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Optical Resolution of 2-(Anilinomethyl)pyrrolidine

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Synopsis. (±)-2-(Anilinomethyl)pyrrolidine, prepared from (±)-5-oxopyrrolidine-2-carboxylic acid, was effectively resolved into a pair of the enantiomers by fractional crystallization of its mandelic acid salt. Moreover, the preferential crystallization of its *p*-hydroxybenzoic acid salt was found to give both enantiomers in high optical purities by alternate seeding.

Optically active 2-(anilinomethyl)pyrrolidine is widely used as an effective chiral source for asymmetric inductions.[1)] The diamine has been prepared from optically active proline[1a)] or glutamic acid[2)] maintaining the asymmetric center. The methods have a problem in total yield, chemical purity and/or optical purity, especially in the case of the preparation in a large scale, since they involve multiple reaction steps or drastic reaction conditions. In this paper, we wish to report a convenient and practical method for the preparation of a pair of the enantiomers of 2-(anilinomethyl)pyrrolidine.

(±)-(Anilinomethyl)pyrrolidine ((±)-**1**) was easily prepared by the reaction of commercially available (±)-5-oxopyrrolidine-2-carboxylic acid and aniline according to the procedure in the literature, followed by the reduction with $LiAlH_4$. After several examinations of a suitable resolving agent for the resolution of (±)-**1**, it was found that the effective fractional crystallization was achieved by utilizing optically active mandelic acid (**2**) to give almost optically pure (+)- and (−)-**1** over 65% yields without recrystallization. Moreover, the efficiency of the resolution was found to unchange by reducing the amount of **2** to 0.8 equimolar amount because there is great difference in the solubilities of the diastereomeric pair and **1** is very soluble in the solvent used.

Next, to find out the derivative of **1** resolvable by preferential crystallization which gives more conveniently both enantiomers, salts of **1** with achiral carboxylic acids such as acetic, cinnamic, phthalic, *cis*-cyclohexanedicarboxylic, benzoic, *p*-nitrobenzoic, *p*-chlorobenzoic, and *p*-hydroxybenzoic acids were prepared. Among these salts, *p*-hydroxybenzoic acid salt (**3**) was found to be deposited as conglomerate, which can be resolved by preferential crystallization.

Actually, 1.73 g of (+)-**3** was obtained in 94% optical purity by seeding of optically pure (+)-**3** to the supersaturated solution of (±)-**3** and (±)-**1**·(±)-lactic acid salt, which is readily soluble in the solvent employed and plays as a kind of buffer to decrease the concentration change of 2-(anilinomethyl)pyrrolidinium ion during the crystallization. Alternate seeding of (−)- or (+)-**3** to the supersaturated solution in a similar magnitude gave (−)- or (+)-**3** in 93—98% optical purity. The initial part of the preferential crystallization is shown in Table 1.

Experimental

Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The values of specific rotation were measured on a JASCO DIP-181 digital polarimeter.

Materials. 5-Oxopyrrolidine-2-carboxanilide was prepared in 82% yield from 0.5 ml of (±)-5-oxopyrrolidine-2-carboxylic acid and 320 ml of aniline according to the method described in the literature,[3)] and half the amount of aniline used was able to be recovered after the reaction period. The reaction of 0.36 mol of the anilide with 2.5 molar amounts of $LiAlH_4$ in THF gave (±)-**1** in 89% yield.

The optically pure diastereomeric salts ((+)-**1**·(+)-**2** and (−)-**1**·(−)-**2**) for seeds were prepared by the method described below in one-fourth scale without seeding, followed by recrystallizations from 99% methanol for three times: mp 172—173 °C; $[\alpha]^{18}_{435}$ + and −185.0° (*c* 1.00, 99% MeOH).

Table 1. Preferential crystallization of (±)-**3**

Run	(±)-**3** Added / g	Seed	Cooling Temp/°C	Cooling Time/min	Yield / g	$[\alpha]_{435}$[a)]/°	Optical purity/%[b)]
1	—	(+)	6	120	1.73	+76.9	94
2	2.50	(−)	6	120	3.50	−76.4	93
3	4.00	(+)	6	60	4.50	+78.2	95
4	4.50	(−)	15	50	4.76	−77.8	95
5	4.50	(+)	15	50	4.38	+79.0	96
6	4.50	(−)	15	40	4.23	−79.4	97
·	·	·	·	·	·	·	·
·	·	·	·	·	·	·	·
·	·	·	·	·	·	·	·

a) *c* 1.00, 99% MeOH. b) Based on $[\alpha]_{435}$+or −82.0°.

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Found: N, 8.64%; 8.53%. Calcd for $C_{19}H_{24}N_2O_3$: N, 8.53%.

Racemic and optically active **3** were obtained in 83—88% yields from equimolar amounts of *p*-hydroxybenzoic acid and (±)-, (+)-, and (−)-**1**, respectively, followed by recrystallization from 95% ethanol.

Racemic form: mp 160—162 °C.

Found: N, 8.96%. Calcd for $C_{18}H_{22}N_2O_3$: N, 8.91%.

Optically active forms: mp 176—177 °C, $[\alpha]_{435}^{18.5}$ + and −82.0° (*c* 1.00, 99% MeOH).

Found: N, 9.00%, 8.82%. Calcd for $C_{18}H_{22}N_2O_3$: N, 8.91%.

