busch capillary drawing machine and coated by the static procedure as described earlier[11]. The preparation of the chiral stationary phase XE-60–*S*-valine-*S*-α-phenylethylamide* has also been described previously[4,7]. Gas chromatography was performed in Carlo Erba Model 2101 gas chromatographs with hydrogen as the carrier gas.

RESULTS AND DISCUSSION

Most of our previous attempts to separate the enantiomers of alcohols on stationary phases derived from amino acids, amines or hydroxy acids have failed[2]. The lack of enantioselectivity of these phases for alcohols may be attributed to the fact that only one polar functional group is available for interaction with the stationary phase. We therefore introduced a second polar group by the reaction of alcohols with isopropyl isocyanate to form the corresponding urethanes. A similar approach has been described by Pereira *et al.*[12], who introduced a second chiral centre to form diastereoisomers by using N-(+)-α-phenylethyl isocyanate. The reaction with isopropyl isocyanate seems to proceed quantitatively even with tertiary alcohols in only 20 min with 50–100 molar excess of reagent in dichloromethane solution at 100°C. The excess of reagent (boiling point 74°C) can easily be removed with a stream of nitrogen. The volatility of the urethane derivatives is adequate for many chiral alcohols for elution from a 40-m glass capillary column within a reasonable retention time at temperatures between 70 and 180°C. The stationary phase is derived from commercially available polysiloxane XE-60 and exhibits the highest α-values for chiral alcohol derivatives of all stationary phases of this type that we have synthesized, including XE-60–*S*-valine-*R*-α-phenylethylamide, XE-60–*S*-phenylalanine-*S*-α-phenylethylamide, OV-225–*S*-valine-*R*-α-phenylethylamide and OV-225–*S*-valine-*S*-α-phenylethylamide.

As shown in Figs. 1–3 and Table I, aliphatic, aromatic and monoterpene alcohol enantiomers are separated. For 2-octanol, ipsdienol (1), *trans*-verbenol (2) and menthol (3) the (+)-enantiomers have the longer retention times; for terpinen-4-ol (4) the (+)-enantiomer is eluted first.

Chiral alcohols are important components of the pheromone systems in many insect species. They occur either in optically pure form or defined mixtures of enantiomers[13]. In many instances the "wrong" enantiomers proved to be biologically inactive or showed a repellent effect[14] and species specificity of chemical messages as well as interspecific competition for food and breeding places may well be based on pheromones of opposite chirality[15].

2-Heptanol and 3-octanol are widespread alarm pheromones in the mandibular gland secretions of different ant species[16]. One of the aggregation pheromones of elm bark beetles of the genus *Scolytus* is 4-methyl-3-heptanol[17], the natural com-

* Fused-silica columns with this phase are available from Chrompack, Middelburg, The Netherlands.

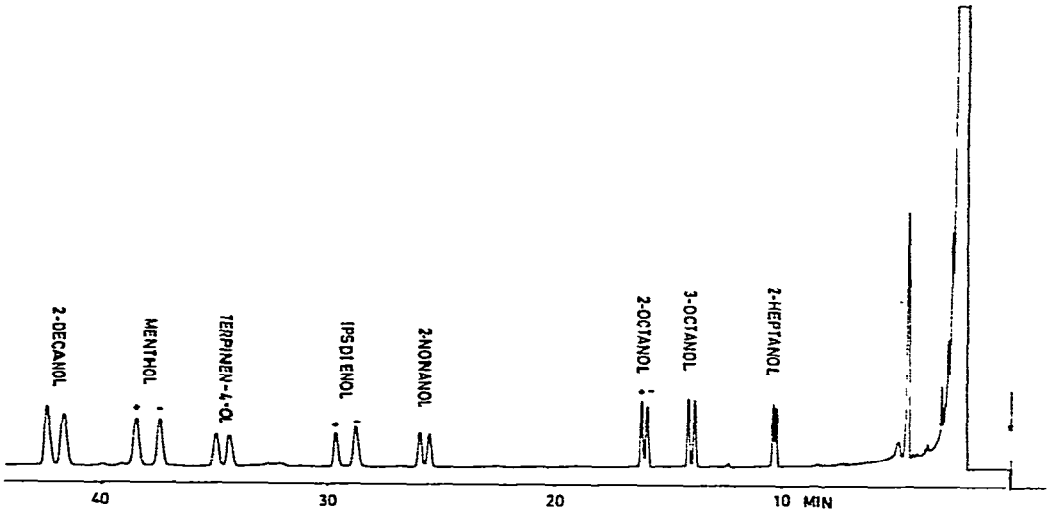

Fig. 1. Enantiomer separation of the isopropyl urethanes of chiral alcohols on a 40-m Pyrex glass capillary column coated with XE-60–*S*-valine-*S*-α-phenylethylamide. Column temperature, 120°C (isothermal).

