Syntheses of α-Amino Acid Menthyl Esters

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l-Menthol[1] has been used as an optically-active moiety in many kinds of stereochemical studies.[2] However, few α-amino acid menthyl esters have been prepared[3] because the conventional esterification methods, such as the hydrogen chloride or sulfuric acid methods, fail to give satisfactory results.

In this paper a new method of preparing α-amino acid menthyl esters is described. The method involves a direct esterification of α-amino acids with menthol, using a Dean and Stark distillation tube[4,5] in azeotropic distillation. *p*-Toluenesulfonic acid was used as a catalyst, and benzene or a benzene-toluene mixture was used as the solvent.[5] The α-amino acid menthyl esters thus prepared were isolated as hydrochlorides; they are abbreviated as amino acid M. HCl.

DL-, D- and L-Amino acid M. HCl's were prepared. It was found that the solubility of D-amino acid M. HCl was generally smaller than that of L-amino acid M. HCl. The fractionation of the diastereomers of DL-amino acid M. HCl during the isolation and recrystallization was checked by comparing the $[\alpha]_D$ value of the DL-amino acid M. HCl with those of the synthesized L- and D-amino acid M. HCl's. The $[\alpha]_D$ values of L-phenylalanine M. HCl and D-phenylalanine M. HCl were $-20.8°$ and $-75.1°$ respectively, so the calculated $[\alpha]_D$ value of DL-phenylalanine M. HCl should be $-48.0°$. The $[\alpha]_D$ values of isolated DL-phenylalanine M. HCl were found to be $-51.4°$ and $-55.2°$, before and after recrystallization respectively (Table I). These results showed that the fractionation of diastereomers occurred during the isolation and recrystallization steps. Table I shows that the yield of D-amino acid M. HCl is generally twice as high as that of L-amino acid M. HCl. This means that the rate of the esterification of D-amino acids with menthol is faster than that of L-amino acids. This suggests the possibility of the fractionation of D- and L-amino acid M. HCl's during the synthesis of these esters.

The menthyl esters of D-phenylalanine and D-methionine were resolved by seeding the supersaturated DL-amino acid M. HCl solution with D-phenylalanine M. HCl and D-methionine M. HCl respectively. The 89% optically-active D-phenylalanine M. HCl and the 65% optically-active D-methionine M. HCl were each isolated in one seeding procedure.

Generally, D- and L-amino acid M. HCl's showed sharp melting points, whereas DL-amino acid M. HCl's showed relatively broad melting points because the DL compounds were a mixture of diastereomers. L-Leucine M. HCl and D-leucine M. HCl did not crystallize, so they were converted to *N*-benzoyl derivatives. D-Alanine and L-alanine M. HCl showed similar $[\alpha]_D$ values (L, -67.3; D, -70.9). These compounds were also converted to *N*-benzoyl derivatives (Table II), which also exhibited similar $[\alpha]_D$ values (L, -57.7; D, -43.2). The free α-amino acid menthyl esters were stable and did not form diketopiperazine derivatives after standing a few days at room temperature. It was difficult to apply the esterification method to the hydroxy amino acids (serine, threonine and phenylserine) or to the basic amino acids (arginine and histidine). The reaction conditions, yields, physical properties and elemental analyses are shown in Tables I and II.

These results might be useful in providing standards for the field of stereochemistry or in the asymmetric synthesis of α-amino acid menthyl esters.

Experimental

L-Phenylalanine Menthyl Ester Hydrochloride.— 8.26 g. (0.05 mol.) ($[\alpha]^{27}_D=-33.4$, H_2O, *c* 1.50) of L-phenylalanine, 12.0 g (0.077 mol.) of *l*-menthol ($[\alpha]^{27}_D=-50.0$, abs. EtOH, *c* 3.5), and 12.0 g. 0.063 mol.) of *p*-toluenesulfonic acid monohydrate were mixed with 100 ml. of a benzene-toluene mixture (7 : 3) and refluxed with a Dean and Stark distillation apparatus[4,5] in azeotropic distillation for 24 hr. The nascent water was then removed azeotropically. The insoluble materials (unreacted

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[1] *l*-Menthol was used throughout in this study; m.p. 42~44°C, $[\alpha]^{27}_D=-50.0°$ (*c* 3.50, in abs. EtOH).

