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OPTICAL RESOLUTION OF α-METHYLBENZYLAMINE AND 1-PHENYL-2-(*p*-TOLYL)ETHYLAMINE BY PREFERENTIAL CRYSTALLIZATION

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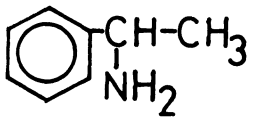
(±)-α-Methylbenzylamine and 1-phenyl-2-(*p*-tolyl)ethylamine have been easily resolved into their optically active forms by preferential crystallization of their racemic salts with cinnamic acid.

Optically active α-methylbenzylamine[(+)- and (-)-1] and 1-phenyl-2-(*p*-tolyl)ethylamine[(+)- and (-)-2] are very useful synthetic chiral agents effective for the resolution of several racemic acids. The resolution of them have been performed by fractional crystallization of their diastereoisomeric salts with tartaric acid[1], malic acid[2] or aspartic acid.[3]

In order to find out more practical methods applicable to large scale resolution, the salts with several achiral acids were prepared and checked for preferential crystallization. Efficient resolutions of 1 and 2 were achieved when cinnamic acid(3) salts of 1 and 2 were employed. In these cases, the infrared spectra of the racemic salts were completely identical with those of the corresponding optically active salts.



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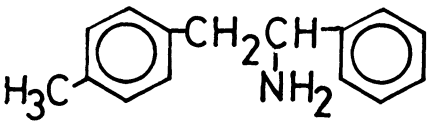

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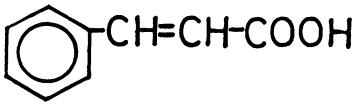

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The result suggested that these racemic salts form racemic mixtures. This was also supported by the additional facts that the melting points of optically active salts were higher than those of the corresponding racemic salts and that the racemic salts were more soluble than the corresponding active salts in suitable solvents.

The following examples are typical runs for these resolutions.[4]

Resolution of (±)-1 A mixture of (±)-1 (12.1 g) and 12M hydrochloric acid[5] (8.3 ml) was dissolved in 100 ml of a mixed solvent (water:methanol=2:3). To the solution was added 15.5 g of (±)-1·3salt[6] and dissolved by heating. The solution was cooled, seeded with pure crystals of (+)-1·3salt[6] (20 mg) and allowed to stand

in water bath for 1 h. White crystals appeared were collected by filtration, washed with a small amount of the solvent and dried to give 3.4 g of (+)-1·3 salt ($[\alpha]_{435}$ +16.0°, 75% optically pure). Subsequently, to the mother liquor was added (±)-1·3 salt[6] (3.5 g) and dissolved at an elevated temperature. The solution was similarly cooled, seeded with (-)-1·3 salt[6] (20 mg) and allowed to stand. Similar treatment of white crystals separated gave 5.4 g of (-)-1·3 salt($[\alpha]_{435}$ -18.2°, 85% optically pure). The process was repeated in a similar manner, and (+)- and (-)-1·3 salts were obtained alternately. The crystals having the same sign of optical rotation were put together and 10.0 g each of enantiomeric salt, which was obtained from three times each of crystallizations, was recrystallized from 60 ml of methanol to give 6.4 g of pure (+)-1·3 salt[6] and 7.5 g of pure (-)-1·3 salt[6], respectively. Decomposition of the salts with alkali and extraction with benzene followed by distillation gave optically pure (+)-1(2.6 g, bp 84-85°C (21 mmHg), $[\alpha]_{589}^{20}$ +40.3°, (neat)) and (-)-1(3.0 g, bp 84-85°C (21 mmHg), $[\alpha]_{589}^{20}$ -40.3°, (neat)).

Resolution of (±)-2 A mixture of (±)-2(5.29 g), 3(0.74 g), and acetic acid[5] (1.20 g) were dissolved in 40 ml of a mixed solvent (methanol:water=5:3) by heating. The solution was cooled, seeded with (-)-2·3 salt[7] (10 mg) and allowed to stand for 2 h to give 0.9 g of (-)-2·3 salt($[\alpha]_{435}^{20}$ -139.2°, 88% optically pure). To the mother liquor was added (±)-2·3 salt[7] (1.0 g) and dissolved at an elevated temperature. The mixture was cooled, seeded with (+)-2·3 salt[7] (10 mg) and allowed to stand for 2 h to give 0.91 g of (+)-2·3 salt($[\alpha]_{435}^{20}$ +126.3°, 80% optically pure). The process was repeated analogously. The crystals with the same sign of the rotation were put together and 2.7 g each of enantiomeric salt, which was obtained from three times each of crystallizations, was recrystallized from 27 ml of methanol to give 1.8 g each of pure active salts.[7] The salts were decomposed with 6M NaOH, extracted with ether to give 1.0 g each of (+)- and (-)-2, respectively($[\alpha]_{589}^{30}$ +62.9° and -62.8°, (c 1, MeOH)).

References and Notes

1) A. Ault, Org. Synth., Coll. Vol. V, 932 (1973).
2) A. W. Ingersoll, Org. Synth., Coll. Vol. II, 506 (1943).
3) Y. Suzuki, Ger. Offen. 2023426 (1970);Chem. Abstr., 74, 42121y (1971).
4) A similar resolution of (±)-1 was possible in the form of *cis*-1,2-cyclohexanedicarboxylic acid salt of (±)-1. Racemic salt; mp 145-147°C, active salts; mp 154-156°C, $[\alpha]_{435}^{20}$ + and -12.0°(c 1, EtOH); Found; N,4.84%. Calcd for $C_{16}H_{23}NO_4$: N,4.78%. In this case, however, several times of recrystallization were needed to obtain optically pure salts.
5) In these procedures, the readily soluble racemic salts with hydrochloric acid or acetic acid act as a kind of buffer, stabilizing the preferential crystallization significantly.
6) Racemic salt; mp 145-147°C, active salts; mp 165-167°C, $[\alpha]_{435}^{27}$ + and -21.4° (c 1, EtOH); Found: N,5.37%. Calcd for $C_{17}H_{19}NO_2$: N,5.20%.
7) Racemic salt; mp 151-152°C, active salts; mp 169-170°C; $[\alpha]_{435}^{20}$ + and -158.0° (c 1, MeOH); Found: N,3.85%. Calcd for $C_{24}H_{25}NO_2$: N,3.90%.

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