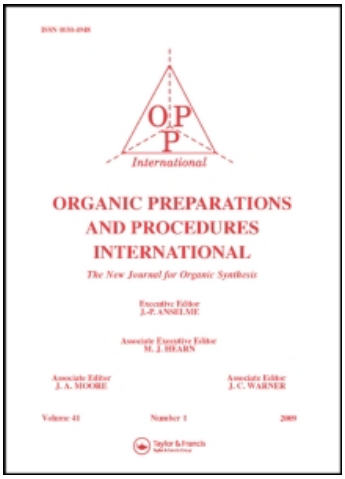

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Elberling, J. A. , Zera, R. T. , Magnan, S. D. J. and Nagasawa, H. T.(1979) 'N-PHTHALOYL-L-GLUTAMIC ANHYDRIDE (2-PHTHAL IMIDOGLUTARIC ANHYDRIDE)', Organic Preparations and Procedures International, 11: 2, 67 — 70
To link to this Article: DOI: 10.1080/00304947909354843
URL: http://dx.doi.org/10.1080/00304947909354843

ORGANIC PREPARATIONS AND PROCEDURES INT. 11(2), 67-70 (1978)

N-PHTHALOYL-L-GLUTAMIC ANHYDRIDE (2-PHTHALIMIDOGLUTARIC ANHYDRIDE)

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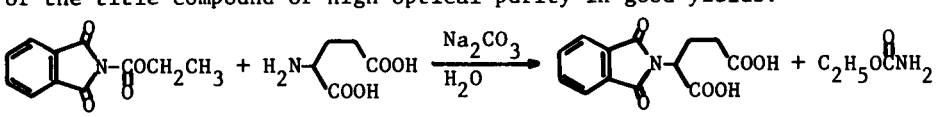
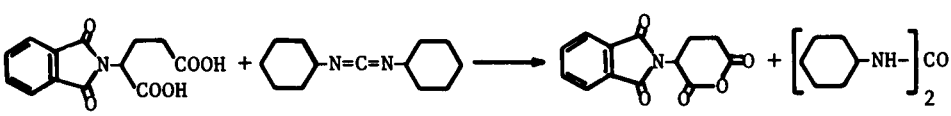
Contemporary interest in γ-glutamyl peptides[1] and other γ-glutamyl amides of biological origin[2] has accelerated the need for suitable synthetic methods for the preparation of these γ-glutamyl derivatives. A useful intermediate in this regard is the amino-protected, carboxy-activated glutamic acid derivative, N-phthaloyl-L-glutamic anhydride. The sterically less hindered γ-carbonyl group of this anhydride is preferentially attacked by alcohols, amines, and amino acid esters; hence, this compound has been used for the synthesis of γ-glutamyl esters, amides, and peptides.[3,4] This regioselectivity is in contrast to N-carbobenzoxy-L-glutamic anhydride which gives mixtures of the α- and γ-glutamyl derivatives.[5]

We present here a convenient two-step procedure for the preparation of the title compound of high optical purity in good yields.





Although a one-step procedure for the preparation of N-phthaloyl-L-glutamic anhydride from L-glutamic acid is available,[6] racemization is

encountered, and the usual method for preparing this optically-active anhydride is the five-step synthesis by King and Kidd,[3] or modifications thereof.[4,7] The major disadvantage of this latter procedure—aside from the number of steps—is the use of acetic anhydride in excess and with heating to cyclize N-phthaloyl-L-glutamic acid to the anhydride. This can lead to a partially racemized product unless the reaction conditions are carefully controlled.[7] By use of slightly less than one equivalent of N,N'-dicyclohexylcarbodiimide in an inert solvent (tetrahydrofuran, THF), the cyclodehydration can be effected under mild conditions at room temperature to give the desired anhydride in pure state without racemization. This method may also be directly applicable for the preparation of optically-active N-phthaloyl-L-aspartic anhydride.

