

2-Amino-alcohols from α -Amino-acids: a Single-step Mild Procedure

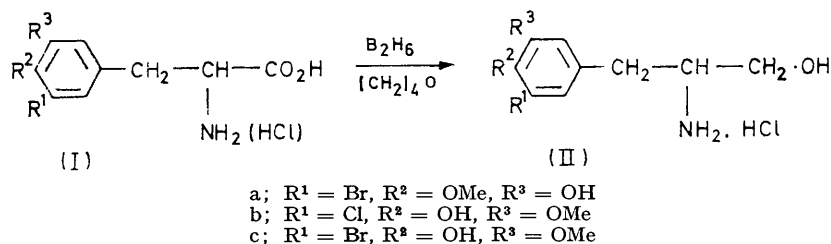
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α -Amino-acids are reduced by diborane in anhydrous tetrahydrofuran to 2-amino-alcohols. Substituted halogeno-phenylalanines are reduced in good yield without hydrogenolysis of the halogen-carbon bond.

YAMADA and his colleagues^{1,2} have reported the ready reduction of optically active α -amino-acid esters to the corresponding 2-amino-alcohols by sodium borohydride in ethanol or aqueous ethanol. However, considered as a reduction of an α -amino-acid, this method requires two steps (esterification and reduction) with a total yield of about 40%. We report here that α -amino-acids (or their hydrochlorides previously treated with an equimolecular amount of sodium hydride) are reduced in one step to the corresponding 2-amino-alcohols by diborane, generated *in situ* from sodium borohydride and boron

ammonium hydroxide in propan-2-ol-methanol (Merck 9162). Elemental analyses were performed with a Hewlett-Packard 185 CHN Analyzer.

2-Amino-3-(3-bromo-5-hydroxy-4-methoxyphenyl)propan-1-ol Hydrochloride (IIa).—Sodium borohydride (1.17 g) was slowly added to a suspension of β -(3-bromo-5-hydroxy-4-methoxyphenyl)alanine (Ia)⁷ (7.1 g) in anhydrous tetrahydrofuran (100 ml), followed dropwise by boron trifluoride-ether complex (5.15 ml). The mixture was stirred for 15 h at room temperature and after a further addition of sodium borohydride (1.17 g) and boron trifluoride-ether (5.15 ml), was stirred for a further 15 h. The excess of diborane was



trifluoride-ether complex. Arene-halogen bonds are not hydrogenolysed by this reagent, and the yields are in the range 65–80%.

Reduction of substituted phenylalanines (or their hydrochlorides) with diborane in tetrahydrofuran at 20 °C

Structure	Time (h)	Yield (%)	M.p. (°C)	Purity (%) [*]
a	30	80	158–160	100
b	15	80	219–219.5	98.5
c	15	67	214	99.2

* By potentiometric titration.

EXPERIMENTAL

¹H N.m.r. spectra were recorded on a Perkin-Elmer R-12 (60 MHz) instrument for solutions in deuterium oxide with sodium 2,2-dimethyl-2-silapentane-1-sulphonate as internal reference. *R_F* Values refer to t.l.c. on silica gel with propan-2-ol-water-ammonia (8 : 1 : 1) as solvent and ninhydrin as spray reagent. Purity of products was determined by potentiometric titration in a non-aqueous solvent,³⁻⁶ using a pH-meter Radiometer 22 equipped with a combined glass-calomel electrode. The amino-group, present as hydrochloride, was estimated by titration with 0.1N-perchloric acid in anhydrous acetic acid (Merck 9065) in the presence of mercury(II) acetate. Phenol and hydrochloride groups were determined by titration with a 0.1N-tetrabutyl-

destroyed with ethanol. The filtrate was acidified with 3N-hydrochloric acid (to pH 1) and the water was removed by azeotropic distillation with propan-2-ol. Mineral salts were filtered off and the solution was concentrated to small volume under a vacuum and diluted with ethyl acetate (300 ml). The crystals were filtered off, washed with ethyl acetate, and dried to yield the *product* (IIa) (5 g, 80%), *R_F* 0.69, m.p. 158–160°; purity by potentiometric titration, 100% (NH₂); 95.3% (HCl and phenol) (Found: C, 38.2; H, 4.8; N, 4.2. C₁₀H₁₄BrNO₃·HCl requires C, 38.4; H, 4.8; N, 4.5%); δ 7.11 (1H, d, aromatic, *J*_{meta} 2.3 Hz), 6.87 (1H, d, aromatic, *J*_{meta} 2.3 Hz), 3.87 (3H, s, OMe), 3.76 (2H, m, CH₂O), 3.64 (1H, m, CH), and 2.92 (2H, m, ArCH₂).

