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Optical Resolution of *α*-Ethylbenzylamine and Its Application as a Resolving Agent

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Synopsis. (±)-*α*-Ethylbenzylamine ((±)-**1**) was efficiently resolved into a pair of enantiomers by fractional crystallization as its *cis*-2-benzamidocyclohexanecarboxylic acid (**2**) salt. Moreover, it was found that each of both enantiomers was obtained by mutual resolution between (±)-**1** and (±)-**2**. The optically active amine (**1**) was substantially capable of resolving a variety of chiral carboxylic acids.

Among the many synthetic resolving agents, optically active *α*-methylbenzylamine is widely used for resolving chiral carboxylic acids. But the amine is not necessarily an effective resolving agent for all chiral carboxylic acids. Especially, it is not so effective for resolving such chiral carboxylic acids as chrysanthemic acid (**3**)[1] and pantolactone (**4**). We therefore intend to report on the optical resolution and effective application of **1** as a new synthetic resolving agent which can be used widely.

Optically active *α*-ethylbenzylamine (**1**) is expected to be as effective as *α*-methylbenzylamine on account of their structural similarity. Although many attempts have been made so far for resolving (±)-**1** by fractional crystallization as the salts with (*S*)-(−)-malic acid and (2*R*, 3*R*)-(+)-tartaric acid,[2] and *N*-acetyl-3,5-dibromo-L-tyrosine,[3] no successful method have been reported since a recrystallization of the diastereomeric salt must be repeated several times. Moreover, optically active amine **1** as a resolving agent remains unexplored.

(±)-**1** is readily synthesized from propiophenone, which is commercially available in large quantities by reductive amination with ammonia and hydrogen in the presence of a Raney nickel catalyst.

After primary examinations looking for a suitable resolving agent for (±)-**1**, it was found that optically active *cis*-2-benzamidocyclohexanecarboxylic acid (**2**)[4] gave almost pure (+)- and (−)-**1** in good yields without any recrystallization.

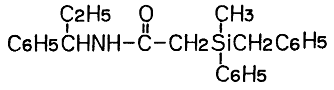
1

2

In the process of the optical resolution described above, such physical properties as the melting point and solubility, infrared spectra of the less soluble salts ((+)-**1**·(−)-**2** and (−)-**1**·(+)-**2**) and those of the racemic salt ((±)-**1**·(±)-**2**) were determined. The less soluble salts did have higher melting points (mp 190—191 °C) and lower solubilities toward methanol than the racemic salt (mp 156—157 °C), and their infrared spectra were found to be identical. These results indicate that crystals of the racemic salt are deposited as a conglomerate and that the racemic salt is resolvable by preferential crystallization, namely mutual resolution.

Actually, (+)-**1**·(−)-**2** salt could be cleanly crystallized from a supersaturated solution of (±)-**1**·(±)-**2** salt in methanol when (+)-**1**·(−)-**2** salt was seeded in the solution. Alternate seeding of (−)-**1**·(+)-**2** or (+)-**1**·(−)-**2** salt to the supersaturated solution gave (−)-**1**·(+)-**2** or (+)-**1**·(−)-**2** salt in moderate to high optical purity. Then, crystals having the same sign of optical rotation were combined, recrystallized, and decomposed with an alkaline solution and hydrochloric acid to give optically pure (+)-**1**, (−)-**2** and (−)-**1**, (+)-**2**, respectively.

The optical purities of the resolved amines were determined by measuring the ^{1}H NMR spectra of the diastereoisomeric amides (**5**) derived from (+)-**1** or (−)-**1** and (+)-(benzylmethylphenylsilyl)acetic acid.[5]



$$\mathrm{C_6H_5}\overset{\mathrm{C_2H_5}}{\mathrm{CH}}\mathrm{NH}-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{CH_2}\underset{\mathrm{C_6H_5}}{\overset{\mathrm{CH_3}}{\mathrm{Si}}}\mathrm{CH_2C_6H_5}$$

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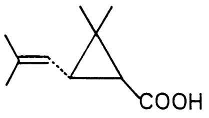
Then, the optically active amine (**1**) was applied in order to resolve such chiral carboxylic acids as chrysanthemic acid (**3**), pantolactone (**4**), and *N*-carbamoylmethionine(**6**), which were not efficiently resolved using *α*-methylbenzylamine.



