

Note

Facile and Large-Scale Synthesis of L-Theanine

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Teas have a wide spectrum of physiological and biological effects in experimental animals and humans.¹⁾ These effects arise mainly from catechins and caffeine, which are major constituents in various kinds of tea (green, oolong, and black). For example, cholesterol metabolism is affected by both tea catechins^{2,3)} and caffeine.⁴⁻⁶⁾ Theanine (*N*²-ethylglutamine) is found in green tea.⁷⁾ Theanine elicits *umami* (flavour potentiation) and a sweet taste, and the quality of green tea is influenced by the theanine content. Little information is available about the physiological or biological effects of theanine, because experiments on animals are not feasible because a large amount of the compound is not readily available; theanine is expensive, the isolation of the compound from tea or other sources is complicated, and the cost of isolation is high. Theanine has been chemically synthesized,⁸⁻¹⁵⁾ but the methods are unsuitable for large-scale synthesis of the compound because of their low yield and complexity, and because the reaction in which anhydrous ethylamine is used for amide formation with glutamic acid γ -ester, is hazardous.

We planned animal experiments about the physiological and biological effects of theanine, and as a first step set out to develop a new method suitable for large-scale synthesis. Our strategy was to do one-batch synthesis, with purification done not by chromatography but by recrystallization, and we decided not to use anhydrous ethylamine. Of our various trials, the cheapest, easiest, and safest method is described here. It is superior to the enzymatic procedure.¹⁶⁾

γ -Benzyl glutamate (332 g) prepared by the method of Hayakawa *et al.*¹⁷⁾ was dissolved in pyridine (3 liters) in a 5-liter flask, and trytyl chloride (500 g, 1.28 eq) was added to the solution. Trytyl chloride was selected as the reagent to protect the amino group because of its cheapness, unreactivity in the later amide formation because of its bulkiness, and ease of cleavage. The reaction mixture was stirred for 72 hr at room temperature, and the solvent was evaporated off. A 70% solution of ethylamine (1.8 liters) was added to the residue in the flask and the solution was stirred for 48 hr at room temperature. The reaction mixture was concentrated and dried under reduced pressure, and 50% acetic acid (1.2 liters) was added to the residue obtained. After the solution was heated for 5 min at 100°C, distilled water was added to the mixture for removal of carbinol as a precipitate. After filtration of the suspension, the filtrate was concentrated and dried under reduced pressure. The residue obtained was crystallized from hot ethanol and the resulting crystals were filtered and then recrystallized from ethanol-water. Theanine

(82.7 g, 33.9% from glutamic acid benzyl ester) was obtained as white crystals. Concentration of the mother liquor afforded a second crop of 10.0 g of the compound, giving a combined yield of 38.0%. This compound obtained was identical in mp (214–216°C), $[\alpha]_D = +8.6$ ($c = 1.00$, H₂O), IR, ¹H-NMR, and FBMS results to the authentic sample (findings from the last three, not shown).

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