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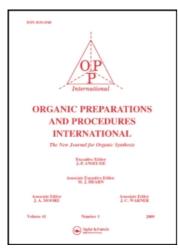
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IMPROVED SYNTHESIS AND PURIFICATION OF N⁴-ETHYL-L-ASPARAGINE

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(By J.-P. Anselme Editor)

IMPROVED SYNTHESIS AND PURIFICATION OF N¹4-ETHYL-L-ASPARAGINE

Submitted by R. W. Dineen* and D. O. Gray (11/23/76)

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The naturally occurring non-protein amino acid, N⁴-ethylasparagine¹ has been synthesized several times.²⁻⁶ However, one of the procedures⁴ leads to racemic product while two others^{2,3} are complex and tedious. The reaction conditions and purification methods of simple direct esterification route which previously^{5,6} had given poor yields (15-19%) have been improved to afford N⁴-ethyl asparagine in 48% overall yield and in 99% purity.

$$\text{Ho}_2 \text{CCH}_2 \text{CH}(\text{NH}_2) \text{Co}_2 \text{H} \xrightarrow{\text{EtOH}} \text{Eto}_2 \text{CCH}_2 \text{CH}(\text{NH}_2) \text{Co}_2 \text{H} \xrightarrow{\text{EtNH}_2} \text{EtNHCOCH}_2 \text{CH}(\text{NH}_2) \text{Co}_2 \text{H}$$

EXPERIMENTAL

β-Ethyl-L-aspartate. L-Aspartic acid (5 g) was added to absolute ethanol (50 ml) containing dry hydrogen chloride (3 g). After 4 hrs at 20°, the ethanolic HCl was removed in vacuo at 50° and the white residue was dissolved in 80% (v/v) aqueous ethanol (100 ml). The pH of this solution was adjusted to 4.0 with 2N ammonia in 80% ethanol to precipitate 80% of the residual aspartic acid. The precipitate was removed by centrifu-

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gation and the supernatant liquid taken to dryness as before. The resulting crude β -ethyl-L-aspartate was refluxed with methyl ethyl ketone (30 ml) for 1 hr. to extract contaminating esters and then with 95% (v/v) aqueous ethanol (50 ml) for 30 min. The ethanolic solution-was filtered hot and cooled to -20° to give β -ethyl-L-aspartate in 58% yield contaminated with aspartic acid (5%) and asparagine (0.5%). The amino acids were separated by paper chromatography in n-butanol-acetic acid-water (90:10:29 by vol.) and determined with ninhydrin.

N¹-Ethyl-L-asparagine. - β-Ethyl-L-aspartate (1.2 g) and anhydrous ethyl-amine-absolute ethanol (5:2 v/v, 10 ml) were heated at 50° in a sealed glass tube for 8 hrs. and the resulting solution evaporated in vacuo at 20°. Aspartic acid and ethylamine were then removed by ion exchange. The residual white solid, dissolved in water (10 ml) was applied to a column (11 x 1.6 cm diameter) composed of an intimate mixture of equal volumes of Zeo Karb 226 (Zerolit 226, H⁺ form) and Dowex 1 (AcO⁻ form). The sample was washed through with 150 ml water (1-2 ml/minute), pure N¹-ethyl-L-asparagine being recovered by evaporating the eluate in vacuo at 20°. Paper chromatography⁷ showed that the product was identical with authentic N¹-ethyl-L-asparagine synthesized by another route² and that the only detectable ninhydrin positive impurities present were asparagine (0.1-0.8%) and 1-ethylamidoaspartic acid (0.1-0.2%).

N⁴-Ethyl-L-asparagine, mp. 242° (dec.), lit.^{1,2} mp. 243° (dec.) and 254-255° (dec.); $[\alpha]_D^{25^\circ}$ -4.25 ±0.15° (c = 4.6, water), lit. values $[\alpha]_D^{20^\circ}$ -5.0 ± 0.9° (c = 2.6, water)¹ and $[\alpha]_D^{24^\circ}$ -3.95° (c = 2, water)²; solubility in water: 320 ± 6 g/1. at 23°.

Anal. Calcd for C₆H₁₂N₂O₃: C, 45.0; H, 7.55; N, 17.5 Found: C, 44.4; H, 7.49; N, 17.3.

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AN IMPROVED SYNTHESIS OF 2-HETEROARYL-3-

PHENYL-4(3H)-QUINAZOLINONES

Submitted by T. Hisano*, K. Muraoka and M. Ichikawa (1/3/77)

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A modification of the Niementowski quinazolone synthesis permits the obtention of 2-heteroaryl-3-aryl-4(3H)-quinazolinones by a one-step procedure in which the decarboxylation of a one molar excess of anthra-

I III a) 4-Picoline; b) 2-Picoline; c) 2, 3-Lutidine; d) 2, 5-Lutidine; e) Quinaldine