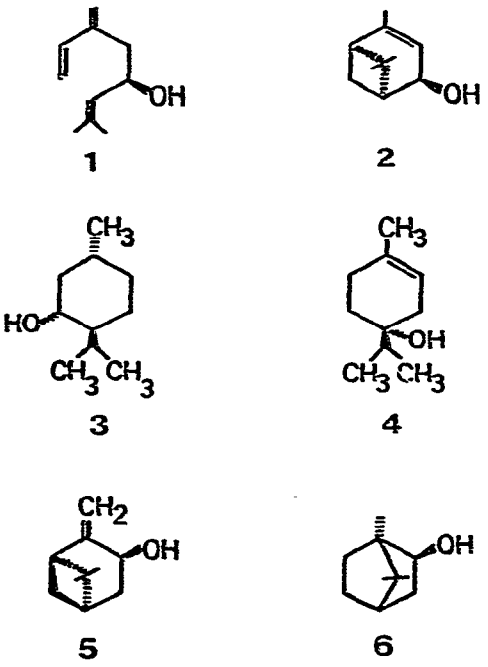

Fig. 2. Structures of some chiral monoterpene alcohols, separated as isopropyl urethanes. 1 = Ipsdienol; 2 = *trans*-verbenol; 3 = menthol; 4 = terpinen-4-ol; 5 = *trans*-pinocarveol; 6 = isoborneol.

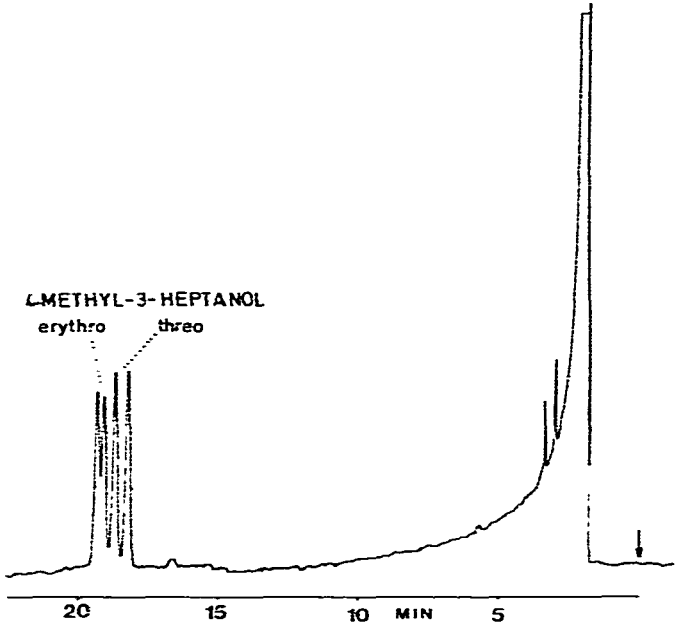

Fig. 3. Enantiomer separation of the four stereoisomers of 4-methyl-3-heptanol as isopropyl urethanes. Column temperature, 115°C; column as in Fig. 1.

TABLE I

SEPARATION FACTORS (α) AND OPERATING TEMPERATURES FOR ENANTIOMER SEPARATION OF CHIRAL ISOPROPYL URETHANES ON A 40-m GLASS CAPILLARY COLUMN COATED WITH XE-60-*S*-VALINE-*S*-α-PHENYLETHYLAMIDE

Racemate	*α-value*	*Column temperature (°C)*
2-Heptanol	1.014	120
2-Octanol	1.017	120
3-Octanol	1.025	120
4-Methyl-3-heptanol (*threo*)	1.024	120
4-Methyl-3-heptanol (*erythro*)	1.012	120
2-Nonanol	1.017	120
2-Decanol	1.019	120
2-Tetradecanol	1.016	170
1-Phenylethanol	1.040	120
1-Phenyl-1-propanol	1.049	120
Menthol	1.030	120
Isoborneol	1.020	140
Ipsdienol	1.033	120
Terpinen-4-ol	1.019	120
trans-Pinocarveol	1.039	140
trans-Verbenol	1.015	140
Sulcatol	1.011	120

pound having (3*S*,4*S*)-configuration[18]. The separation of all four stereoisomers of 4-methyl-3-heptanol is shown in Fig. 3.

trans-Verbenol (2) has been identified as a component of the aggregation pheromone in several bark beetles of the genus *Dendroctonus*[19], while *cis*-verbenol and ipsdienol (1) are important aggregation pheromones among certain *Ips* and *Pityokteines* species[20]. The verbenols are probably oxygenation products of the host terpene α-pinene, ipsdienol is produced from myrcene. *trans*-Pinocarveol (5), another constituent of the odour bouquet of bark beetles, especially *Crypnalus piceae*, may be derived from β-pinene[21].

Terpinen-4-ol (4) was found in several bark beetle species[22] and is the main compound in the aggregation pheromone of *Polygraphus poligraphus*[23]. 6-Methyl-5-hepten-2-ol (sulcatol) is the aggregation pheromone of male ambrosia beetles of the genus *Gnathotrichus*[24].

These examples demonstrate only part of the broad potential of applications of this new procedure for configurational analysis. We also expect that this method will be applied to the investigation of flavour and fragrance constituents and to the control of asymmetric syntheses.

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