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Note

Some N-acyl derivatives of 1-(α-naphthyl)ethylamine as stationary phases for the separation of optical isomers in gas chromatography

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It was reported by Weinstein *et al.*[1] that it suffices for a chiral stationary phase to contain an amide group and an asymmetric carbon atom, attached to the nitrogen atom [RCONHCH(CH_3)R'], in order to show selectivity in its interaction with the enantiomers of amides, and that the best efficiency is obtained when R' is aromatic, particularly α-naphthyl, as in N-lauroyl-(*S*)-1-(α-naphthyl)ethylamine. During the course of our examinations of the influence on the enantioselectivity when the structure of the amide phase is converted to contain two asymmetric carbon atoms attached to both nitrogen and carbon atoms of the amide group, we[2] have found that N-(1*R*,3*R*)-*trans*-chrysanthemoyl-(*R*)-1-(α-naphthyl)ethylamine shows excellent enantioselectivity compared to that of N-lauroyl-(*R*)-1-(α-naphthyl)ethylamine. This result suggested that other N-acyl derivatives of (*R*) or (*S*)-1-(α-naphthyl)ethylamine should also show high stereoselectivity for enantiomeric amides. In this paper we report the chromatographic properties of four new amides derived from (*R*)- and (*S*)-1-(α-naphthyl)ethylamine with (*S*)-mandelic acid and (*S*)-proline as optically active stationary phases.

EXPERIMENTAL

Synthesis of stationary phases

O-Lauroyl-(S)-mandelic acid (S)-1-(α-naphthyl)ethylamide (phase I). To a stirred solution of (*S*)-mandelic acid (0.015 mol), (*S*)-1-(α-naphthyl)ethylamine (0.015 mol) and 1-hydroxybenzotriazole (0.017 mol) in tetrahydrofuran (30 ml) kept at 0°C, N,N'-dicyclohexylcarbodiimide (0.016 mol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was first stirred in an ice-bath for 2 h and then at room temperature for 2 h, filtered and the solution evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed successively with 2 *N* citric acid, saturated sodium bicarbonate solution and water. After drying over sodium sulphate, the crude product was purified by column chromatography on silica gel. The fraction eluted with chloroform was (*S*)-mandelic acid (*S*)-1-(α-naphthyl)ethylamide, which was identified by nuclear magnetic resonance (NMR) and mass spectrometry. Phase I was obtained from the above amide (0.004 mol) by reaction with lauroyl chloride (0.008 mol) in dry dioxan (20 ml) in the presence of

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pyridine (0.01 mol) at 100°C for 4 h. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate and the solution washed successively with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution and water. After drying over sodium sulphate, the crude product was purified by column chromatography on silica gel. The fraction eluted with hexane–ethyl acetate (1:1) was the desired compound (phase I), as demonstrated by NMR and mass spectrometry (found: C, 78.5; H, 8.6; N, 2.9; calculated for $C_{32}H_{41}NO_3$: C, 78.8; H, 8.5; N, 2.9%); $[\alpha]_D^{20}$ + 37° (*c* = 0.16% in chloroform); m.p. 86–88°C.

O-Lauroyl-(S)-mandelic acid (R)-1-(α-naphthyl)ethylamide (phase II). Phase II was synthesized using (*R*)-1-(α-naphthyl)ethylamine instead of (*S*)-1-(α-

TABLE I

GAS CHROMATOGRAPHIC SEPARATION OF ENANTIOMERS

Chromatographed on 40 m × 0.25 mm I.D. glass capillary columns. Carrier gas: helium at 0.7–1.0 ml/min.

