Synthesis of new Amides based on N-Phthaloyle-α-Amino Acids

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Abstract

N-phthaloyl derivatives of aliphatic α-amino acids were synthesized using phthalanhydride under standard conditions. The optimization reaction carried out by the thermal method to obtain the amides of these N-phthaloyl amino acids resulted in transmitted rather than amidation. The target amides of N-phthaloyl-α-amino acids were obtained by acylation of the amine with the corresponding acid chloroanhydrides in dichloromethane. These results were compared with the results of a similar acylation in a non-polar solvent (benzene). The dependence of the direction of the reaction on the duration of the acylation and the amount of amine used was established. The conditions for the formation of the corresponding N-phthaloyl-α-amino acid amides and asymmetric phthalic acid diamides were found. It is noteworthy that the formation of diamides is directly proportional to the equivalent amount of amine and the duration of the reaction, which makes it possible to purposefully control the synthesis in one reactor.

Keywords: N-phthaloyl amino acid, homooveratrylamine, condensation, amide, diamide.

Introduction

Amino acids (peptides) are important biological active compounds that take place in metabolic processes [1], in immune system [2] and keeps signal transactions moderate [3]. The valuable structure of amino acids as a bifunctional and chiral source has led to further popularization of research based on them, offering a wide range of possibilities for pharmacology. In recent years, there has been a trend in medicine to use amino acid-based foods [4-6] and biopharmaceuticals and pharmaceuticals [7-9].

In ongoing studies of amino acids with the carboxyl group, amino group protection is an important step, and sometimes, N-protected amino acids themselves may be the critical point of the study. This condition is largely due to the structure of the selected N-protective agent. Continuing research based on them, of course, will lead to more interesting and significant results. These include N-phthalaoyl amino acids and research based on them for several decades. The study of the synthesis and pharmacological properties of N-phthaloyl derivatives of amino acids is rising to new stages in organic synthesis and medicinal chemistry.

In particular, N-phthaloyl derivatives of isoleucine and phenylalanine have anti-inflammatory properties, while (S)-N-phthaloyltryptophan has immunomodulatory activity with a relatively high rate [10]. Phenacyl esters of N-phthaloyl amino acids showed strong in vitro activity in the inhibited lipase enzyme pancreatin. This suggests that they may be compounds with leading potential in the development of anti-obesity drugs [11]. It has also been found that pseudoesters of phthalimidooxims exhibit strong cytotoxic activity in human cancer cells [12]. When the neurotoxic and antiepileptic properties of compounds obtained by combining gamma amino butyric acid (GABA), phthalimide, hydrazone, and anilides with different pharmacophore properties into a single molecule were studied, most of the compounds showed activity in scSTY and iPIC models [13]. N-phthalamidine derivatives of three substitute purines based on glycine, phenylalanine, and tyrosines [14] and N-phthaloylhydroxamic acids of several amino acids [15] showed high
biological activity against bacteria (in vitro). It should be noted that the amides N,N-phthaloylglycine may be a class of antiepileptic drugs in the future [16]. Carboxamides derived from N-phthaloyl-α-amino acids have also been found to be active against bacteria, especially the activity of carboxamides that retain the cyclopropyl ring has been highly evaluated [17]. In addition, the high anti-inflammatory potential of carboxamides has been proven experimentally [18].

It can be observed in analyzes that N-phthaloyl amino acid derivatives can also be a tool in the complex processes of organic synthesis. N-phthaloyl-(S)-aminoacyl chlorides with alkyl and aryl side chains [19-21] serve as a favorable agent for enantiomer separation of heterocyclic amines. Mannich [22] and Pictet-Spengler reactions [23] have been shown to form product enantiomers with a large relative difference between them when administered sterically using N,N-phthaloyl-tret-leucinylchloride. Also, non-racemate chiral reducing agent based on N, N-phthaloylamine acids have been used effectively in the enantioselective reduction of prochiral cyclic iminos to obtain important alkaloid derivatives [24].

The unlimited possibilities of obtaining amides with different pharmacophore groups and symmetric phthalic acid diamides from N-phthaloyl amino acids serve to further enrich the existing multidisciplinary pharmacological properties and bring them to new stages. In this study, we developed the effect of factors on the targeting of the condensation reaction on which they are based, as well as on the effective synthesis of N-phthaloyl amino acids.