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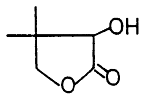

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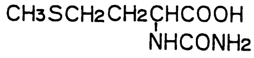

$$\mathrm{CH_3SCH_2CH_2}\underset{\mathrm{NHCONH_2}}{\mathrm{CH}}\mathrm{COOH}$$

6

As summarized in Table 1, the amine (**1**) have apparently clear advantages for the optical resolution of the above-mentioned chiral carboxylic acids.

Experimental

All melting points were measured by a Laboratory Devices MEL-TEMP apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360 Digital Polarime-

Table 1. Resolution of Racemic Carboxylic Acids Using (+)- or (−)-**1**

Salt				Liberated acid			
	Recrystallization solvent	Mp/°C	$[\alpha]_D$/° [a] (°C)		Total yield/% [b]	$[\alpha]_D$/° (°C)	Optical purity (%)
(−)-**3**·(+)-**1**	MeOH	138—140	−9.5 (20)	(−)-**3**	28	−13.1 (16) (*c* 1.0, EtOH)	94 [c]
(+)-**4′**·(−)-**1**	MEK	123—125	+22.2 (21)	(−)-**4**	56	−40.7 (25) (*c* 1.0, H_2O)	80 [d]
(−)-**4′**·(+)-**1**	MEK	125—127	−25.3 (25)	(+)-**4**	60	+47.8 (24) (*c* 1.0, H_2O)	95 [d]
(+)-**6**·(+)-**1**	H_2O	191—195	+3.3 (19)	(+)-**5**	42	+17.4 (19) (*c* 1.0, EtOH)	100 [e]

a) (*c* 1.0, MeOH). b) Based on half the amount of (±)-carboxylic acid used. c) Based on $[\alpha]_D^{25}$−14.01° (*c* 1.535, EtOH) from Merk Index. d) Based on $[\alpha]_D^{25}$−50.7° (*c* 2.05, H_2O) and $[\alpha]_D^{25}$+50.1° (*c* 2.0, H_2O) from Merk Index. e) Based on $[\alpha]_D^{26}$+17.4° (*c* 1.0, EtOH), optically active *N*-carbamoylmethionine derived from optically pure methionine.

ter. The ^{1}H NMR spectra were recorded with a JEOL FX-90Q spectrometer. The IR spectra were determined on a JASCO A-302 spectrophotometer.

Fractional Crystallization of 1·2 Salt. A clear solution of (±)-**1** (20.25g, 150 mmol) and (+)-**2** (29.68 g, 120 mmol) in methanol (150 ml) at an elevated temperature was allowed to cool slowly at room temperature and stand overnight. The white precipitates which appeared were collected by filtration to give almost pure (−)-**1**·(+)-**2** salt (20.97 g, 54.8 mmol) without any recrystallization: Mp 187—190 °C: $[\alpha]_D^{26}$+27.4° (*c* 1.00, MeOH).

Found: C, 72.07; H, 7.84; N, 7.30%. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.90; N, 7.23%.

To the salt was added a 1M NaOH solution (65 ml) in order to decompose the salt. The liberated amine was extracted with ether (2×45 ml), and the ethereal extracts were combined, dried over potassium hydroxide pellets, and concentrated under reduced pressure to give (−)-**1** (7.26 g, 53.7 mmol): $[\alpha]_D^{24}$−6.27° (*c* 1.276, EtOH); optical purity 95% ee.

The plus enriched amine recovered from the mother liquor (12.4 g, 92.2 mmol) was similarly reacted with (−)-**2** (22.80 g, 92.2 mmol) in methanol on heating. Cooling the solution at room temperature gave (+)-**1**·(−)-**2** salt (18.17 g, 47.5 mmol): Mp 187—191 °C ; $[\alpha]_D^{20}$−26.2° (*c* 1.098, MeOH). The similar treatment of the salt gave (+)-**1** (6.16 g, 45.6 mmol): $[\alpha]_D^{18}$+5.98° (*c* 1.00, EtOH); 91% ee.