Compound	*Column temp. (°C)*	*Optically active stationary phase*		
		Phase I		
		*Retention time (min)**		*α***
		1st peak	*2nd peak*	
N-TFA Amines				
2-Octylamine	100	36.58	37.89	1.036
1-Phenylethylamine	100	115.5(+)	127.5(−)	1.104
1-(α-naphthyl)ethylamine***	150	100.4(+)	110.9(−)	1.105
N-TFA Amino acid isopropyl esters				
Alanine	100	12.03(D)	12.61(L)	1.048
Valine	100	14.89(D)	15.53(L)	1.043
Leucine	100	35.60(D)	36.87(L)	1.036
O-TFA α-hydroxycarboxylic acid isopropyl ester				
Mandelic acid	100	37.62(−)	38.57(+)	1.025
Carboxylic acid tert.-butyl amides				
2-Phenylpropionic acid	130	63.78(+)	68.44(−)	1.073
3,3-Dimethyl-2-ethylbutyric acid	100	34.09		1.000
2-Bromo-3,3-dimethylbutyric acid	100	57.79(−)	63.23(+)	1.094
2-(4-Chlorophenyl)isovaleric acid	150	128.3(+)	136.7(−)	1.065
Carboxylic acid ethyl esters				
trans-Chrysanthemic acid	100	17.36		1.000
cis-Chrysanthemic acid	100	16.65		1.000
trans-3-(2,2-Dichlorovinyl)-cyclopropanecarboxylic acid	100	65.13		1.000
cis-3-(2,2-Dichlorovinyl)-cyclopropanecarboxylic acid	100	50.56		1.000
Nitriles				
2-(2-Fluorophenyl)isovaleronitrile	100	41.89	42.16	1.006
2-(4-Chlorophenyl)isovaleronitrile	120	113.1	115.2	1.019
Alcohol				
Pantoyl lactone	100	46.40	46.92	1.011

* Measured from solvent peak.
** Separation factor calculated by second peak/first peak.
*** Resolved as N-pentafluoropropionyl derivative.

naphthyl)ethylamine according to the procedure described in the synthesis of phase I. The final product had NMR and mass spectra which agreed with the expected structure (found: C, 78.2; H, 8.8; N, 3.1; calculated for $C_{32}H_{41}NO_3$: C, 78.8; H, 8.5; N, 2.9%); $[\alpha]_D^{20}$ + 51° (c = 0.18% in chloroform); m.p. 56–57°C.

N-Lauroyl-(S)-proline (S)-1-(α-naphthyl)ethylamide (phase III). To a stirred solution of N-*tert.*-butoxycarbonyl-(*S*)-proline (0.01 mol), (*S*)-1-(α-naphthyl)-ethylamine (0.01 mol) and 1-hydroxybenzotriazole (0.011 mol) in tetrahydrofuran (20 ml) kept at 0°C, N,N′-dicyclohexylcarbodiimide (0.011 mol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was first stirred in an ice-bath for 2 h and then at room temperature for 2 h, filtered and the solution was evaporated

Phase II			*Phase III*			*Phase IV*		
*Retention time (min)**		α**	*Retention time (min)**		α**	*Retention time (min)**		α**
1st peak	*2nd peak*		*1st peak*	*2nd peak*		*1st peak*	*2nd peak*	
37.57	38.44	1.023	37.36	39.70	1.048	81.30		1.000
94.93(−)	103.7(+)	1.092	168.0(+)	187.6(−)	1.117	234.7(−)	247.0(+)	1.052
111.8(−)	118.5(+)	1.060	88.75(+)	100.2(−)	1.129	214.0(−)	222.4(+)	1.039
10.43(L)	10.78(D)	1.034	8.40(D)	8.82(L)	1.050	17.52(L)	18.04(D)	1.030
13.16(L)	13.60(D)	1.033	9.10(D)	9.62(L)	1.057	19.30(L)	20.14(D)	1.044
31.59(L)	32.36(D)	1.024	26.25		1.000	54.60(L)	57.69(D)	1.057
37.15(+)	38.08(−)	1.025	33.29(−)	34.57(+)	1.038	36.40		1.000
63.82(−)	67.37(+)	1.056	57.95(+)	63.49(−)	1.096	61.43(−)	63.62(+)	1.036
30.38	31.14	1.025	20.96		1.000	49.78	50.90	1.022
55.90(+)	59.33(−)	1.061	45.47(−)	51.49(+)	1.132	109.3(+)	116.0(−)	1.061
136.5(−)	142.6(+)	1.045	105.0(+)	111.4(−)	1.061	218.1(−)	224.5(+)	1.029
16.85	16.78	1.012	8.16		1.000	18.63		1.000
16.01	16.21	1.012	8.16		1.000	18.63		1.000
64.43	65.52	1.017	33.73	34.09	1.011	78.49	79.17	1.009
49.97	50.91	1.019	26.54		1.000	61.65		1.000
40.35		1.000	21.93		1.000	50.98		1.000
135.4	136.8	1.010	65.81	67.45	1.025	158.0		1.000
44.57		1.000	51.60	54.50	1.054	116.4	118.5	1.018

