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### AN IMPROVED SYNTHESIS OF $\gamma$ -L-GLUTAMYL-TAURINE

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AN IMPROVED SYNTHESIS OF  $\gamma$ -L-GLUTAMYL-TAURINE

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(05/22/86)

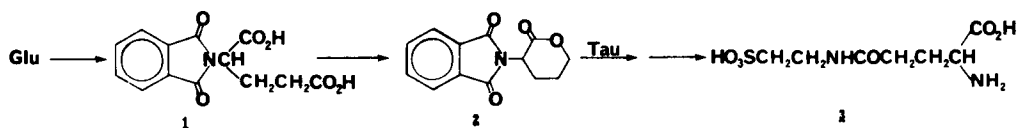
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$\gamma$ -L-Glutamyl-aurine [Glutaurine; Glu(Tau)<sup>1</sup>, 3] isolated from bovine parathyroids<sup>2</sup> has been reported to influence the metabolism of Vitamin A,<sup>3</sup> to antagonize the glucocorticoids and triiodothyronine<sup>4</sup> and to possess radioprotective properties;<sup>5</sup> other physiological and therapeutic properties of the substance have also been discussed.<sup>6</sup>

Glutaurine has been previously synthesized by us<sup>7</sup> and by Felix.<sup>8</sup> The best overall yield of our earlier synthesis,<sup>7</sup> based on the amount of the starting Glu was 23%, while the overall yield of Felix's synthesis<sup>8</sup> starting from commercially available Boc-Glu-OBu-t<sup>9</sup> was 72%.

Since acylation with 2 produces predominantly  $\gamma$ -amides with different amine compounds,<sup>10</sup> this anhydride was reacted directly with Tau to yield



Pht-Glu(Tau). The use of tetramethylguanidine (TMG) as the base resulted in rapid dissolution of Tau in acetonitrile; the phthaloyl group was removed by hydrazinolysis without prior isolation of the intermediate. The product was purified by ion exchange on Dowex 50 using an acidic (pH 2.1) eluent. Glu(Tau) passed the column while contaminants (e. g. TMG, traces of Glu) were retained. After recrystallization from EtOH-water, the pure product was obtained in 73% yield. No  $\alpha$ -isomer was detectable by paper electrophoresis at pH 3.5. The physical constants were identical to those

previously reported.<sup>7,8</sup> Thus the new three-step synthesis starting from glutamic acid (Glu) with an overall yield of up to 44% would seem suitable for large scale preparations.

#### EXPERIMENTAL SECTION

Materials and Methods.— Phthaloyl-L-glutamic anhydride was prepared according to Mohr et al.<sup>11</sup> Tau, TMG and hydrazine hydrate (all of reagent grade) were purchased from Fluka AG, Buchs, Switz. The other reagents and solvents were also of reagent grade purity. Paper electrophoretic tests were carried out on a cooled flat plate apparatus (Labor MIM, Hungary) at pH 2.1 and 3.5. Tlc were performed on Kieselgel 60 plates (Merck, Darmstadt, FRG).

Glutaurine.— Phthaloyl-L-glutamic anhydride (2) (3.05 g, 11 mmol) was mixed with MeCN (15 ml) and cooled to 0°. Then a solution of Tau (1.25 g, 10 mmol) and TMG (2.56 ml, 20 mmol) in MeCN (5 ml) was added dropwise with stirring. The mixture was stirred at 0° for 30 min and at 20° for 30 min; a clear solution was obtained. Then 70% hydrazine hydrate (1.4 ml, 20 mmol) in ethanol (10 ml) was added. The mixture was allowed to stand overnight at room temperature then evaporated and the residue was dissolved in water (50 ml); acetic acid (1.2 ml) was added and the precipitate which formed was removed by filtration. Then the pH of the filtrate was adjusted to 2.5 with formic acid, the solution was applied to a Dowex 50 x 2 column (200-400 mesh, 2.2 x 40 cm) previously equilibrated with a formic acid-acetic acid-water mixture (1:4:45 by vol.) and eluted with the same solvent mixture (200 ml). The eluate was then evaporated and the crystalline residue was crushed with dry acetone, then dried in vacuo, over NaOH. The crude product was recrystallized from ethanol-water (4:1 by vol.) to yield 1.85 g (73%) of colorless crystals, mp. 222-223° (dec. uncorr.), lit.<sup>7</sup> 222-223°; lit.<sup>8</sup> 223.5-224°.  $[\alpha]_{346}^{25} = + 28.2^\circ$ ;  $[\alpha]_{D}^{25} = + 23.3^\circ$  (c, 2.06, 1N HCl). IR(KBr): 3315 (NH amide), 1758 (CO), 1662 (CO amide), 1576 (NH<sub>3</sub><sup>+</sup>); 1296-1031 (SO<sub>3</sub><sup>-</sup>) cm<sup>-1</sup>. R<sub>f</sub> = 0.19 (EtOAc-AcOH-water 9:2:2); 0.12 (BuOH-AcOH-water 4:1:1). Paper electrophoretic mobilities at pH 2.1 and 3.5

relative to those of Cys(O<sub>3</sub>H) were: 0.53 and 0.73, respectively.

Anal. Calcd. for C<sub>7</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>S: C, 33.07; H, 5.55; N, 11.02; S, 12.61

Found: C, 33.27; H, 5.67; N, 10.98; S, 12.45

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