*Fractional Crystallization of **1·2** Salt.* To a gently refluxing solution of (±)-**1** (35.25 g, 0.200 mol) in 99% methanol (300 ml) was added a solution of (+)-**2** (24.32 g, 0.160 mol) in 99% methanol (100 ml) in a period of 15 min. The solution was seeded with crystals of (+)-**1**·(+)-**2** salt (50 mg), stood for 40 min at room temperature, and cooled with an ice bath for 2.5 h. The precipitates appeared were collected by filtration, washed with a small amount of 99% methanol, and dried over P_2O_5 to yield 23.74 g (72%) of (+)-**1**·(+)-**2** salt: mp 172.5—173.5 °C; $[\alpha]_{435}^{14.5}$ +184.5° (*c* 0.99, 99% MeOH). The suspension of the salt in benzene (170 ml) was treated with 1 M NaOH solution (110 ml) to decompose the salt. After separation of the organic layer, the aq. solution was extracted with benzene (2×100 ml). The organic layer and the extracts were combined, dried with K_2CO_3, and concentrated under reduced pressure. Distillation of the oil remained gave 11.89 g (67% total yield) of (+)-**1**: bp 134—135 °C/80 Pa; $[\alpha]_{589}^{20}$ +19.3° (*c* 0.98, abs. EtOH).

The minus enriched diamine recovered from the mother liquor (21.70 g, 0.123 mol) in 99% methanol (200 ml) was similarly reacted with (−)-**2** (18.70 g, 0.123 mol) in 99% methanol (100 ml), and the solution was seeded with (−)-**1**·(−)-**2** salt (50 mg) to give 25.54 g (78%) of (−)-**1**·(−)-**2** salt: mp 172—173 °C; $[\alpha]_{435}^{15}$ −184.0° (*c* 0.96, 99% MeOH). The similar treatment of the salt with 1 M NaOH solution gave 12.66 g (72% total yield) of (−)-**1**: bp 133—134 °C/80 Pa; $[\alpha]_{589}^{18}$ −19.2° (*c* 1.07, abs. EtOH).

GLC analysis of the products, (+)- and (−)-**1**, gave no peak other than one arising from **1**. No rise of the specific rotations of (+)-**1**·(+)-**2** and (−)-**1**·(−)-**2** salts ($[\alpha]_{435}$ + and −185.0°) used as seeds was observed by recrystallizations for more three times, and the specific rotations at 589 nm in abs. ethanol of (+)- and (−)-**1** liberated from the salts were + and −19.3°, respectively, which were considered to be maximal values of the specific rotations. Based on the data, the chemical and optical purities of (+)- and (−)-**1** obtained here were considered to be over 99%.

The resolving agents used, (+)- and (−)-**2**, were satisfactorily recovered over 93% yield without racemization from the corresponding aq. solution by acidification with aq. HCl solution, followed by extraction with ether.

*Preferential Crystallization of **3**.* A refluxed clear solution of (±)-**3** (11.62 g) and (±)-**1**·(±)-lactic acid (12.78 g) in 95% ethanol (60 ml) was allowed to cool at about 40 °C, seeded with (+)-**3** (20 mg), and stood for 2 h at around 6 °C. The precipitates appeared were collected by filtration, washed with a small amount of 95% ethanol, and dried over P_2O_5 to give 1.73 g of (+)-**3** (94% optical purity). Successively, (±)-**3** (2.50 g) was added to the filtrate and dissolved at an elevated temperature. The solution was similarly cooled, seeded with (−)-**3** (20 mg), and stood at 6 °C for 2 h to yield 3.50 g of (−)-**3** (93% optical purity). The process was repeated in a similar manner supplying 4.50 g of (±)-**3** in each run to give 4.0—4.8 g of optically active **3** in 93—98% optical purity. The initial six runs is shown in Table 1. The crystals having the same sign of optical rotation were combined and recrystallized from 95% ethanol, giving almost optical pure (+)- or (−)-**3** in 86—90% yield. For examples, recrystallization of 10.30 g of (+)-**3** (95% optical purity on the average) from 95% ethanol (85 ml) gave almost optically pure (+)-**3**: 9.02 g (88%); $[\alpha]_{435}^{15}$ +81.7° (*c* 1.01, 99% MeOH); >99% optical purity. Suspension of the salt in benzene (60 ml) was treated with 3 M NaOH solution (120 ml). After separation of the organic layer, the aq solution was extracted with benzene (2×50 ml). The organic layer and the extracts were combined, dried with K_2CO_3, and concentrated under reduced pressure. Bulb to bulb distillation of the crude product gave 4.21 g (94%) of (+)-**1**: bp 150 °C (bath temperature)/106 Pa; $[\alpha]_{589}^{19}$ +19.2° (*c* 1.45, abs. EtOH); >99% chemical and optical purities.

Similarly, recrystallization of 12.19 g of (−)-**3** (95% optical purity on the average) gave almost optically pure (−)-**3**: 10.56 g (87%); $[\alpha]_{435}^{18.5}$ −81.8° (*c* 1.02, 99% MeOH). Decomposition of the salt, followed by distillation gave 5.01 g (93%) of (−)-**1**: $[\alpha]_{589}^{19}$ −19.3° (*c* 1.39, abs. EtOH); >99% chemical and optical purities.

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