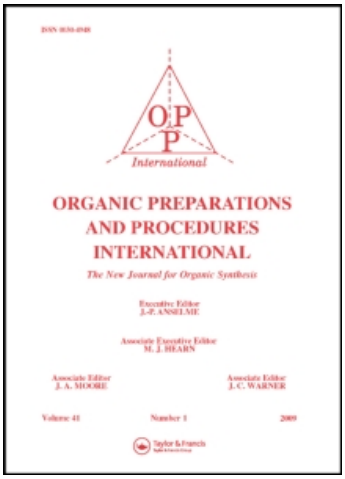

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AN IMPROVED PREPARATION OF (±) 3-HYDROXY-2-PYRROLIDINONE

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AN IMPROVED PREPARATION OF (±) 3-HYDROXY-2-PYRROLIDINONE

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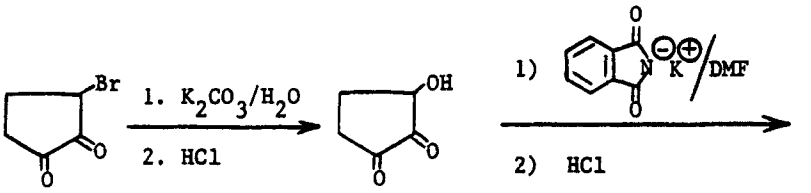
Certain compounds derived from 3-hydroxy-2-pyrrolidinone (V) are of current pharmacological interest as cognition activators.[1] We have developed an efficient large scale synthesis of (±) 3-hydroxy-2-pyrrolidinone which is described in this communication.

4-Amino-2-hydroxybutyric acid (III) is the preferred intermediate for the synthesis of V. A recent review[2d] on the antibiotic amikasin summarizes the methods of preparation for III. The esterification of III followed by cyclization is reported[3] to give 3-hydroxy-2-pyrrolidinone in 35% yield. There are also reports[4a,b] of preparing V by 1,3-dipolar addition reactions which however give mixtures not of substantial preparative value. Herein, we report an improved method for the preparation of 4-amino-2-hydroxybutyric acid, its efficient conversion to the title compound and isolation of the latter in 100-200 g quantities.

2-Bromo-γ-butyrolactone is a convenient starting material as it is commercially available or can be prepared in high yield[5a,b] from γ-butyrolactone. It was hydrolyzed to the 2-hydroxy-γ-butyrolactone in 85% yield by the literature method.[6]

The 2-hydroxy-γ-butyrolactone ring was opened by reaction with potassium phthalimide in boiling DMF to yield 2-hydroxy-4-phthalimidobutyric acid K salt in 67% yield. It was necessary to convert this salt into the



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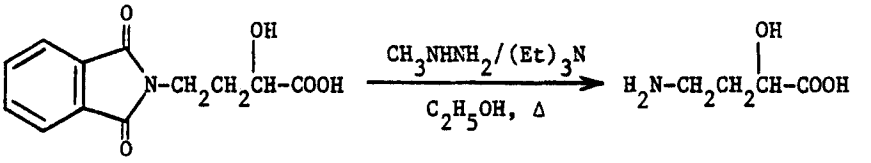
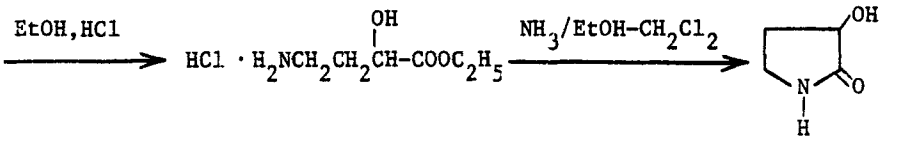


II III



IV V

carboxylic acid (II) prior to removal of the phthaloyl group.[7] When the more polar N-methylformamide was used as solvent in place of DMF only N-methylphthalimide was obtained.

