Short Communication

Optical Resolution of 2-(4-Chlorophenyl)-3-methylbutanoic Acid by Preferential Crystallization with Achiral Amines

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Recently, fenvalerate [α -cyano-3-phenoxybenzyl 2-(4-chlorophenyl)-3-methylbutanoate] (**1**), one of the synthetic pyrethroids, has been used as an agricultural insecticide, for especially pest control on cotton.¹⁾ As **1** has two asymmetric centers in the molecule, four optical isomers theoretically exist. Although it is known that (*S*)-(+)- α -cyano-3-phenoxybenzyl (*S*)-(+)-2-(4-chlorophenyl)-3-methylbutanoate is the most powerful isomer for the biological activity, fenvalerate is supplied as an equivalent mixture of the four isomers at present.

Optically active 2-(4-chlorophenyl)-3-methylbutanoic acid (**2**) had already been obtained by fractional crystallization using (–)- α -methylbenzylamine or (+)-1-phenyl-2-(4-methylphenyl)ethylamine as a resolving agent.²⁾ From an industrial point of view, preferential crystallization, which is applicable in optical resolution without an expensive resolving agent, is generally more attractive than fractional crystallization.

In the course of our studies on optical resolutions by preferential crystallization,³⁾ we

were interested in the resolution of **2**. Through preliminary experiments,⁴⁾ the salt of **2** with diethylamine seemed to be possible for success. The preferential crystallization of **2** was carried out using a supersaturated solution of equimolar amounts of **2** and diethylamine in water. The structural assignment of the precipitated crystalline solid was made by nitrogen analysis (Found: N, 2.80%. Calcd for $C_{26}H_{37}Cl_2NO_4$: N, 2.81%), and its NMR spectrum [(CDCl₃) (δ) 0.67, 1.03 (d, $J=6.5$ Hz, 12H, $-C(CH_3)_2$), 1.00 (t, $J=7.0$ Hz, 6H, $C-CH_3$), 2.0~2.5 (m, 2H, $-CH-$), 2.70 (q, $J=7.0$ Hz, 4H, $N-CH_2$), 3.04 (d, $J=11.0$ Hz, 2H, $CH-CO$), 7.28 (s, 4H, C_6H_4), 9.82 (s, 3H, $-COOH$, NH)]. These data indicate that the salt consisted of 2 mol of **2** and 1 mol of diethylamine. It is interesting that the solubilities of the salts of **2** with diethylamine in water change dramatically depending on the constitution of the salt; *i.e.*, the salt which consists of equimolar amounts of **2** and diethylamine is easily soluble in water, while that of 2 mol of **2** and 1 mol of diethylamine (**3**) is hardly soluble in water. Thus, it is considered that the former salt acts as a kind of buffer to stabilize the supersaturation of the unseeded antipode of **3**.³⁾

Although the details of the crystalline structure of the precipitated salt (**3**) has not yet been examined, two molecules of **2** in the precipitated salt fortunately have the same sign of optical rotation. Thus the preferential crystallization of (+)-**3** and (–)-**3** was successfully carried out in an alternating and sequential manner by supplying each time to the filtrate the corresponding amounts of ($\pm$)-**2** and diethylamine (2:1) to the precipitated (+)- or (–)-**3**.

In a typical experiment, (+)-**3** (2.5 g) and ($\pm$)-**3** (2.5 g) were dissolved in a solution of ($\pm$)-**2** (36.2 g, 0.17 mol) and diethylamine

TABLE I. THE RESULT OF THE PREFERENTIAL CRYSTALLIZATION OF 3

Run	Added ($\pm$)-3 (g)	Precipitated optically active salt			
		Yield (g)	$[\alpha]_{435}^{\circ}$ (<i>c</i> 2.0, MeOH)	Temp. (°C)	Optical purity (%)
1	—	4.8	+28.6	13	93.1
2	4.8	5.6	−26.0	25	85.2
3	5.6	6.0	+27.9	21	91.5
4	5.0	5.2	−26.7	20	87.5
5	5.0	4.2	+26.1	21	85.6
6	7.0	6.3	−28.7	21	94.1
7	9.0	8.6	+27.2	20	89.2

(12.4 g, 0.17 mol) in water (150 ml) at about 80°C. The solution was stirred slowly with external cooling. Optically pure (+)-3 (250 mg, $[\alpha]_{435}^{21} + 30.5^{\circ}$ (*c* 2.0, MeOH)) was seeded to the solution at about 47°C. The solution was cooled with stirring to about 25°C, and then allowed to stand for 10 min at this temperature. The precipitates which appeared were collected by filtration to give (+)-3 (4.8 g, 93.1% optical purity). Successively, ($\pm$)-3 (4.8 g) was added to the filtrate and dissolved at an elevated temperature. The solution was similarly cooled, seeded with (−)-3 (250 mg, $[\alpha]_{435}^{21} - 30.5^{\circ}$ (*c* 2.0, MeOH)), and allowed to stand at 25°C for 10 min. The precipitated crystals were filtered to give (−)-3 (5.6 g, 85.2% optical purity). The process was repeated in a similar manner and (+)- and (−)-3 were alternately obtained. The result of these procedures is summarized in Table I.

Recrystallization of these combined portions of (+)-3 (10 g) from a mixed solvent (water–2-propanol=1:1) (18 ml) gave 7.4 g (74%) of (+)-3 ($[\alpha]_{435}^{21} + 30.1^{\circ}$ (*c* 2.0, MeOH), 98.7% optical purity). By treating the salt with

1 M HCl, followed by extraction with ether, 6.7 g (96%) of (+)-2 ($[\alpha]_D^{21} + 47.5^{\circ}$ (*c* 2.0, CHCl₃), 99.0% optical purity) was obtained.

In a similar manner to that described above 6.2 g of (−)-2 ($[\alpha]_D^{20} - 46.9^{\circ}$ (*c* 2.0, CHCl₃), 97.7% optical purity) was obtained from 10 g of (−)-3.

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- 3) H. Nohira, M. Kai, M. Nohira, J. Nishikawa, T. Hoshiko and K. Saigo, *Chem. Lett.*, **1981**, 951.
- 4) The salts of 2 with several amines such as isopropylamine, butylamine, cyclohexylamine, benzylamine, dimethylamine, dibutylamine and diisopropylamine, and the sodium potassium, and ammonium salts were prepared and their properties (melting point, solubility, and IR spectrum) examined.