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OPTICAL RESOLUTION OF N-BENZOYL-*CIS*-2-AMINOCYCLOHEXANECARBOXYLIC ACID BY PREFERENTIAL CRYSTALLIZATION

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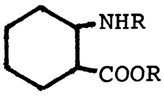
(±)-N-Benzoyl-*cis*-2-aminocyclohexanecarboxylic acid has been resolved smoothly by preferential crystallization procedure in the form of its benzylamine salt. A typical run for this procedure has been presented.

It has been recently found that optically active N-benzoyl-*cis*-2-aminocyclohexanecarboxylic acids [(+) and (-)-*cis*-**1**] are a pair of useful optical resolving agents effective for the resolution of menthol, ephedrine and 1-amino-2-propanol.[1)]



1 R = COC_6H_5 R' = H
2 R = COC_6H_4X R' = H
3 R = COC_6H_5 R' = $NH_3CH_2C_6H_5$

The resolution of (±)-*cis*-**1** can be performed by fractional crystallization of its cinchonidine salt.[2)] However, it is not easy to obtain the pure (-)-isomer, because the (-)-isomer forms the more soluble diastereoisomeric salt.

In order to find out a more practical method for the resolution of (±)-*cis*-**1**, the acid itself and its variously substituted derivatives (*cis*-**2**) were tested for preferential crystallization by following the case of its *trans*-isomer (*trans*-**1**).[3,4)]

In this direction of work, however, none of the derivatives suitable for the preferential crystallization could be found.[5)]

A successful resolution was encountered when the benzylamine salt of *cis*-**1** was adopted. In this case, both X-ray diffraction patterns and infrared spectra of the active salt and the racemic salt are identical, and the racemic salt is more soluble than the active salt in water, a suitable solvent for the crystallization.

The following example is a typical run for the new procedure. In this procedure, the readily soluble salt of the racemic acid with 1-amino-2-propanol, for example, acts as a kind of buffer, stabilizing the preferential crystallization significantly.

A mixture of 24.7g of (±)-*cis*-**1** (mp 176°C)[6)] and 7.5g of 1-amino-2-propanol was dissolved in 120ml of water. To this solution was added 7.1g of (±)-*cis*-**3** (mp 85-87°C),[7)] and dissolved at an elevated temperature. The mixture was cooled, seeded with 0.03g of (+)-*cis*-**3** (mp 104-105°C, $[\alpha]^{25}_{589}$ +24.5°, c=1.06 EtOH) and allowed to stand for 2 hr. The precipitated crystals were collected by filtration, washed with a small amount of cold water and dried. The crystals weighed 2.69g ([α]$^{25}_{589}$ +23.3°, optical purity 95.5%). Subsequently, to the mother liquor was added 4.0g of (±)-*cis*-3, and dissolved at an elevated temperature. The mixture was cooled, seeded with pure crystals of (-)-*cis*-3 (mp 104-105°C, [α]$^{25}_{589}$ -24.5°) and allowed to stand for 2 hr to give 5.51g of (-)-*cis*-3 ([α]$^{25}_{589}$ -23.5°, optical purity 96.0%). The process was repeated analogously. Crystals with the same sign of the rotation were put together and recrystallized from water to give a pair of pure active salts. The salts were decomposed with 4N-hydrochloric acid to give the carboxylic acids, which were recrystallized from ethanol to give pure (+) and (-)-*cis*-1 (mp 209-210°C, [α]$^{25}_{589}$ + and -41.0°, c=1.11 EtOH).

References and Notes

1) H. Nohira, H. Miura, M. Kurokawa, Y. Takada, and A. Tomita, to be presented at the 34th Meeting of the Chemical Society of Japan, April 1976.
2) W. L. F. Armarego and T. Kobayashi, J. Chem. Soc. (C), 1969, 1635, and 1970, 1597.
3) H. Nohira, K. Ehara, and A. Miyashita, Bull. Chem. Soc. Japan, 43,2230 (1970).
4) H. Nohira, and H. Miura, Nippon Kagaku Zasshi, 1975, 1122.
5) The following substituted benzoyl derivatives (*cis*-2) have been prepared. The substituents cited correspond to X in *cis*-2, *r* and *a* denote *racemic* and *active*. Melting points and [α]$^{25}_{589}$ (c=1, EtOH) are shown in [ ] and ( ), respectively.

o-CH_3;	*r*,	[162-164°C],	*a*,	[143-145°C],	(+25.6°)
m-CH_3;	*r*,	[175-177°C],	*a*,	[174-177°C],	(+ 2.2°)
o-Cl ;	*r*,	[184-186°C],	*a*,	[178-179°C],	(+21.8°)
p-Cl ;	*r*,	[180-182°C],	*a*,	[178-180°C],	(+14.7°)
m-NO_2;	*r*,	[193-194°C],	*a*,	[195-198°C],	(+34.8°)

6) Prepared from *cis*-cyclohexane-1,2-dicarboxylic acid anhydride through ammonolysis, Hofmann degradation$^{2)}$ and benzoylation.
7) Prepared from (±)-*cis*-1 and benzylamine, and recrystallized from water.

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