The cleavage of the phthaloyl group from II with hydrazine hydrate in refluxing ethanol gave a mixture of III and phthalhydrazide which could not be separated by the published method.[3] We experimented with the method of Boissonnas[8] by which phthaloyl-L-leucine was converted to L-leucine in high yield by refluxing an ethanolic solution with phenylhydrazine and tri-n-butylamine. Application of this method on II gave III in 51% yield which was 91% pure by HPLC. However, when we substituted a combination of methylhydrazine and triethylamine, the desired product III was isolated pure in 92% yield on a large scale. The ethyl ester IV was obtained by refluxing an ethanolic solution of III containing a large

excess of dry HCl gas. Only a trace of III remained after 18 hrs of reflux (tlc).

The free 2-hydroxy-4-aminobutyric acid ethyl ester generated from the hydrochloride salt (IV) could not be cyclized to the lactam V by heating it neat or in diglyme (steam bath). However, when dissolved in a mixture of ethanol and methylene chloride saturated with dry ammonia gas, it slowly cyclized to V at room temperature. The lactam V is, presumably, formed by the cyclization of the intermediate amide. The formation of an intermediate and its gradual disappearance into V can be monitored by tlc. The pure product was isolated in 56% yield by extraction of the evaporated residue with methylene chloride and crystallization.

EXPERIMENTAL SECTION

All compounds reported had satisfactory microanalyses. The melting points were taken in capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were recorded on a XL-200 or XL-300 instrument. The IR spectra were obtained on the Nicolet MX-1 instrument. The HPLC data were obtained on the Waters or the Varian 5500 instruments using an Alltech C_{18} 10 μm column. The eluting solvent was 0.002 M Pica in water (tetrabutylammonium hydrogen sulfate). A 440 UV detector with extended wavelength module was used. TLC determinations were carried out on silica gel plates (EM) and developed with CH_3CN:THF 43:37 and 20 parts water containing 1% NH_4HCO_3; detector UV or ninhydrin.

2-Hydroxy-γ-butyrolactone (I).- To a solution of 1.27 kg (9.2 moles) of potassium carbonate in 6.7 ℓ of deionized water stirred and heated to reflux, was slowly added 1.0 kg (6.1 moles) of 2-bromo-γ-butyrolactone (97%) while maintaining reflux. Concentrated HCl (1.02 ℓ) was added slowly and the solution was concentrated under reduced pressure. The moist residue was extracted with 2-3 ℓ of boiling anhydrous ethanol 3A (contains approx. 4.8% v/v CH_3OH). The insoluble potassium chloride was further extracted with three 1 ℓ portions of boiling 3A ethanol. The extracts were combined and the solvent removed. The residue was distilled under reduced pressure to give 536 g (87%) of a colorless liquid, bp.

111-123°/1 mm pressure, (lit.[6] 123-129°/14 mm). GC indicated 98.3% purity (OV-17 column, 100-300° @ 10°/min). IR (neat) 1778 cm^{-1}, 3300 cm^{-1}; NMR ($CDCl_3$) δ 2.29 (m, 1H), 2.61 (m, 1H), 3.82 (S, 1H, disappeared in the presence of D_2O), 4.24 (m, 1H), 4.48 (m, 2H)

Anal. Calcd for $C_4H_6O_3$: C, 47.06; H, 5.92

Found: C, 47.75; H, 5.91

2-Hydroxy-4-phthalimidobutyric acid (II). - To a refluxing solution of 850 g (4.59 moles) of potassium phthalimide in 2.1 ℓ of dimethylformamide was slowly added 520 g (5.1 moles) of 2-hydroxy-γ-butyrolactone. The mixture was refluxed for 10 hrs and then cooled to room temperature. The product was collected, washed with three 1 ℓ portions of tetrahydrofuran, and dissolved in 4 ℓ of water. Charcoal was added and the solution was filtered and acidified to pH 1.6 with conc. HCl. The slurry was cooled to 5° and the precipitated product collected, washed with water and dried in a vacuum oven at 45° to give 760 g (66%) of a white solid, mp. 113.5-116°, which resolidified and remelted at 144.5-146°, lit.[2a] 147-148°, IR (KBr): 1710 cm^{-1}, 1766 cm^{-1}, 3360 cm^{-1}; NMR (d_6 DMSO): δ 1.86 (m, 2H), 3.66 (t, 2H, J = 7.4 Hz), a.98 (m, 1H), 7.82 (m, 4H); R_f 0.33

