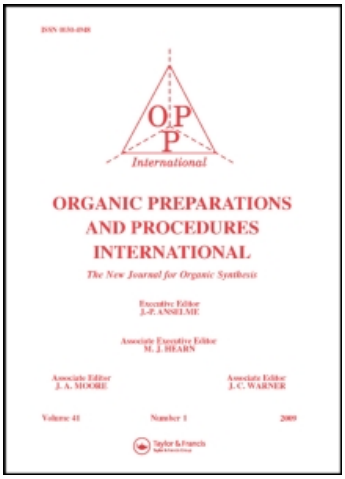

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IMPROVED SYNTHESIS AND PURIFICATION OF N⁴-ETHYL-L-ASPARAGINE

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OPPI BRIEFS

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IMPROVED SYNTHESIS AND PURIFICATION OF N^4-ETHYL-L-ASPARAGINE

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The naturally occurring non-protein amino acid, N^4-ethylasparagine[1] has been synthesized several times.[2-6] However, one of the procedures[4] 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 N^4-ethyl asparagine in 48% overall yield and in 99% purity.

$$HO_2CCH_2CH(NH_2)CO_2H \xrightarrow[H^+]{EtOH} EtO_2CCH_2CH(NH_2)CO_2H \xrightarrow{EtNH_2} EtNHCOCH_2CH(NH_2)CO_2H$$

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-

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.

N^4-Ethyl-L-asparagine.- β-Ethyl-L-aspartate (1.2 g) and anhydrous ethylamine-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 N^4-ethyl-L-asparagine being recovered by evaporating the eluate in vacuo at 20°. Paper chromatography[7] showed that the product was identical with authentic N^4-ethyl-L-asparagine synthesized by another route[2] and that the only detectable ninhydrin positive impurities present were asparagine (0.1-0.8%) and 1-ethylamidoaspartic acid (0.1-0.2%).

N^4-Ethyl-L-asparagine, mp. 242° (dec.), lit.[1,2] mp. 243° (dec.) and 254-255° (dec.); $[\alpha]_D^{25°}$ -4.25 ± 0.15° (c = 4.6, water), lit. values $[\alpha]_D^{20°}$ -5.0 ± 0.9° (c = 2.6, water)[1] and $[\alpha]_D^{24°}$ -3.95° (c = 2, water)[2]; solubility in water: 320 ± 6 g/l. at 23°.

Anal. Calcd for $C_6H_{12}N_2O_3$: 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

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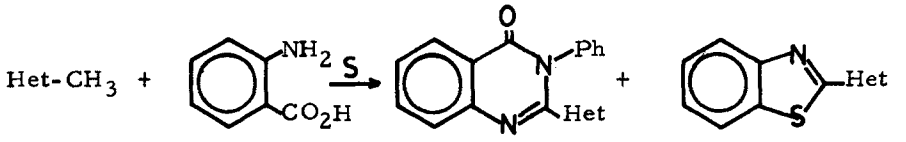
A modification of the Niementowski quinazolone synthesis[1] permits the obtention of 2-heteroaryl-3-aryl-4(3H)-quinazolinones by a one-step procedure in which the decarboxylation of a one molar excess of anthra-



I II III

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