Preferential Crystallization of (±)-1·(±)-2 Salt. A refluxed clear solution of an equimolar amount of (±)-**1** (3.53 g) and (±)-**2** (6.47 g) in methanol (35 ml) was allowed to cool at about 40 °C, seeded with (−)-**1**·(+)-**2** salt (41 mg, Mp 190—191 °C, $[\alpha]_D^{30}$+28.8° (*c* 1.00, MeOH)) and kept overnight at room temperature. The precipitates which appeared were collected by filtration, washed with a small amount of methanol, and dried over P_2O_5 to give 0.25 g of (−)-**1**·(+)-**2** salt ($[\alpha]_D^{28}$+24.6° (*c* 0.85, MeOH)). Successively, (±)-**1**·(±)-**2** salt (0.30 g) was added to the filtrate and dissolved at an elevated temperature. The solution was similarly cooled, seeded with (+)-**1**·(−)-**2** salt (46 mg, Mp 190—191 °C, $[\alpha]_D^{27}$−28.8° (*c* 1.00, MeOH)) and kept overnight at room temperature to yield 0.29 g of (+)-**1**·(−)-**2** salt ($[\alpha]_D^{26}$−27.1° (*c* 0.96, MeOH)). The process was repeated in a similar manner by supplying about 0.50 g of (±)-**1**·(±)-**2** salt in each run to give 0.30—0.63 g of optically active **1**·**2** salt. From the initial six runs, 1.34 g of (+)-**1**·(−)-**2** salt and 0.93 g of (−)-**1**·(+)-**2** salt were obtained, and recrystallized from methanol to give 0.98 g of (+)-**1**·(−)-**2** salt (Mp 190—191 °C, $[\alpha]_D^{27}$−28.8° (*c* 1.11, MeOH)) and 0.65 g of (−)-**1**·(+)-**2** salt (Mp 189—191 °C, $[\alpha]_D^{27}$+28.2° (*c* 1.00, MeOH)). Decomposition of the salts gave (+)-**1** (0.29 g), (−)-**2** (0.60 g) and (−)-**1** (0.21 g), (+)-**2** (0.40 g) respectively.

(+)-**1**: $[\alpha]_D^{30}$+6.6° (*c* 1.49, EtOH); 100 % ee.

(−)-**2**: Mp 205—207 °C; $[\alpha]_D^{26}$−36.4° (*c* 1.00, EtOH); 100% ee.

(−)-**1**: $[\alpha]_D^{30}$−6.5° (*c* 2.00, EtOH); 98% ee.

(+)-**2**: Mp 202—205 °C; $[\alpha]_D^{31}$+35.6° (*c* 0.86, EtOH); 98% ee.

Resolution of (±)-Pantolactone ((±)-4) with (−)-1 and (+)-1. A solution of 6.50 g (50 mmol) of (±)-**4** in water (25 ml) was treated with sodium hydroxide (2.24 g) and heated to 80—90 °C to hydrolyze the lactone. After cooling the the solution, the pH of the solution was adjusted to 8.5 with 2M HCl (1M=1 mol dm^{-3}). To the solution was added 6.76 g (50 mmol) of (−)-**1**, which was dissolved in 2M HCl (25 ml). The solution was concentrated under reduced pressure and the organic salts were extracted with 2-butanone (MEK) (60 ml). The extract was concentrated (10 ml) and allowed to stand overnight. The white precipitates which appeared were collected by filtration and dried over P_2O_5 to yield the salt (4.27 g, 15.1 mmol) of (+)-2,4-dihydroxy-3,3-dimethylbutyric acid ((+)-**4′**) and (−)-**1**: Mp 123—125 °C; $[\alpha]_D^{21}$+22.2° (*c* 1.00, MeOH).

After treating the salt with 1M NaOH (18 ml), the liberated amine was extracted with ether (2×10 ml). To the aqueous layer was added 2M HCl (10 ml); the solution was then evaporated in vacuo. The residue was then extracted with ether (2×5 ml) and dried over Na_2SO_4; the solvent was evaporated to give (−)-**4** (1.82 g, 14.0 mmol): Mp 84—87 °C; $[\alpha]_D^{25}$−40.7° (*c* 1.00, H_2O); 80.3% ee.

A similar treatment of the plus enriched lactone recovered from the mother liquor with (+)-**1** (4.72 g, 34.9 mmol) gave (−)-**4′**·(+)-**1** salt (4.54 g, 16.0 mmol): Mp 125—127 °C; $[\alpha]_D^{25}$−25.3° (*c* 1.00, MeOH). Decomposition of the salt gave (+)-**4** (1.96 g, 15.1 mmol): Mp 85—88 °C; $[\alpha]_D^{24}$+47.8° (*c* 1.00, H_2O); 95.4% ee.

Results of the resolution of (±)-**3** and (±)-**5** with (+)-**1** are shown in Table 1.

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