2-Amino-3-(3-chloro-4-hydroxy-5-methoxyphenyl)propan-1-ol Hydrochloride (IIb).—Sodium borohydride (11.7 g) was slowly added to a mixture of a 58% suspension of sodium hydride in oil (4.14 g) and β -(3-chloro-4-hydroxy-5-methoxyphenyl)alanine hydrochloride (Ib)⁷ (28.2 g) in anhydrous tetrahydrofuran (200 ml) followed, 30 min later, by boron trifluoride-ether (51.5 ml) (dropwise). After 15 h stirring at 20°, the excess of diborane was destroyed with ethanol, the filtrate was acidified with 6N-hydrochloric acid (to pH 1) and the organic solvent was removed under vacuum. The aqueous solution (pH 2) was passed through an Amberlite IRA 400 (OH⁻) exchange resin; the amine crystallized on the column. Elution with methanol gave a solution which

⁴ S. Siggia, 'Quantitative Organic Analysis via Functional Groups,' 3rd edn., Wiley, New York, 1963.

⁵ W. Hubert, 'Titrations in Nonaqueous Solvents,' Academic Press, New York, 1967.

⁶ I. C. Gyenes, 'Titration in Non-aqueous Media,' Iliffe Books Ltd., London, 1967.

⁷ M. L. Anhoury, P. Crooy, R. De Neys, and J. Eliaers, *Bull. Soc. chim. belges*, in the press.

¹ H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 995.

² K. Koga, H. Matsuo, and S. Yamada, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 243.

³ A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Wiley, New York, 1962.

was concentrated under vacuum, diluted with water, acidified (to pH 2) with hydrochloric acid, and decolourised with charcoal if necessary. The *product* was precipitated with propan-2-ol, filtered off, washed with propan-2-ol, and dried; yield 21 g (80%), R_F 0.49, m.p. 219.0–219.5°; purity by potentiometric titration, 98.5% (NH_2) (Found: C, 44.7; H, 5.8; N, 5.4. $\text{C}_{10}\text{H}_{14}\text{ClNO}_3, \text{HCl}$ requires C, 44.8; H, 5.6; N, 5.2%); δ 6.89 (1H, d, aromatic, J_{meta} 1.6 Hz), 6.85 (1H, d, aromatic, J_{meta} 1.6 Hz), 3.90 (3H, s, OMe), 3.77 (2H, m, CH_2O), 3.71 (1H, m, CH), and 2.91 (2H, m, ArCH_2).

2-Amino-3-(3-bromo-4-hydroxy-5-methoxyphenyl)propan-1-ol Hydrochloride (IIc).—The foregoing procedure applied to β -(3-bromo-4-hydroxy-5-methoxyphenyl)alanine hydro-

chloride (Ic) ⁸ (32.7 g) gave the corresponding *alcohol* (IIc) (21 g, 67%), R_F 0.54, m.p. 214°; purity by potentiometric titration, 99.2% (NH_2) (Found: C, 38.7; H, 4.7; N, 4.2. $\text{C}_{10}\text{H}_{14}\text{BrNO}_3, \text{HCl}$ requires C, 38.4; H, 4.8; N, 4.5%); δ 7.06 (1H, d, aromatic, J_{meta} 1.7 Hz), 6.92 (1H, d, aromatic, J_{meta} 1.7 Hz), 3.93 (3H, s, OMe), 3.80 (2H, m, CH_2O), 3.66 (1H, m, CH), and 2.94 (2H, m, ArCH_2).

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⁸ P. Crooy and J. Eliaers, *J. Chem. Soc.*, 1969, 559.