under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed successively with 2 *N* citric acid and water. The solvent was evaporated under reduced pressure, the residue was dissolved in 4 *N* hydrochloric acid in dioxan (20 ml) and the solution was stirred at room temperature for 6 h. The solution was evaporated under reduced pressure, and the residue was dissolved in chloroform and extracted with water. The aqueous layer was made alkaline with ammonia solution and then re-extracted with chloroform. The extract was dried over sodium sulphate and evaporation of the chloroform gave (*S*)-proline-(*S*)-1-(α-naphthyl)ethylamide, which was identified by NMR and mass spectrometry. Phase III was obtained from the above amide (0.005 mol) by reaction with lauroyl chloride (0.009 mol) in dry dioxan (20 ml) in the presence of pyridine (0.01 mol) at room temperature for 2 h. After evaporation of the solution under reduced pressure, the residue was dissolved in ethyl acetate and the solution was washed succesively with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution and water. After drying over sodium sulphate, the crude product was purified by column chromatography with silica gel. The fraction eluted with chloroform was the desired compound (phase III), as demonstrated by NMR and mass spectrometry (found: C, 77.3; H, 9.6; N, 6.1; calculated for $C_{29}H_{42}N_2O_2$: C, 77.3; H, 9.4; N, 6.2%); $[\alpha]_D^{20}$ − 66° (*c* = 0.23% in chloroform); m.p. 59–62°C.

N-Lauroyl-(S)-proline (R)-1-(α-naphthyl)ethylamide (phase IV). Phase IV was synthesized using (*R*)-1-(α-naphthyl)ethylamine instead of (*S*)-1-(α-naphthyl)-ethylamine according to the procedure described for the synthesis of phase III. The final product had NMR and mass spectra which agreed with the expected structure (found: C, 77.3; H, 9.7; N, 6.2; calculated for $C_{29}H_{42}N_2O_2$: C, 77.3; H, 9.4; N, 6.2%); $[\alpha]_D^{20}$ − 114° (*c* = 0.28% in chloroform) m.p. 67–68°C.

Thermogravimetric analysis

The experiments were performed with a Rigaku Thermoflex instrument provided with a thermobalance. The amount of sample was 8–12 mg. The temperature was raised at a rate of 10°C/min using α-alumina as the reference between 50 and 450°C.

Gas chromatography

The experiments were carried out with a Shimadzu GC-7A gas chromatograph equipped with a flame ionization detector. The glass capillary columns (40 m × 0.25 mm I.D.) were coated with a 5% solution of each stationary phase in chloroform.

RESULTS AND DISCUSSION

The gas chromatographic results are given in Table I. The four stationary phases (I–IV) show excellent enantioselectivity. They separate amino acid, amine and carboxylic acid enantiomers, although they do not show very much higher separation factors than N-lauroyl-(*S*)-1-(α-naphthyl)ethylamine[1] which contains only one asymmetric centre. It should be emphasized that some carboxylic acid ester, nitrile and alcohol enantiomers can be separated on these new amides as well as on N-(1*R*,3*R*)-*trans*-chrysanthemoyl-(*R*)-1-(α-naphthyl)ethylamine which was reported by us previously[2]. It is interesting that phase II partially separates all four isomers of ethyl