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TABLE I. α-AMINO ACID MENTHYL ESTER HYDROCHLORIDES, $\text{R-}\underset{\text{NH}_2\cdot\text{HCl}}{\text{CH}}\text{-COOM}$

α-Amino acid menthyl ester hydrochloride	Reaction solvent[a]	Reaction time, hr.	Yield %	Recryst. solvent[b]	M. p. °C[c]	After recryst. $-[\alpha]_D^{26\sim27}$ [d]	*c*	Molecular formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Gly	B	24	88	Et	*253~256	66.9	0.615	$C_{12}H_{24}O_2NCl$	57.70	9.68	5.61	57.10	9.78	5.54
L-Ala	B-T	30	69	A	218	67.3	1.14	$C_{13}H_{26}O_2NCl$	59.18	9.93	5.31	59.41	9.70	5.13
D-Ala	B-T	30	79	A	188~189	70.9	1.08	$C_{13}H_{26}O_2NCl$	59.18	9.93	5.31	59.12	9.93	5.08
DL-Ala	B-T	30	58	A	*166~168	70.2	1.03	$C_{13}H_{26}O_2NCl$	59.18	9.93	5.31	59.19	9.78	5.30
L-Val	B-T	24	11	A	224~225	48.3	0.697	$C_{15}H_{30}O_2NCl$	61.72	10.36	4.80	61.72	10.28	4.72
D-Val	B-T	24	23	A	209~210	78.6	0.701	$C_{15}H_{30}O_2NCl$	61.72	10.36	4.80	61.95	10.24	4.52
DL-Val	B-T	24	17	A	183~185	62.9	0.839	$C_{15}H_{30}O_2NCl$	61.72	10.36	4.80	61.43	10.26	4.67
L-Leu	B-T	24	—	—	Oil	—	—	$C_{16}H_{32}O_2NCl$	62.82	10.55	4.58	—	—	—
D-Leu	B-T	24	—	—	Oil	—	—	$C_{16}H_{32}O_2NCl$	62.82	10.55	4.58	—	—	—
DL-Leu	B-T	24	64	E-PE	*87~ 90	51.9	0.847	$C_{16}H_{32}O_2NCl$	62.82	10.55	4.58	62.96	10.30	4.51
L-α-NH$_2$-but	B-T	48	33	A	207~208	55.7	0.912	$C_{14}H_{28}O_2NCl$	60.52	10.16	5.04	60.41	10.06	4.90
D-α-NH$_2$-but	B-T	48	71	A	185~186	74.5	0.768	$C_{14}H_{28}O_2NCl$	60.52	10.16	5.04	60.21	9.80	5.05
DL-α-NH$_2$-but	B-T	48	76	Et	159~162	67.0	0.735	$C_{14}H_{28}O_2NCl$	60.52	10.16	5.04	60.99	9.90	4.97
L-Phe	B-T	24	32	Et	165~166	20.8	0.774	$C_{19}H_{31}O_2NCl$	66.93	9.16	4.10	66.89	8.90	4.26
D-Phe	B-T	24	75	A	185~186	75.1	1.07	$C_{19}H_{31}O_2NCl$	66.93	9.16	4.10	66.65	8.92	4.16
DL-Phe	B-T	24	66	A	*147~160	55.2	0.743	$C_{19}H_{31}O_2NCl$	66.93	9.16	4.10	67.05	9.15	4.20
L-Met	B-T	24	31	Et	115~116	42.4	1.03	$C_{15}H_{30}O_2NSCl$	55.61	9.33	4.32	55.95	9.19	4.42
D-Met	B-T	24	73	Et	154~156	63.4	1.02	$C_{15}H_{30}O_2NSCl$	55.61	9.33	4.32	55.66	9.34	4.32
DL-Met	B-T	24	41	Et	*115~122	50.8	0.702	$C_{15}H_{30}O_2NSCl$	55.61	9.33	4.32	55.98	9.36	4.37
L-Pro	B	30	64	A	185	87.0	0.975	$C_{15}H_{27}O_2NCl$	62.16	9.74	4.83	62.39	9.55	4.83
DL-Pro	B	30	41	A	*142~166	71.2	0.859	$C_{15}H_{27}O_2NCl$	62.16	9.74	4.83	62.00	9.89	5.01
DL-Phenylgly	B-T	24	52	A	*153~156	63.0	1.15	$C_{18}H_{28}O_2NCl$	66.34	8.66	4.30	66.74	8.53	4.30

