

DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF N-PHTHALOYL DERIVATIVES OF AMINO ACIDS

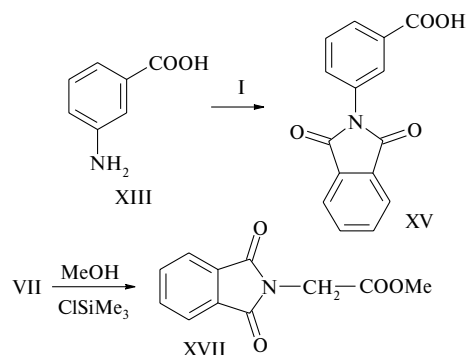
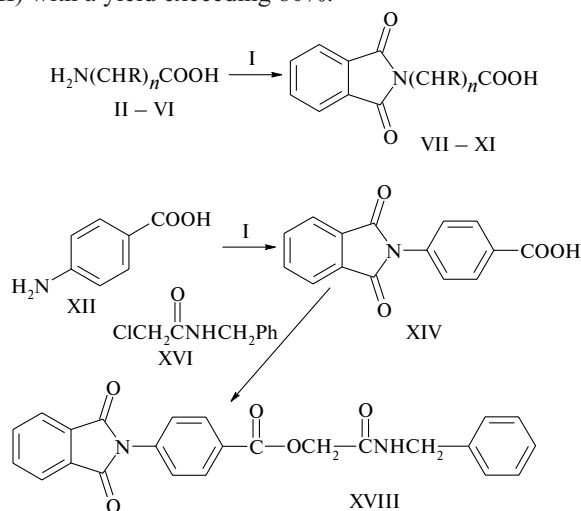
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N-Phthaloyl derivatives of amino acids are used as semiproducts in the synthesis of compounds possessing hypolipidemic [1], analgesic [2], antibacterial [3], and antitumor [4] activity. These N-phthaloyl amino acids (PAAs) are usually synthesized through cyclocondensation of amino acids with phthalic anhydride [5 – 8]. Some PAAs, representing the N-phthaloyl derivatives (VIII – X) of *DL*-alanine, β -alanine, and γ -aminobutyric acid (GABA), can be also obtained by fusing phthalic acid (I) with the corresponding amino acids (III – V) at 170 – 190°C [9].

However, the possibility of using this method for the synthesis of other PAAs was not considered in [9]. Recently [10] we have demonstrated that glycine (II) can be brought into reaction with I in a medium of boiling propionic acid, which simultaneously performs the functions of solvent and condensing agent. The reaction yielded N-phthaloylglycine (VII) with a yield exceeding 80%.



R = H, $n = 1$ (II, VII); R = CH₃, $n = 1$ (III, VIII); R = H, $n = 2$ (IV, IX);
R = H, $n = 3$ (V, X); R = H, $n = 4$ (VI, XI)

The purpose of this study was to expand the method proposed in [10] to other amino acids and to study the influence of carboxylic acids, used as the reaction media, on the N-phthaloylation process.

As the objects for modification, we selected glycine, *DL*-alanine, β -alanine, γ -aminobutyric acid (GABA), δ -aminovaleric acid (DAVA) (II – VI), and 4- and 3-aminobenzoic acids (XII, XIII). It was found that the N-phthaloylation of acids II – V by interaction with phthalic acid (I) can be successfully performed in both propionic and acetic acid with the formation of products VII – X. Reaction of I with DAVA, proceeding under more rigid conditions (in propionic acid, in the presence of ClSiMe₃), leads to PAA XI. It was established that an effective reactant for the N-phthaloylation of aromatic amino acids XII and XIII is caproic acid, in which the reaction proceeded smoothly with a high yield of PAAs XIV and XV.

The proposed structures of the synthesized compounds were confirmed by comparison with known samples (no melting point depression) and by the data of TLC and ¹H

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NMR measurements (see Table 1 and the experimental part below). In order to characterize N-phthaloylglycine (VII) and N-phthaloyl-4-aminobenzoic acid (XIV), these compounds were treated with a mixture of MeOH and ClSiMe_3 (for compound VII) and with a mixture of N-(chloroacetyl)benzylamine (XVI), NaHCO_3 , KI, and DMSO (for XIV) so as to obtain the corresponding esters (XVII and XVIII, respectively).

The method proposed for the synthesis of N-phthaloyl amino acids is simple and provides for a high yield of the target products, which makes it competitive with other reaction pathways described previously [5–9].

EXPERIMENTAL CHEMICAL PART

The ^1H NMR spectra were measured on a Bruker AM-300 spectrometer using samples dissolved in DMSO-d_6 . The course of the reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in a benzene–ethyl acetate (1 : 1) system; the spots were visualized under UV illumination. Some physicochemical characteristics of the synthesized compounds are listed in Table 1, where the melting points and yields are indicated for nonrecrystallized products. When necessary, the primary products can be purified by recrystallization from water (VII–XI) or AcOH (XIV–XV). The data of elemental analyses agree with the results of calculations according to the empirical formulas.

N-Phthaloylglycine (VII). A mixture of 1 g (6 mmole) of phthalic acid (I) and 0.45 g (6.3 mmole) of glycine in 5 ml of AcOH was treated for 4 h at 160–170°C (here and below, the bath temperature), cooled to ~20°C, diluted with water, and allowed to stand at this temperature for 24 h. The precipitate of compound VII was separated by filtration, washed with water, and dried in air; ^1H NMR spectrum (δ , ppm): 4.25 (s, 2H, CH_2), 7.90 (m, 4H, H_{arom}).

