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# Preparative Separation of Tetrahydrofurfurylamine Enantiomers

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**Abstract**—Tetrahydrofurfurylamine enantiomers were separated on a preparative scale by fractional crystallization of diastereoisomeric salts with natural L-tartaric acid. (*R*)-Tetrahydrofurfurylamine was isolated in 68% yield with an optical purity of more than 98.5% according to the HPLC data.

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Tetrahydrofurfurylamine (**I**) is widely used in the synthesis of various medical agents such as diuretics [1–3], enzyme inhibitors [4–7], analgesics [8–10], and neurotropic [11] and anticarcinogenic drugs [12]. Separation of tetrahydrofurfurylamine enantiomers by crystallization of diastereoisomeric salts with natural L-tartaric acid was reported in [13, 14]; however, no experimental details were given, and enantiomeric purity of the obtained compound was not specified.

Using L-tartaric acid as chiral resolving agent, we have developed an effective preparative procedure for the isolation of enantiomerically pure tetrahydrofurfurylamine from commercially available racemate. Enantiomer (*R*)-**I** with a purity of better than 98.5% (according to the HPLC data) was isolated in 68% yield. From the mother liquor we isolated (*S*)-**I** with an enantiomeric purity of 79%.

## EXPERIMENTAL

Racemic tetrahydrofurfurylamine (**I**) and L-tartaric acid from Lancaster Synthesis were used. Chiral compound **I** was analyzed for enantiomeric purity by HPLC of the corresponding benzamide which was prepared by treatment of **I** or its salt with tartaric acid with benzoyl chloride in the two-phase system ethyl acetate–aqueous potassium carbonate.

High-performance liquid chromatography was performed on an HPP 5001 Laboratorni pristroje Praha equipped with an LCD 2563 UV-Vis detector (λ = 254 nm); 250×4.6-mm Chiralcel OD column (Daicel Chem. Industries, Osaka, Japan); eluent hexane–propan-2-ol (95:5, by volume), flow rate 2 ml/min; temperature 20°C. The retention times of the (*R*)- and (*S*)-enantiomers of *N*-tetrahydrofurfurylbenzamide are 26.91 and 27.80 min, respectively. The absolute configurations were assigned using a commercial sample of (*R*)-(–)-**I** from Acros Organics. The optical rotations were measured on a Spectropol-1 spectropolarimeter.

**Separation of the (*R*)- and (*S*)-enantiomers of tetrahydrofurfurylamine (I).** L-(+)-Tartaric acid, 386 g (2.57 mol), was dissolved in 1200 ml of water, 260 g (2.57 mol) of (*RS*)-**I** and 3 l of acetone were added, the mixture was kept for 24 h at 4°C, and the colorless crystalline solid was filtered off and washed with a mixture of 500 ml of acetone and 100 ml of water. The salt was recrystallized from a mixture of 1 l of acetone with 250 ml of water, dried in air, and treated with a solution of 200 g of potassium hydroxide in 500 ml of water. The oily material separated and was extracted into THF (3×250 ml). The extracts were combined, dried over solid alkali, and distilled under atmospheric pressure. Yield of (*R*)-(–)-**I** 88.4 g (68%), bp 152–153°C; published data [14]: bp 154–157°C; the optical purity was higher than 98.5% ((HPLC), $[\alpha]_D^{20}$ = –12.15° (*c* = 5.05, $CHCl_3$). From the mother liquor we isolated 128 g of (*S*)-(+)-**I**, $[\alpha]_D^{20}$ = + 9.73° (*c* = 5.05, $CHCl_3$), enantiomeric purity 79%.

## REFERENCES

1. Horstmann, H., Wollweber, H., and Meng, K., UK Patent no. 1031916, 1966; *Chem. Abstr.*, 1969, vol. 70, p. 19915u.
2. Cragoe, E.J., Jr., US Patent no. 3577409, 1971; *Chem. Abstr.*, 1971, vol. 75, no. 35739y.

3. Sturm, K., Muschaweck, R., and Hropot, M., *J. Med. Chem*., 1983, vol. 26, p. 1174.
4. Lee, S.J., Konishi, Y., Yu, D.T., Miskowski, T.A., Riviello, C.M., Macina, O.T., Frierson, M.R., Kondo, K., Sugitani, M., Sircar, J.C., and Blazejewski, K.M., *J. Med. Chem*., 1995, vol. 38, p. 3547.
5. Suh, J.T., Skiles, J.W., Williams, B.E., Youssefyeh, R.D., Jones, H., Loev, B., Neis, E.S., Schwab, A., Mann, W.S., Khandwala, A., Wolf, P.S., and Weinryb, I., *J. Med. Chem*., 1985, vol. 28, p. 57.
6. Li, Zh., Ortega-Vilain, A.-C., Patil, G.S., Chu, D-L., Foreman, J.E., Eveleth, D.D., and Powers, J.C., *J. Med. Chem*., 1996, vol. 39, p. 4089.
7. Bratenko, M.K., Chornous, V.A., and Vovk, M.V., *Russ. J. Org. Chem*., 2001, vol. 37, p. 552.
8. Merz, H., Stockhaus, K., and Wick, H., *J. Med. Chem*., 1975, vol. 18, p. 996.
9. Merz, H. and Stockhaus, K., *J. Med. Chem*., 1979, vol. 22, p. 1475.
10. Harris, A., Middlemiss, D., Mills, K., Gower, A.J., and Tyers, M.B., *J. Med. Chem*., 1983, vol. 26, p. 55.
11. Limbeck, M. and Gündisch, D., *J. Heterocycl. Chem*., 2003, vol. 40, p. 895.
12. Tsujihara, K., Ozeki, M., Morikawa, T., Kawamori, M., Akaike, Y., and Arai, Y., *J. Med. Chem*., 1982, vol. 25, p. 441.
13. Belanger, P.C. and Williams, H.W.R., *Can. J. Chem*., 1983, vol. 61, p. 1383.
14. Cooper, K.D. and Walborsky, H.M., *J. Org. Chem*., 1981, vol. 46, p. 2110.