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OPTICAL RESOLUTION OF 3-*endo*-BENZAMIDO-5-NORBORNENE-2-*endo*-CARBOXYLIC ACID AND ITS APPLICATION AS A NEW RESOLVING AGENT

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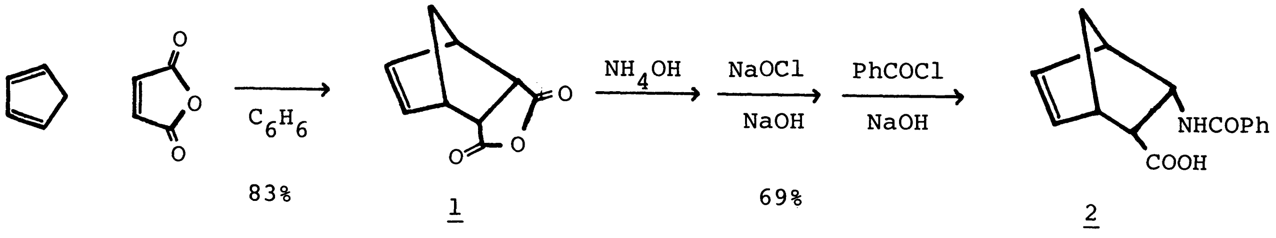
3-*endo*-Benzamido-5-norbornene-2-*endo*-carboxylic acid was synthesized from 5-norbornene-2-*endo*,3-*endo*-dicarboxylic anhydride in one pot and easily resolved into a pair of optically active forms by preferential crystallization of its dibenzylamine salt. The optically active acid was successfully applied to the optical resolution of (±)-ephedrine as a new resolving agent.

In the previous papers, it was reported that *cis*-2-benzamidocyclohexanecarboxylic acid can be resolved into the optically active forms by preferential crystallization1) and is successfully applied to the optical resolution2) of chiral alcohols and amines as a resolving agent. We present here the synthesis and the optical resolution of 3-*endo*-benzamido-5-norbornene-2-*endo*-carboxylic acid, which is expected to be useful in the optical resolution of amines as a new acidic resolving agent.

3-*endo*-Benzamido-5-norbornene-2-*endo*-carboxylic acid (2) was easily synthesized in one pot from 5-norbornene-2-*endo*,3-*endo*-dicarboxylic anhydride (1), prepared



from cyclopentadiene and maleic anhydride, *via* three reaction steps, *i.e.*, ammonolysis, the Hofmann reaction, and the Schotten-Baumann reaction.

The resolution of (±)-2 was performed by fractional crystallization of its [(*cis*-2-benzylamino)cyclohexyl]methanol[3] salt.[4] However, the fractional crystallization of the diastereomeric salt is unsuitable for the resolution of (±)-2 in a large scale because recrystallization for several times is required to obtain the diastereomer in a high optical purity.

In order to find out a more practical method applicable to a large scale resolution, the preferential crystallization of the acid itself and its salts with several achiral amines were examined. An efficient resolution was achieved when dibenzylamine salt (3) of 2 was employed. The infrared spectra and the X-ray diffraction patterns of racemic 3 and optically active 3 are completely identical, and the solubility of racemic 3 in 65% methanol is greater than that of optically active 3. These facts indicates that crystal of 3 deposits as a conglomelate from 65% methanol. The success of the preferential crystallization can be attributed to crystal of 3 being a conglomerate.

Synthesis of (±)-2. 5-Norbornene-2-*endo*,3-*endo*-dicarboxylic anhydride (1) was prepared by the procedure described in a literature.[5] To a mixture of 25% NH_4OH (55 ml) and water (200 ml) was added powdered 1 (30 g, 0.18 mol) in small portions at 0°C with stirring, and a cold solution of NaOH (22 g, 0.55 mol) in water (100 ml) was successively added to the resulting clear solution at 0°C. After evaporation of excess ammonia at around 40°C, 2.04 M NaOCl (90 ml, 0.18 mol) was added to the solution diluted with water (300 ml) in a period of 1 hr with stirring at 0°C, and the mixture was stirred for additional 10 min. The solution was then warmed at around 70°C for 5 min. After cooling again at 0°C, a solution of benzoyl chloride (27.2 g, 0.21 mol) in dioxane (25 ml) was added to the solution in a period of 1 hr with vigorous stirring, and the reaction mixture was stirred for an additional 1 hr. Insoluble materials were filtered off, and 4 M HCl (138 ml) was added to the filtrate, giving crude (±)-2. The precipitates were washed with hot water (300 ml), decolored with active carbon, and recrystallized from 99% ethanol to give 32.6 g (69% total yield) of pure (±)-2 (mp 197-198°C; Found: N, 5.18%. Calcd for $C_{15}H_{15}NO_3$: N, 5.44%).