The present procedure starts with L-glutamic acid to give as intermediate, N-phthaloyl-L-glutamic acid, which is prepared by adaptation of the one-step method of Nefkens, Tesser, and Nivard.[8] All other methods for the preparation of this compound are multi-steps with the exception of the fusion-hydrolysis method[6,9] using L-glutamic acid and phthalic anhydride. The fusion method, however, leads to a partially racemized product.[7]

EXPERIMENTAL

L-Glutamic acid, $[\alpha]_D^{26} = +30.0°$ (c 1.00, 5 N hydrochloric acid), was purchased from Sigma Chemical Company. Dicyclohexylcarbodiimide was purchased from Pierce Chemical Company and the silica gel was a product of EM Reagents. N-Carbethoxyphthalimide can be purchased from Aldrich Chemical Company; alternatively, it may be prepared by "Method A" of Nefkens, Tesser, and Nivard.[8] Infrared absorption spectra were determined on a Beckman IR-10 infrared spectrophotometer and optical rotations on a Perkin-Elmer Model 141 polarimeter. Melting points were determined on a Mettler FP-2 hot stage mp apparatus and are corrected.

N-Phthaloyl-L-glutamic Acid.- To a solution of 116.0 g (1.10 mol) of sodium carbonate in 1.0 L of water in a 2 L three-necked round-bottomed flask equipped with a magnetic stirring bar and a thermometer was added

73.6 g (0.50 mol) of L-glutamic acid. The mixture was stirred until the solids dissolved and then cooled to 0-5° in an ice bath. Stirring speed was increased and 109.6 g (0.50 mol) of N-carbethoxyphthalimide was added in portions at such a rate that the temperature of the reaction mixture never rose above 10°. After addition was complete, the ice bath was removed, and stirring was continued at lower speed at room temperature overnight (15 hrs). The reaction mixture was then filtered to remove any suspended solids and the filtrate was carefully acidified with 200 mL of conc. hydrochloric acid. The product which initially separated as an oil solidified when kept in a refrigerator overnight. This product was collected, washed with a small amount of cold water, and recrystallized from water to give, after drying *in vacuo*, 89.0 g (64.2% yield) of colorless crystals, mp 158.5-160.5°, $[\alpha]_D^{26} = -46.1°$ (c 1.00, 95% EtOH) (lit.[7]: mp 158-159°, $[\alpha]_D^{21} = -42.6°$ [c 1.00, 95% EtOH]); IR (KBr, cm^{-1}), 2600 (bd, COOH), 1780 (sh), 1725 (bd, s, phthalimide CO's, COOH), 1380 (s, CH_2), 700 (m, aromatic C-H deformation, *ortho*-disubstituted benzene).

Anal. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05.
Found: C, 56.37; H, 4.00; N, 5.19.

N-Phthaloyl-L-glutamic Anhydride. Caution! Dicyclohexylcarbodiimide is a skin irritant, and its vapors can be injurious to the eyes.- To a solution of 70.0 g (0.253 mol) of N-phthaloyl-L-glutamic acid prepared above in 850 mL of THF in a 2 L Erlenmeyer flask equipped for magnetic stirring was added, with vigorous stirring at room temperature, a solution of 51.5 g (0.250 mol) of dicyclohexylcarbodiimide in 150 mL of THF. Stirring was continued for 45 minutes, the reaction mixture was then cooled in a refrigerator overnight and the precipitated dicyclohexylurea was removed by filtration. The filtrate was percolated through a silica gel column (4 x 24 cm, 30-70 mesh, 100 g) using an additional 500 mL of THF

as the eluting solvent. This treatment insured the removal of traces of starting acid that remained uncyclized. Samples were spotted on fluorescent silica gel plates and the fluorescence-quenching eluates (viewed under 254 nm wavelength UV light) were combined and concentrated under reduced pressure to a volume of approximately 1 L on a rotating evaporator. The solution was then heated to boiling on a steam bath, removed from the heat source and diluted with "hexanes" (500 mL). After storage under refrigeration overnight the product that had crystallized was collected and dried, 36.1 g (55.7% yield), mp 201-202° with softening at 196°, $[\alpha]_D^{25} = -43.8°$ (c 1.69, dioxane). Tipson reports $[\alpha]_D^{21} = -43.1°$ (c 1.80, dioxane) and mp 195-196°. A second crop, 12.6 g (19.4% yield), mp 197-200°, $[\alpha]_D^{24} = -42.3°$ (c 1.69, dioxane), was obtained by concentration of the mother liquor. Total yield, 48.7 g (75.1%). The product should be protected from moisture and stored in a freezer to prevent deterioration. IR (KBr, cm^{-1}), 1830 (s, anhydride CO), 1775 and 1720 (s, phthalimide CO's), 1380 (s, CH_2), 710 (m, aromatic C-H deformation, *ortho*-disubstituted benzene).

Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40.

Found: C, 60.40; H, 3.47; N, 5.37.

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(Received December 7, 1978; in revised form February 20, 1979)