

1,3-Butanediamine

Resolution into Optical Antipodes
and the Determination of Their
Absolute Configurations

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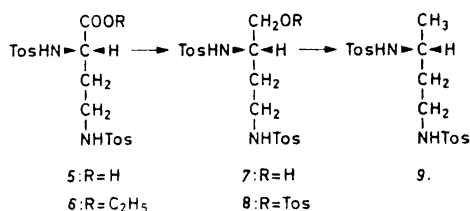
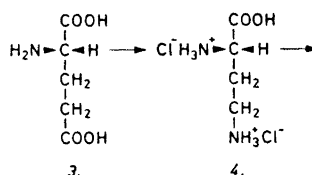
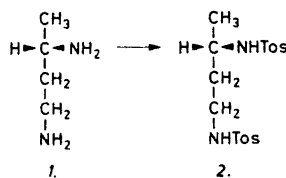
In the light of the ample information obtained by studies of metal complexes of optically active 1,2-propanediamine, it seems to be worth while investigating the potentials of the corresponding optically active chelate ligand with one more methylene group between the ligators. Such studies should make use of the known absolute configuration of the amine. Therefore, we here report on the resolution of the racemic 1,3-butanediamine and on the determination of the *S* configuration for the dextrorotatory isomer.

The configuration was determined by synthesizing (*R*)(+)_D-*N,N'*-ditosyl-1,3-butanediamine (9) from (*S*)-glutamic acid and comparing the former with the levorotatory ditosylate (2) of (*S*)(+)_D-1,3-butanediamine (1).

The two compounds (9) and (2) gave identical solution IR and NMR spectra. The specific rotations at 589 nm and at five mercury lines were numerically identical but of opposite signs. However, the melting points for the two are different as are also IR spectra of samples in KBr discs and Guinier X-ray powder diagrams. This difference persisted in spite of many recrystallizations from different solvents.

The apparent discrepancy was overcome since a mixture of equal amounts of the claimed enantiomers dissolved in ethanol by evaporation gave the ditosylate of racemic 1,3-butanediamine. The identity

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was proved by melting points and Guinier powder diagrams.

Experimental. (*S*)(+)_D-1,3-Butanediammonium bis(+)_Dhydrogentartrate. To 335 g (2.2 mol) of (+)_D-tartaric acid suspended in 200 ml water was added slowly and under stirring 100 ml (1.1 mol) of 1,3-butanediamine (Sharpless). The solution was left overnight at 5°C, and then the formation of crystal seeds was aided by placing a layer of 50 ml ethanol over the solution. After a few days at 5°C crystallization had finished. The precipitate was efficiently separated from the mother liquor by means of basket centrifugation. Yield 160 g (+)_D-1,3-butanediammonium bis(+)_Dhydrogentartrate monohydrate.

The diastereoisomer was recrystallized by dissolution in 150 ml of hot water and the solution was filtered while hot. Under stirring the solution was allowed to cool to room temperature and then 150 ml ethanol was added dropwise. Cooling in ice bath. The precipitate was isolated by basket centrifugation. One careful recrystallization is sufficient to obtain a diastereoisomer which has unaltered specific rotation and melting point upon further recrystallizations. Yield 140 g. M.p. 185° (at slow rate of heating). $[\alpha]_{\text{D}}^{25} +17.2^\circ$ ($c=1.44$, H₂O). (Found after drying over P₂O₅: C 37.09;

H 6.20; N 7.19. Calc. for $C_{12}H_{24}N_2O_{12}$: C 37.11; H 6.23; N 7.21).

(R)(-)_D-1,3-Butanediammonium bis(+)_Dhydrogentartrate. The mother liquor from the precipitation of the least soluble diastereoisomer gave by addition of 500 ml of ethanol and prolonged cooling at 5°C a floccy precipitate of the more soluble diastereoisomer. Recrystallization from 50% ethanol until constant rotation. Yield 100 g. M.p. 90–95°. $[\alpha]_D^{23} + 22.3^\circ$ ($c=1.67$, H₂O). (Found after drying over NaOH: C 34.60; H 6.55; N 6.80. Calc. for $C_{12}H_{24}N_2O_{12} \cdot 1.5H_2O$: C 34.71; H 6.55; N 6.75).