Anal. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62

Found: C, 57.60; H, 4.43; N, 5.68

4-Amino-2-hydroxybutyric acid (III). - A stirred slurry of 2-hydroxy-4-phthalimidobutyric acid (625.8 g, 2.5 moles) and dry triethylamine (358 ml, 2.57 moles) in 3.8 ℓ of absolute ethanol was heated. A solution was obtained at 30°C. Methylhydrazine (272.6 ml, 5.02 moles) was then carefully added. The thick precipitate initially formed gradually dissolved as reflux temperature was reached and then a new solid started

to precipitate. The mixture was refluxed for 3 hrs and then evaporated to dryness. The residue was dissolved in 4 ℓ of water and the remaining ethanol removed under reduced pressure (~1 ℓ of distillate). The solution was stirred and acidified to pH 4.9 with acetic acid. The insoluble solid was removed by filtration and washed with three 500 ml portions of water. The combined filtrates were concentrated in vacuo at 50° to ~ 1 ℓ volume. The residue was triturated with 1 ℓ of boiling 95% ethanol, cooled to 5° and the product collected by filtration. It was washed with three 100 ml portions of cold ethanol and 300 ml of ether to yield 276 g (92%) of the dried product, mp. 192.5-193.5° (dec). No impurities were detected by HPLC. IR (KBr): 1571 cm^{-1}, 1653 cm^{-1}, 3435 cm^{-1}; NMR (D_2O) δ 2.0 (m, 2H), 3.1 (t, 2H, J = 7.5 Hz), 4.1 (m, 1H); R_f 0.61, R_f of byproduct 0.26

Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76

Found: C, 40.35; H, 7.71; N, 11.71

3-Hydroxy-2-pyrrolidinone (V). - 4-Amino-1-hydroxybutyric acid (275 g, 2.3 moles) was gradually added to a cold, stirred solution of anhydrous HCl gas (405 g) in 1.5 ℓ of absolute ethanol. The mixture was slowly heated to reflux and maintained at reflux for 18 hrs after which time tlc[9] indicated near complete conversion to the ethyl ester. The solvent and HCl were carefully removed under reduced pressure. The residue was dissolved in two 300 ml portions of ethanol and stripped each time. The colorless syrup (456 g) was dissolved in 500 ml of absolute ethanol and 2 ℓ of methylene chloride. Anhydrous ammonia gas was bubbled into the clear solution. The precipitated ammonium chloride was removed by filtration. The filtrate was again saturated with ammonia gas and allowed to stand at room temperature for 64 hrs.[10] The solvent was removed under reduced pressure and the viscous residue was extracted portionwise with a

total of 8 ℓ of boiling methylene chloride. The extract was filtered to remove insolubles and the filtrate was reduced in volume to 1 ℓ and the resulting slurry cooled to 0°. The product was collected, washed with cold ether and dried in vacuo to yield 128.3 g (56%) of product, mp. 80-81°.

IR (KBr): 1700 cm^{-1}, 3320 cm^{-1}; NMR (D_2O) δ 1.75 (m, 1H), 2.31 (m, 1H), 3.14(m, 2H) 4.22 (t, 1H, J = 8.5 Hz); no impurities were detected by HPLC, R.T. 5.3 min.

Anal. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.85

Found: C, 47.30; H, 6.80; N, 13.82

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7. Surprisingly, the subsequent cleavage of the phthaloyl group did not proceed at all on the potassium salt but was essentially complete when carried out on the acid using methylhydrazine and triethylamine.

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9. R_f of ethyl ester 0.36, starting acid remained at the origin.

10. Progress of the reaction was followed by tlc. The product appeared at R_f 0.5. An intermediate was seen formed at R_f 0.23 which gradually diminished to the product.

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