Synthesis of 5-Aminolevulinic Acid

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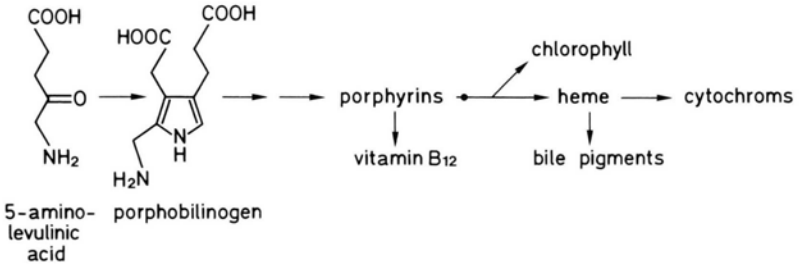
5-Aminolevulinic Acid

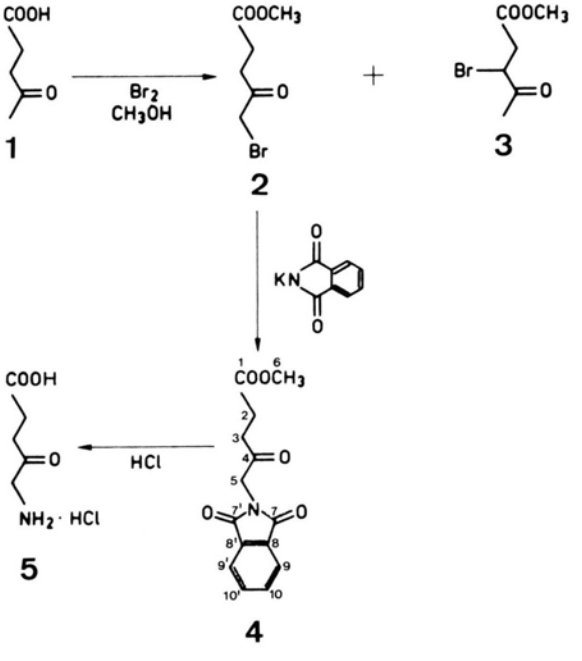
A 3-step synthesis of 5-aminolevulinic acid is described.

Introduction

5-Aminolevulinic acid is the first common precursor in the biosynthesis of all tetrapyrroles (Fig. 1).



Therefore, it is often used for biochemical investigations and a simple synthesis would be useful. Till now, a number of synthesis have been described, which are mostly time-consuming or result in difficult to clean product(s) (for a complete list see [1–3]). Some years ago, McDonald [4] published the bromination of levulinic acid yielding 3-bromo- and 5-bromolevulinic acid which can be separated by distillation. We obtained 5-aminolevulinic acid from 5-bromolevulinic acid by a 2-step sequence (Gabriel-synthesis and hydrolysis) in 33% overall yield (Fig. 2).



Materials and Methods

Melting points are uncorrected and measured with a Kofler hot stage microscope (Reichert). IR spectra were taken on a Perkin Elmer 599 Infrared Spectrophotometer, the intensity of absorption is indicated as follows: s = strong, m = medium, w = weak, br = broad. NMR spectra were recorded on a Bruker AM 360 instrument equipped with an Aspect 3000 computer. MS spectra were measured on a VG 7070 E spectrometer.

5-Phthalimidolevulinic acid methyl ester (**4**)

80 g 5-bromolevulinic acid methyl ester (**2**) [4] were dissolved in 300 ml dimethyl formamide and 80 g potassium phthalimide were slowly added under stirring. The solution was stirred for 1 h at room temperature, filtered and worked up with

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chloroform and water. The organic layer was washed with 0.2 M NaOH (4×) and water (3×). After drying over anhydrous sodium sulfate, the solvent was removed with a rotatory evaporator and (**4**) recrystallized from methanol. Yield: 62 g (59%) of white crystals, m.p. 97 °C.

IR (KBr) (cm^{-1}): 2955 w, 2920 w, 2850 w, 1775 m, 1740 s, 1730 s, 1710 s, 1468 w, 1445 w, 1415 s, 1387 w, 1350 m, 1310 m, 1268 w, 1200 m, 1180 m, 1102 m, 1015 w, 990 w, 970 w, 925 w, 905 w, 795 w, 745 w, 710 m, 605 w, 530 w, 340 w.

^{1}H NMR (360 MHz) ($CDCl_3$) (ppm): 2.67 (t, J = 6.6 Hz, 2H, $H_2C(2)$), 2.85 (t, J = 6.6 Hz, 2H, $H_2C(3)$), 3.69 (s, 3H, $H_3CO(6)$), 4.56 (s, 2H, $H_2C(5)$), 7.71–7.76 (AA'XX'-system, 2H, HC(10)+HC(10')), 7.85–7.90 (AA'XX'-system, 2H, HC(9)+HC(9')).

^{13}C NMR (100 MHz) ($CDCl_3$) (ppm): 27.60 (t, C(2)), 34.51 (t, C(3)), 46.52 (t, C(5)), 51.91 (q, C(6)), 123.51 (d, C(9)+C(9')), 132.03 (s, C(8)+C(8')), 134.13 (d, C(10)+C(10')), 167.50 (s, C(7)+C(7')), 172.47 (s, C(1)), 200.61 (s, C(4)).

MS (70 eV) m/e (%): 275(3), M^+; 244(10), M^+-OCH_3; 216(18), $M^+-CO_2CH_3$; 160(69), $C_8H_4O_2N-CH_2^+$; 115(100), $H_3CO_2CCH_2CH_2CO^+$.

5-Aminolevulinic acid hydrochloride (**5**)

20 g of **4** were refluxed with 200 ml of 6 M HCl for 8–10 h. After cooling to −20 °C, the precipitated phthalic acid was removed by suction filtration and the clear filtrate brought to dryness in a vacuum desiccator over KOH. The dry product was recrystallized from methanol/isopropanol. Yield: 11.2 g (92%) of white crystals, m.p. 147 °C.

IR (KBr) (cm^{-1}): 3000 br, 2710 w, 2620 w, 1715 s, 1580 w, 1470 m, 1400 w, 1370 s, 1348 m, 1300 m, 1227 w, 1213 m, 1175 w, 1140 m, 1090 m, 1035 w, 985 w, 970 w, 935 m, 850 m, 765 m, 645 w, 615 w.

^{13}C NMR (100 MHz) (D_6-DMSO) (ppm): 27.34 (t, C(2)), 34.40 (t, C(3)), 46.53 (t, C(5)), 173.27 (s, C(1)), 202.66 (s, C(4)).

MS (70 eV) m/e (%): 131(9), M^+-HCl; 115(25), M^+-NH_2HCl.

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