(S)(+)_D-1,3-Butanediamine (1). Concentrated sodium hydroxide solution was in small portions poured onto 74.1 g (183 mmol) of (S)(+)_D-1,3-butanediammonium bis(+)_Dhydrogentartrate monohydrate under cooling. At first a solid mass of crystals (sodium tartrate) was formed and addition of sodium hydroxide solution was continued until the sodium tartrate began to dissolve. Too great an excess of sodium hydroxide should be avoided in order to minimize the loss of amine. After standing for a few minutes the amine separated at the surface and was pipetted off. The amine was dried over sodium hydroxide pellets for 24 h, during which water separated. The amine was pipetted off and new sodium hydroxide pellets added. This drying procedure was repeated three times. Finally the amine was dried over sodium for one hour and distilled. Yield 6.25 g (70.8 mmol, 39%). B.p. 144.0–146.5°. $\alpha_D^{25} + 1.80^\circ$ (neat, $l=2$ cm).

(S)(-)_D-N,N'-Ditosyl-1,3-butanediamine (2). To a chilled solution of 1 g (11.4 mmol) of (I) in 10 ml of dry pyridine was added under cooling a solution of 5.8 g (30.5 mmol) of *p*-toluenesulfonyl chloride in 10 ml of dry pyridine. After standing for three days at 5°, the reaction mixture was poured into ice water and extracted with one 80 ml portion and four 40 ml portions of ether. The pooled ether fractions were washed with three 40 ml portions of 4 N hydrochloric acid and 40 ml of water. The ether solution was dried over anhydrous magnesium sulfate and treated with charcoal. After evaporation of the ether the residual crystals were dissolved in 50 ml of chloroform, treated once more with charcoal and reprecipitated with 200 ml of petrol ether. Yield 1.4 g (3.5 mmol, 32%). Recrystallized from benzene and petrol ether, it melted at 112.0–113.5°. (Found: C 54.70; H 6.06; N 7.06; S 16.19. Calc. for $C_{18}H_{24}N_2O_4S_2$: C 54.54; H 6.10; N 7.07; S 16.18). $[\alpha]_D^{25} - 30.5$ ($c=1.14$, CHCl₃).

(S)(+)_D-2,4-Diaminobutyric acid dihydrochloride (4) was prepared from (S)-glutamic acid (3) according to Adamson.¹ M.p. 204° (decomp.). $[\alpha]_D^{25} + 15.1^\circ$ ($c=3.82$, H₂O). (Lit. m.p. 195–196°, $[\alpha]_D^{25} + 14.6^\circ$ ($c=3.67$, H₂O)).

(S)(+)_D-N,N'-Ditosyl-2,4-diaminobutyric acid (5). 4 g (20.9 mmol) of (4) was tosylated following the procedure of Fischer and Lipschitz² to give 7.7 g (18.8 mmol, 86%) of the ditosylate. Recrystallized twice from chloroform-petrol ether, it melted at 150.5–153.0°. (Found: C 50.60; H 5.22; N 6.51; S 15.14. Calc. for $C_{18}H_{22}N_2O_6S_2$: C 50.70; H 5.20; N 6.57; S 15.04). $[\alpha]_D^{25} + 16.3^\circ$ ($c=0.123$, CH₃OH).

(S)(+)_D-N,N'-Ditosyl-2,4-diaminobutyric acid ethyl ester (6). 10.2 g (23.8 mmol) of (5) was esterified with hydrogen chloride in 100 ml of abs. ethanol. After refluxing for one hour another portion of 100 ml of ethanol was added and the refluxing was continued for 3 h. After 16 h of standing 100 ml of dry benzene was added and a mixture of benzene, ethanol, and water was distilled off (55 ml) and the whole procedure was repeated. Finally 100 ml of dry benzene was added and the reaction mixture was concentrated to about 75 ml. The same amount of water was added and an oily precipitate was formed, which became crystalline on scratching. Yield 9.9 g (21.7 mmol, 91%). Recrystallized from ethanol and from chloroform-petrol ether it melted at 105.5–106.5°. (Found: C 52.88; H 5.87; N 6.02; S 14.25. Calc. for $C_{20}H_{26}N_2O_6S_2$: C 52.85; H 5.77; N 6.16; S 14.11). $[\alpha]_D^{25} + 33.4^\circ$ ($c=1.06$, CHCl₃).

