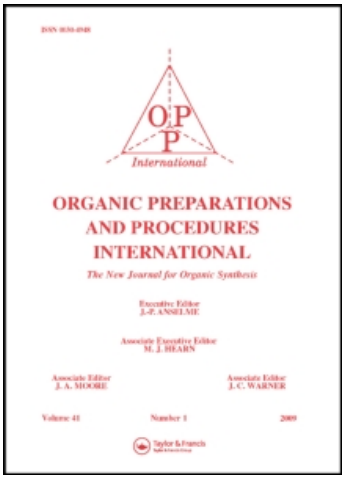


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A CONVENIENT PREPARATION OF D(-)-p-HYDROXYPHENYLGLYCINE

R. F. Eizember[a]; A. S. Ammons[a]
[a] Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

To cite this Article Eizember, R. F. and Ammons, A. S.(1976) 'A CONVENIENT PREPARATION OF D(-)-p-HYDROXYPHENYLGLYCINE', Organic Preparations and Procedures International, 8: 4, 149 — 153
To link to this Article: DOI: 10.1080/00304947609355613
URL: http://dx.doi.org/10.1080/00304947609355613

ORGANIC PREPARATIONS AND PROCEDURES INT. 8(4), 149-153 (1976)

A CONVENIENT PREPARATION OF D(-)-p-HYDROXYPHENYLGLYCINE

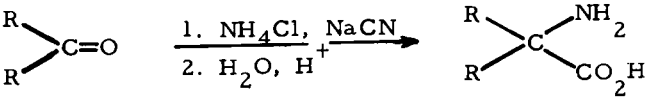
R. F. Eizember* and A. S. Ammons

Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46206

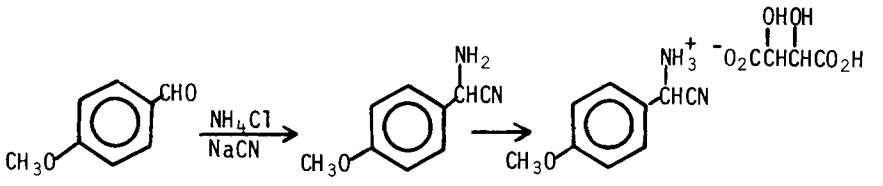
During the course of our work, it became necessary to synthesize moderate quantities of D(-)-m- and D(-)-p-hydroxyphenylglycines. Most of the known procedures for preparing optically active phenylglycines employ a resolution of the racemic amino acid by selected optically active acids[1] or bases,[2] enzymes,[3] or combinations thereof.[4,5] The procedures vary widely in their synthetic efficiency and practicality.

Work was therefore begun on a more general synthesis and resolution procedure that would provide adequate quantities of the desired optically active amino acids. The following will describe the most successful approach to the preparation of D(-)-p-hydroxyphenylglycine which utilizes a recently published technique.[5]

Most syntheses of α-amino acids employ some form of the Strecker[4b]

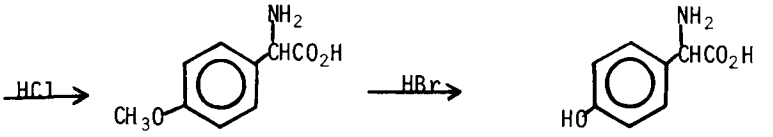


reaction which combines aldehydes and ketones with sodium cyanide and ammonium chloride or their precursors.[6] A modified Strecker reaction on anisaldehyde (I) produced the desired amino nitrile (II)[7] which was then treated with d-tartaric acid to form the tartrate salt (IIIa), $[\alpha]_D^{24}$ = +40.2°. This diastereomeric salt of the desired configuration can be



I II III a) $[\alpha]_D^{24} = +40.2°$

b) $[\alpha]_D^{24} = +43.3°$



IV $[\alpha]_D^{25} = -141°$ V $[\alpha]_D^{25} = -140°$

hydrolyzed to D(-)-p-methoxyphenylglycine which is 85 to 95% optically pure.[3]

To enhance optical purity, IIIa is converted to the free amino nitrile (II) which is then treated with d-tartaric acid to again form the tartrate salt (IIIb), $[\alpha]_D^{24} = +43.3°$. This reconversion of the tartrate salt (IIIa → IIIb) increases optical purity significantly. The purified nitrile salt (IIIb) is hydrolyzed with 6N hydrochloric acid to D(-)-p-methoxyphenylglycine (IV), $[\alpha]_D^{25} = -141°$. Methyl ether cleavage of IV with 48% hydrobromic acid affords D(-)-p-hydroxyphenylglycine (V), $[\alpha]_D^{25} = -140°$. Comparison of these optical rotations to those published[3] for an enzymatic resolution (IV, $[\alpha]_D^{25} = -149°$ and V, $[\alpha]_D^{25} = 161°$ [both c 1.0 in HCl]) suggests that IV contains 98% of D(-)-p-methoxyphenylglycine and V contains 94% of the D(-)-p-hydroxyphenylglycine. The decrease in optical purity of the D(-)-antipode after the hydrobromic acid treatment indicates that some racemization is occurring during the ether cleavage reaction.

Some advantages of the above synthesis and resolution procedure are: 1) the synthesis and resolution technique can be scaled up readily;

2) both anisaldehyde and d-tartaric acid are economical starting materials; and 3) the D(-)-p-hydroxyphenylglycine can be obtained in 30% yield from anisaldehyde.

This same procedure was attempted in the synthesis of the analogous amino nitrile derived from m-methoxybenzaldehyde. However, resolution of this amino nitrile with d-tartaric acid was unsuccessful.