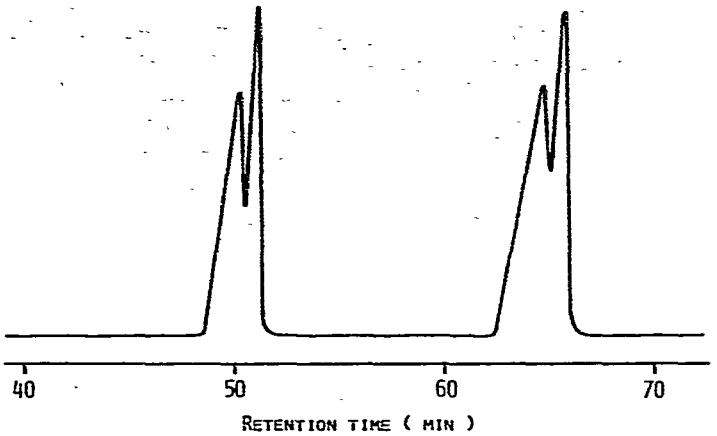

Fig. 1. Gas chromatogram of racemic ethyl *cis,trans*-3-(2,2-dichlorovinyl)cyclopropanecarboxylate. Column, glass capillary column (40 m × 0.25 mm I.D.) coated with O-lauroyl-(*S*)-mandelic acid (*R*)-1-(α-naphthyl)ethylamide; temperature, 100°C; carrier gas (helium) flow-rate, 0.9 ml/min.

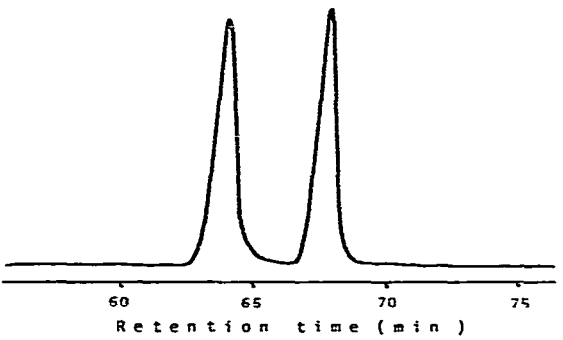

Fig. 2. Gas chromatogram of racemic 2-(4-chlorophenyl)isovaleric acid isopropylamide. Column, glass capillary column (40 m × 0.25 mm I.D.) coated with O-lauroyl-(*S*)-mandelic acid (*S*)-1-(α-naphthyl)ethylamide; temperature, 180°C; carrier gas (helium) flow-rate, 0.7 ml/min.

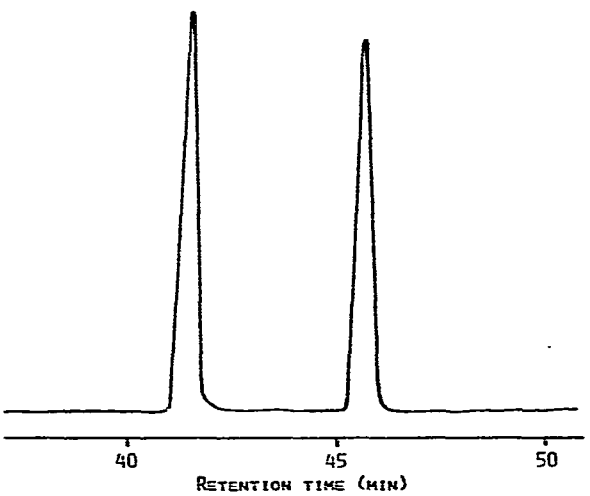

Fig. 3. Gas chromatogram of racemic N-pentafluoropropionyl-1-(α-naphthyl)ethylamine. Column, glass capillary column (40 m × 0.25 mm I.D.) coated with N-lauroyl-(*S*)-proline (*S*)-1-(α-naphthyl)ethylamide; temperature, 180°C; carrier gas (helium) flow-rate, 1.0 ml/min.

chrysanthemate and ethyl 3-(2,2-dichlorovinyl)cyclopropanecarboxylate, to our knowledge for the first time. A typical chromatogram is shown in Fig. 1.

It is also notable that these new amides have excellent thermal stability. Thermogravimetric analysis showed that bleeding should start only at about 200°C. As can be seen in Figs. 2 and 3, stable baselines were obtained when operating at 180°C with the instrument set at 8×10^{11} A full-scale deflection. We suggest these new phases could be useful for the separation of optical isomers of some less volatile N-acyl amines or carboxylic acid amides.

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