a) Solvent: B=benzene; B-T=benzene-toluene mixture (7:3)

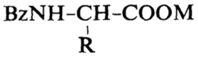
b) Recrystallization solvent: A=alcohol and ether; Et=ethyl acetate and ether; E-P=ether and petroleum ether

c) All melting points are uncorrected.

d) Optical rotation: All samples were measured in abs. ethanol at 26~27°C.
All samples exhibited negative rotations.

* Melting points are not sharp.

TABLE II. BENZOYL DERIVATIVES OF AMINO ACID MENTHYL ESTER,



$\mathrm{BzNH\text{-}\underset{R}{\underset{|}{C}}H\text{-}COOM}$

Benzoyl-amino acid menthyl ester	Yield %	Recryst. solvent[a]	M. p. °C[b]	After recryst. $-[\alpha]_D^{26\sim27}$ [c]	c	Molecular formula	Calcd., %			Found, %		
							C	H	N	C	H	N
Bz gly	88	E-PE	105～106	51.0	0.772	$C_{19}H_{27}O_3N$	71.89	8.57	4.41	71.87	8.63	4.37
Bz L-ala	85	E-PE	112～113	57.7	0.852	$C_{20}H_{29}O_3N$	72.47	8.82	4.23	72.71	9.01	4.07
Bz D-ala	63	E-PE	93～ 94	43.2	0.845	$C_{20}H_{29}O_3N$	72.47	8.82	4.23	72.65	9.09	4.10
Bz DL-ala	86	E-PE	104～105	50.9	0.893	$C_{20}H_{29}O_3N$	72.47	8.82	4.23	72.72	8.91	4.08
Bz L-leu	75	E-PE	119～121	60.6	0.824	$C_{23}H_{35}O_3N$	73.95	9.45	3.75	73.90	9.56	3.68
Bz D-leu	76	E-PE	110～112	28.6	0.802	$C_{23}H_{35}O_3N$	73.95	9.45	3.75	74.03	9.28	3.70
Bz DL-leu	81	E-PE	112～114	41.7	0.796	$C_{23}H_{35}O_3N$	73.95	9.45	3.75	74.18	9.56	3.81
p-NO_2Bz gly	55	Et	160～163	43.6	0.982	$C_{19}H_{26}O_5N_2$	62.96	7.23	7.73	63.46	7.09	7.97

a) Recrystallization solvent: E-PE=ether and petroleum ether; Et=ethyl acetate and ether
b) All melting points are uncorrected.
c) All samples were measured in abs. ethanol at 26～27°C.
All samples exhibited negative rotations.

L-phenylalanine and its *p*-toluenesulfonate) were removed by filtration, and the solvent was evaporated to about 30 ml. in vacuo. To this was added about 30 ml. of ether, and then the acidic material was extracted with 8% sodium hydrogen carbonate. The organic layer was washed once with water and dried with anhydrous sodium sulfate. To this dried solution, dry hydrogen chloride gas was introduced to precipitate the L-phenylalanine M. HCl. The crystals were filtered and washed with ether and petroleum ether. Yield, 5.45 g. (32%); $[\alpha]_D^{27}=-21.8°$ (c 0.623, in abs. EtOH). This was recrystallized from ethyl acetate and ether.