EXPERIMENTAL

D(-)-α-Amino-p-methoxyphenylacetonitrile-d-hemitartrate (III)

To a solution of 49.0 g (1.0 mole) sodium cyanide, 58.5 g (1.13 mole) ammonium chloride, and 50 ml ammonium hydroxide in 10 ml water was added a solution of 136.0 g (1.0 mole) anisaldehyde and 400 ml methanol. After stirring for two hours at 37°C, the methanol was removed in vacuo, and the residue containing the crude amino nitrile was diluted with water and extracted with benzene. The benzene solution was washed with water, dried over magnesium sulfate, filtered, and diluted to 1 liter with benzene. A solution of 130.0 g (0.87 mole) d-tartaric acid in 500 ml methanol was added and the resulting slurry was stirred at room temperature for 2.5 hours. The solid was filtered, washed with a 150 ml solution of 2 parts benzene and 1 part methanol, and then dried to yield 84.1 g (62%) of dense solid ($[\alpha]_D^{24}$ +40.2° (c 0.2 H_2O)).

Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97.
Found: C, 49.79; H, 5.33; N, 9.19.

The tartrate salt (75.0 g, 0.24 mole) was slurried in 250 ml water and the pH was adjusted to 7.0 with 10% NaOH solution. The amino nitrile was extracted into benzene which was dried over magnesium sulfate, filtered, and diluted to 400 ml with benzene. A solution of 33.0 g (0.22 mole) d-tartaric acid in 200 ml methanol was added and the resulting slurry

was stirred for 30 minutes. The solids were filtered, washed with a 150 ml solution of two parts benzene and one part methanol and dried to yield 64.6 g (77%) of white crystalline D(-)-α-amino-p-methoxyphenylacetonitrile-d-hemitartrate: ($[\alpha]_D^{24}$ + 43.3 (c 0.2 H_2O)); nmr: (D_2O/DCl) S(TMS), 3.93 (S, CH_3), 4.85 (S, methine-tartaric acid), 5.87 (s, benzyl), 7.45 (m, ArH).

Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97.
Found: C, 50.01; H, 5.32; N, 8.81.

D(-)-p-Methoxyphenylglycine (IV)

The tartrate salt IIIb (50.0 g, 0.016 mole) was refluxed for one hour in 50 ml 6N hydrochloric acid. The resulting solution was diluted with 100 ml of water, treated with activated carbon, and adjusted to a pH of 6.0 with concentrated ammonium hydroxide. After cooling 30 minutes in an ice bath, the reaction mixture was filtered and the solids were washed with 50 ml of cold water and 50 ml of acetone. The white platelets were dried in vacuo to yield 23.4 g (80%) of D(-)-p-methoxyphenylglycine (IV) ($[\alpha]_D^{25}$ -141° (c 1.0 1N HCl)); nmr: (D_2O/DCl) S(TMS), 3.85 (S, CH_3), 5.26 (S, benzyl), 7.29 (m, ArH).

Anal. Calcd for $C_9H_{11}N_1O_3$: C, 59.66; H, 6.12; N, 7.73.
Found: C, 59.65; H, 6.33; N, 7.68.

D(-)-p-Hydroxyphenylglycine (V)

Twenty grams of D(-)-p-methoxyphenylglycine (IV) was refluxed for 2 hours in 150 ml 48% hydrobromic acid. The resulting solution was evaporated to a wet solid in vacuo, dissolved in a minimum amount of water, treated with activated carbon, and with cooling, adjusted to a pH of 6.0 with concentrated ammonium hydroxide. The gel which formed during this operation was broken by heating. After stirring for 30 minutes in an ice bath, the solids were filtered, washed with 50 ml each of cold water and acetone, and then dried to yield 15.3 g (82%) dense white crystals of D(-)-p-hydroxy-

phenylglycine ($[\alpha]_D^{25}$ -140° (c 1.0 1N HCl)); nmr: (D_2O/Dcl) S(TMS), 5.28 (S, benzyl), 7.25 (m, ArH).

Anal. Calcd for $C_8H_9N_1O_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.63; H, 5.59; N, 8.17

REFERENCES

1. T. Leigh, Chem. and Ind., 1016 (1970); T. A. Mentzka, T. L. Pindell, and J. D. Matiskella, J. Org. Chem., 33, 3993 (1968).
2. L. Velluz, G. Amiard, and R. Heymes, Bull. Soc. Chim. France, 201 (1955); W. Theilaker and H. G. Winkler, Chem. Ber., 87, 690 (1954); A. Fredgg, B. Sjöberg, and R. Sandber, Acta Chem. Scand., 11, 1609 (1957).
3. D. N. McGregor, U.S. 3,483,188 (Chem. Abstr., 72, 121522s (1970)); L. B. Crast, U.S. 3,489,750 (Chem. Abstr., 72, 100726w (1970)).
4. a) J. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, p. 697, Wiley and Sons, N. Y., 1961.
   b) Ibid., p. 715.
   c) C. Ryan, The Lilly Research Laboratories, private communication.
5. J. G. Schawartz, Hungarian Patent 154,410 (Chem. Abstr., 69, 107076f (1968)).
6. R. E. Steinger, "Organic Syntheses," Coll. Vol. 3, p. 84, Wiley and Sons, N. Y., 1955
7. The crude amino nitrile slowly decomposes liberating ammonia and hydrogen cyanide.

(Received May 24, 1976; in revised form July 2, 1976)