Optical Resolution of (±)-3 by Preferential Crystallization. To a saturated solution of (±)-3[6] (11.9 g) in 65% methanol (50 ml), in which 1-amino-2-propanol salt[7] of (±)-2 (11.0 g) was coexisted, was added (±)-3 (2.00 g), and the mixture was refluxed, giving a clear solution. The solution was cooled, seeded with (+)-3[8] (0.10 g), and stirred gently with a mechanical stirrer at around 10°C for 90 min. White crystals appeared were collected by filtration, washed with a small amount of 65% methanol, and dried over P_2O_5, giving 2.50 g of (+)-3 ($[\alpha]_{435}^{20}$ +185°; 92% optical purity). Successively, (±)-3 (2.80 g) was added to the filtrate and dissolved at an elevated temperature. The solution was similarly cooled, seeded with (-)-3[8] (0.10 g), stirred at 10°C for 40 min. Similar treatment of white crystals separated gave 2.48 g of (-)-3 ($[\alpha]_{435}^{21}$ -180°; 89% optical purity). The process was repeated in a similar manner, and (+)- and (-)-3 were alternately obtained. The crystals having the same sign of optical rotation were combined and recrystallized from 65% methanol, giving a pair of optically pure 3 ($[\alpha]_{435}$ + and -202°). The salts were decomposed with 2 M NaOH, and liberated dibenzylamine was extracted with ether. Acidification of the aqueous solutions with 2 M HCl yielded (+)- and (-)-2, respectively (mp 180-181°C; $[\alpha]_{435}^{20}$ + and -254°, $[\alpha]_{589}^{20}$ + and -112° (c 1.00, MeOH); Found: N, 5.23 and 5.19%. Calcd for $C_{15}H_{15}NO_3$: N, 5.44%).

Resolution of (±)-Ephedrine (4) Using (+)-2 as a Resolving Agent. To a solution of (+)-2 (779 mg, 3.03 mmol) and (±)-4 (500 mg, 3.03 mmol) in 95% ethanol (1 ml) was added ether (7 ml), giving white mass (759 mg). A suspension of the powdered mass in a mixture of 95% ethanol (0.5 ml) and ether (5 ml) was refluxed for 30 min, and insolubilized crystals and precipitates deposited on cooling were filtered together, powdered finely, and dried over P_2O_5 to give 449 mg (70% yield)[9] of (+)-2·(+)-4 salt (mp 158-159°C; $[\alpha]_{589}^{20}$ +122.2° (c 1.00, MeOH)). Treatment of the salt (300 mg) with 2 M HCl (3 ml) liberated white precipitates. After filtration, the filtrate was washed with ether (20 ml), concentrated, and dried over P_2O_5 to give 138 mg (97% yield) of (+)-4·HCl salt (mp 212-216°C; $[\alpha]_{589}^{19}$ +34.8° (c 1.00, H_2O); 98% optical purity based on the specific rotation reported in a literature).[10]

References and Notes

1) H. Nohira, K. Watanabe, and M. Kurokawa, *Chem. Lett.*, 1979, 299.

2) H. Nohira, H. Miura, M. Kurokawa, Y. Takada, and A. Tomita, *Preprints for the 34th Annual Meeting of Chemical Society of Japan, Tokyo, April 1976*, Vol. III, p 600, 1C38.

3) Optically active [(*cis*-2-benzylamino)cyclohexyl]methanol was easily prepared by the $LiAlH_4$ reduction of optically active *cis*-2-benzamidocyclohexanecarboxylic acid.
J. Nishikawa, T. Ishizaki, F. Nakayama, H. Kawa, K. Saigo, and H. Nohira, *Nippon Kagaku Kaishi*, 1979, 754.

4) Recrystallization of the diastereomeric salt from ethyl acetate for three times followed by decomposition of the resulting salt gave (+)- and (-)-2 (mp 179-180°C; $[\alpha]_{435}$ + and -254° (c 0.50, MeOH)).

5) O. Diels and K. Alder, *Liebig Ann. Chem.*, 460, 98 (1928).

6) Prepared from (±)-2 and dibenzylamine and recrystallized from 65% methanol (mp 134-135°C; Found: N, 5.94%. Calcd for $C_{29}H_{30}N_2O_3$: N, 6.16%).

7) In this procedure, the readily soluble 1-amino-2-propanol salt of (±)-3 plays as a kind of buffer, stabilizing the preferential crystallization significantly.

8) mp 147-148°C; $[\alpha]^{25}_{435}$ + and -202°, $[\alpha]^{25}_{589}$ + and -88.6° (c 1.00, MeOH); Found: N, 5.91 and 5.87%. Calcd for $C_{29}H_{30}N_2O_3$: N, 6.16%.

9) Based on half the amount of (±)-4 used.

10) R. H. F. Manske and T. B. Johnson, *J. Am. Chem. Soc.*, 51, 1906 (1929).

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