(S)(+)_D-N,N'-Ditosyl-2,4-diaminobutanol (7). A solution of 5 g (11 mmol) of (6) was added dropwise during one hour to a boiling solution of 1.8 g of lithium aluminium hydride in 75 ml of tetrahydrofuran. After refluxing for 4 h the reaction mixture was treated with water in tetrahydrofuran and 4 N sulfuric acid. Two phases appeared and the upper phase was separated, filtered and evaporated to give a mass of white crystals. Yield 4.2 g (10.2 mmol, 92%). M.p. 133.0–133.5°. (Found: C 52.48; H 5.98; N 6.84; S 15.56. Calc. for $C_{18}H_{24}N_2O_3S_2$: C 52.42; H 5.86; N 6.79; S 15.55). $[\alpha]_D^{25} + 16.5^\circ$ ($c=1.17$, CHCl₃).

(S)(-)_D-N,N',O-Tritosyl-2,4-diaminobutanol (8). To a chilled solution of 3.7 g (19.4 mmol) of *p*-toluenesulfonyl chloride in 20 ml of dry pyridine was added 3.7 g (8.95 mmol) of (7) in 20 ml of dry pyridine. After standing for 60 h at 5° the reaction mixture was poured into ice water and extracted with two 80 ml and four 40 ml portions of ether. The ether phase was washed with three 40 ml portions of 4 N hydrochloric acid, then with 40 ml of water

and finally dried over anhydrous magnesium sulfate. The yellow solution was decolorized by treating with charcoal. Evaporation of the ether left an oily product which became crystalline on washing with ether. Yield 2.60 g (4.6 mmol, 51 %). M.p. 104.5–106.5°. (Found: C 52.90; H 5.38; N 5.00; S 16.74. Calc. for $C_{25}H_{30}N_2O_7S_3$: C 52.99; H 5.34; N 4.94; S 16.87). $[\alpha]_D^{25} -17.1^\circ$ ($c=1.22$, $CHCl_3$).

(R)(+)_D-N,N'-Ditosyl-1,3-butanediamine (9). A solution of 1.6 g (2.8 mmol) of (8) in 80 ml of ether and 55 ml of tetrahydrofuran was added dropwise during one hour to a boiling solution of 0.6 g (15.8 mmol) of lithium aluminium hydride in ether. Refluxing was continued for 5.5 h when the reaction mixture was treated first with ether saturated with water and then with 4 N sulfuric acid. The two phases were separated and the aqueous phase extracted with five 50 ml portions of ether. The pooled ether fractions were dried over anhydrous magnesium sulfate and evaporated to give an oily residue. Washing with ether and toluene changed the oil to a white crystalline product. Yield 0.65 g (1.64 mmol, 58 %). M.p. 103.0–104.5°. (Found: C 54.62; H 6.06; N 6.90; S 16.31. Calc. for $C_{18}H_{24}N_2O_4S_2$: C 54.54; H 6.10; N 7.07; S 16.18). $[\alpha]_D^{25} +31.2^\circ$ ($c=0.93$, $CHCl_3$).

Acknowledgements. The authors wish to thank Professor J. Bjerrum for providing the racemic 1,3-butanediamine obtained from Sharpless Chem. Comp.

1. Adamson, D. W. *J. Chem. Soc.* **1939** 1564.
2. Fischer, E. and Lipschitz, W. *Ber.* **48** (1915) 362.

Received July 1, 1969.

Correction to "Studies of Conformational Changes in Glycerolaldehyde-3-Phosphate Dehydrogenase Accompanying its Catalytic Action"*

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In Table 3, p. 1648, second comparison from below

for $b_0 +$ read $b_0 -$.

This means that the occurrence of a conformational change accompanying the binding of a stoichiometric quantity of NAD only is indicated by the change in λ_c . However, Kirschner *et al.*¹ have later obtained independent conclusive evidence from chemical relaxation experiments of this conformational change.

1. Kirschner, K., Eigen, M., Bittman, R. and Voigt, B. *Proc. Natl. Acad. Sci. U.S.* **56** (1966) 1661.

Received August 20, 1969.

* *Acta Chem. Scand.* **19** (1965) 1643.