***l*-Menthyl *N*-Benzoyl L-Leucinate.**—3.28 g. (0.025 mol.) ($[\alpha]_D^{27}=+15.3°$, 5 N HCl, c 2.01) of L-leucine, 6.0 g. (0.0385 mol.) of menthol, and 6.0 g. (0.0315 mol.) of *p*-toluenesulfonic acid monohydrate were mixed with 50 ml. of a benzene-toluene mixture (7 : 3) and refluxed with the Dean and Stark distillation apparatus[4,5] for 24 hr. The reaction mixture was then filtered and the solvent removed in vacuo to about 20 ml. Then 20 ml. of ether was added to the solution, and this was extracted with 8% sodium hydrogen carbonate three times. The organic layer was dried with anhydrous sodium sulfate. Dry hydrogen chloride was introduced into the free menthyl ester solution. No hydrochloride of the menthyl ester crystallized. The solvent was removed, and the syrupy ester hydrochloride was dissolved in ether. The ether solution was extracted with 8% sodium hydrogen carbonate to make the free ester. The ethereal solution of the free menthyl ester was dried with anhydrous sodium sulfate. A part of the solution was titrated in an aqueous condition with 0.1 N hydrochloric acid, using methyl red as an indicator to determine the free ester content (0.015 mol., 60%). The solution was then strongly agitated, together with a slight excess of benzoyl chloride (2.39 g., 0.017 mol.) and triethylamine (1.82 g., 0.018 mol.) in ice water. The reaction mixture was washed with 5% sodium hydrogen carbonate, 0.5 N hydrochloric acid, and water. The ethereal solution was dried with anhydrous sodium sulfate. To this solution, petroleum ether was added to precipitate the *N*-benzoyl L-leucine menthyl ester. Yield, 3.84 g. (0.0103 mol.); 75% from free ester. $[\alpha]_D^{27}=-61.0°$ (c 0.960, in abs. EtOH). This was recrystallized from ether and petroleum ether.

Benzoyl D-, L- and DL-Alanine Menthyl Ester.—The benzoylation of the D-, L- and DL-alanine menthyl esters was carried out by the use of sodium ethoxide and benzoyl chloride in absolute alcohol. The yields of the benzoyl derivatives were 85.2, 63.2 and 86.2% respectively. Physical and analytical data are shown in Table II. The *p*-nitrobenzoyl glycine menthyl ester was also prepared by the use of sodium ethoxide and *p*-nitrobenzoyl chloride in absolute alcohol; yield, 55.0%.

The Fractionation of Diastereomers of the DL-Phenylalanine Menthyl Ester.—Two grams of DL-phenylalanine M. HCl was dissolved in 100 ml. of hot ethyl acetate and filtered. About 3 mg. of powdered D-phenylalanine M. HCl in 5 ml. of absolute ether was then added to the filtrate and kept at room temperature for 3 hr. The D-rich crystals obtained weighed 0.40 g.; $[\alpha]_D^{27}=-72.1°$ (c 1.25, in abs. EtOH) (D: 94.5%; L: 5.5%). To the mother liquor 80 ml. of ether was added, and the resulting solution was seeded with D-phenylalanine M. HCl. After standing for 3 hr. at room temperature, an additional 0.52 g. of a D-rich fraction was obtained. $[\alpha]_D^{27}=-64.4°$ (c 1.05, in abs. EtOH) (D: 80.3%; L: 19.7%). By use of the seeding procedure, the first D-rich crystals were fractionated and obtained as pure D-phenylalanine M. HCl. 0.22 g. $[\alpha]_D^{27}=-75.6$ (c 1.29, in abs. EtOH).

The fractionation of DL-methionine M. HCl (1.0 g.) followed essentially the same pattern. However, crystallization was carried out by lefting it stand in the cold for three days. 0.32 g. of D-rich crystals were obtained. $[\alpha]_D^{27}=-59.7°$ (D: 82.7%; L: 17.3%). From the mother liquor, an additional 0.30 g. of D-rich fraction was obtained by evaporation, $[\alpha]_D^{27}=-54.6°$ (D: 55.6%; L: 44.4%).

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