N-Phthaloyl derivatives of DL-alanine, β -alanine, and GABA (VIII–X). General Method. A mixture of 1 g

(6 mmole) of acid I and 6.2 mmole of amino acid (III, IV, or V) was heated for 4 h in 8 ml of AcOH (at 160–170°C) or in 7 ml of EtCOOH (170–180°C). Then the mixture is cooled to ~20°C and evaporated at a reduced pressure (water-jet pump). The residue is diluted with water and allowed to stand for 12 h at ~20°C. The precipitate is separated by filtration, washed with water, and dried in air to obtain PAA VII, IX, or X; ^1H NMR spectrum (δ , ppm): compound VIII, 1.60 (d, 3H, CH_3), 4.90 (m, CH), 7.9 (m, 4H, H_{arom}); compound IX, 2.61 (t, 2H, CH_2), 3.80 (t, 2H, CH_2), 7.85 (m, 4H, H_{arom}); compound X, 1.85 (s, 2H, CH_2), 2.25 (m, 2H, CH_2), 3.63 (m, 2H, CH_2), 7.86 (m, 4H, H_{arom}).

N-Phthaloyl- δ -aminovaleric acid (XI). A mixture of 1 g (6 mmole) of acid I and 0.72 g (6.1 mmole) of DAVA in 10 ml of EtCOOH was heated for 2 h at 170–180°C and cooled to ~20°C. Then 5 ml of ClSiMe_3 was added and the mixture was heated for 3 h at 140–150°C, cooled to ~20°C, and evaporated at reduced pressure (water-jet pump). The residue was diluted with water and allowed to stand for 42 h at ~20°C. The precipitate was separated by filtration, washed with water, and dried in air to obtain compound XI; ^1H NMR spectrum (δ , ppm): 1.60 (m, 4H, 2CH_2), 2.23 (m, 2H, CH_2), 3.60 (m, 2H, CH_2), 7.80 (m, 4H, H_{arom}).

N-Phthaloyl derivatives of 4- and 3-aminobenzoic acids (XIV, XV). General Method. A mixture of 1 g (6 mmole) of acid I and 6 mmole of 4-aminobenzoic acid (XII) or 3-aminobenzoic acid (XIII) in 10 ml of caproic acid was heated for 3 h at 210–220°C (for XII) or 220–230°C (for XIII). Then the mixture is cooled to ~20°C and diluted with acetone. The precipitate is separated by filtration, washed with acetone, and dried in air to obtain compound XIV or XV; ^1H NMR spectrum (δ , ppm): compound XIV, 7.60 (m, 2H, H_{arom}), 8.02 (m, 6H, H_{arom}); compound XV, 7.68 (m, 2H, H_{arom}), 7.97 (m, 6H, H_{arom}).

N-Phthaloylglycine methyl ester (XVII). A mixture of 0.5 g of compound VII, 5 ml of MeOH, and 3 ml of ClSiMe_3 was kept for 12 h with periodic stirring at ~20°C and treated with an excess aqueous solution of Na_2CO_3 . The precipitate

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Initial amino acid	Condensing agent	Yield, %	M.p., °C	Empirical formula	Ref.
VII	II	AcOH	90	193–196	$\text{C}_{10}\text{H}_7\text{NO}_4$	[10]
		EtCOOH	83			
VIII	III	AcOH	74	160–163	$\text{C}_{11}\text{H}_9\text{NO}_4$	[9]
		EtCOOH	72			
IX	IV	AcOH	65	149–151	$\text{C}_{11}\text{H}_9\text{NO}_4$	[9]
		EtCOOH	82			
X	V	AcOH	83	114–116	$\text{C}_{12}\text{H}_{11}\text{NO}_4$	[9]
		EtCOOH	90			
XI	VI	EtCOOH + ClSiMe_3	64	115–117	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	[7]
XIV	XII	$\text{CH}_3(\text{CH}_2)_4\text{COOH}$	90	290–292	$\text{C}_{15}\text{H}_9\text{NO}_4$	[11]
XV	XIII	$\text{CH}_3(\text{CH}_2)_4\text{COOH}$	84	285–286	$\text{C}_{15}\text{H}_9\text{NO}_4$	[11]

was separated by filtration, washed with water, and dried to obtain 0.4 g (75%) of methylate XVII; m.p., 112 – 114°C. The product shows no melting point depression in the mixture with a sample synthesized according to [12].

O-(4-Phthalimidobenzoyl)glycolic acid benzylamide (XVIII). A mixture of 0.5 g (1.9 mmole) of acid XIV, 0.35 g (1.9 mmole) of N-(chloroacetyl)benzylamine (XVI) [13], 0.4 g NaHCO₃, and 0.2 g KI in 5 ml of DMSO was kept for 48 h with periodic stirring at ~20°C and treated with an excess aqueous solution of NaHCO₃. The precipitate was separated by filtration, washed with water, and dried in air to obtain 0.6 g (78%) of amide XVIII; C₂₄H₁₈N₂O₅; decomp. temp. > 250°C; ¹H NMR spectrum (δ, ppm): 4.33 (d, 2H, CH₂), 4.83 (s, 2H, CH₂), 7.65 (d, 2H, J 8.0 Hz, H_{arom}), 7.95 (d, 2H, J 8.0 Hz, H_{arom}), 8.18 (d, 2H, J 8.0 Hz, H_{arom}), 8.70 (bs, 1H, NH).

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