**Experimental**

All chemicals were purchased from commercial suppliers and used without further purification. Melting points of all synthesized compounds were determined on a Melt Point Meter HM RD-1 and are uncorrected. The course of the reactions was monitored and the purity of synthesized compounds was checked by TLC using silica gel 60 F-254 Al-plates (Merck, Germany) in CH₂OH: petroleum ether (1:4, system 1), and CH₂OH:CHCl₃:CH₃OH (1:2:7, system 2) solvent system and the spots were visualized using a UV lamp (λ max = 254 or 365 nm). IR spectra were recorded from KBr pellets on a System 2000 FTIR instrument (PerkinElmer). ¹H and ¹³C-NMR spectra were recorded on a Unity-400+ spectrometer (400 MHz, Varian) NMR instrument, using either in CDCl₃, CD₂OD, CD₃COOD, Pyridine-d₅ and CDC₁₃ + CD₃OD as solvent and TMS as internal reference and chemical shifts were expressed in δ values (ppm). Mass spectra were recorded using a gas chromatography-mass spectrometer as part of an Agilent 1100 Infinity high-performance liquid chromatograph (Agilent Technologies, USA) and a 6420 Triple Quad LC / MS mass detector (Agilent Technologies, USA) (electrospray ionization + ESI TIC Scan).

2.1 General procedure for the synthesis of N-phthaloyl amino acid (3a-g) (Scheme 1).

25 mmol phthalic acid anhydride (1) and 25 mmol amino acids (2a-d) were refluxed in 20 ml glacial acetic acid for 5-7 h. The organic solvents were removed in vacuo pressure to get sticky oily mass. 15 ml of water was added to oily mass, acidified with 10% HCl and were refluxed for 1 h. After cooling, the resulting mixture was extracted with ether-water (1:4). The precipitate was filtered off, recrystallised from EtOH:H₂O and dried.

2.1.1 2-(1,3-Dioxoisindolin-2-yl)acetic acid (3a): White needle crystal (water), yield = 81%, - Mp: 199-202°C, Rf:0.50 (system 1); FT-IR (KBr) / cm-1: 3423 (OH); 1773 (N(CO)₂Ar); 1725 (COOH); 1615, 1469.8 (Ar); 1416 (C-N-C); 1389 (C-N-C).

2.1.2 2-(1,3-Dioxoisindolin-2-yl)propionic acid (3b): White crystal (ethanol / water), yield = 91%, - Mp: 147-150°C, Rf:0.45 (system 1); FT-IR (KBr) / cm-1: 3243 (OH); 1744 (N(CO)₂Ar); 1699 (COOH); 1610, 1467 (Ar); 1399 (C-N-C); 1344.7 (C-N-C).

2.1.3 2-(1,3-Dioxoisindolin-2-yl)propanoic acid (3c): White crystal (ethanol / water), yield = 90.5%, - Mp: 78-80°C, Rf:0.47 (system 1); FT-IR (KBr) / cm-1: 3230 (OH); 1770 (N(CO)₂Ar); 1700 (COOH); 1610, 1465 (Ar); 1396 (C-N-C); 1336/C-N-C).

2.1.4 2-(1,3-dioxoisindolin-2-yl)-3-methylbutanoic acid (3d): White powder (ethanol / water), yield = 98%, - Mp: 88-91°C, Rf:0.60 (system 1); FT-IR (KBr) / cm-1: 3473.9 (OH); 1775 (N(CO)₂Ar); 1716.7 (COOH); 1612.9, 1467.7 (Ar); 1430 (C-N-C); 1384 (C-N-C).

2.1.5 2-(1,3-dioxoisindolin-2-yl)-3-methylpentanoic acid (3e): White powder (ethanol / water), yield = 85%, - Mp: 123-125°C, Rf:0.40 (system 1); FT-IR (KBr) / cm-1: 3417.6 (OH); 1773 (N(CO)₂Ar); 1717 (COOH); 1611, 1470 (Ar); 1438 (C-N-C); 1386 (C-N-C).

2.1.6 2-(1,3-dioxoisindolin-2-yl)-3-methylbutanoic acid (3f): White powder (ethanol / water), yield = 82%, - Mp: 138-141°C, Rf:0.55 (system 1); FT-IR (KBr) / cm-1: 3479.7 (OH);
1779 (N(CO₂)₂Ar); 1732 (COOH); 1614, 1466.9 (Ar); 1445.8 (C=N-C); 1380 (C=N-C).

### 2.2 Preparation of 2-(3,4-dimethoxyphenethyl) isoidoline -1,3-dione (5) (Scheme 2)

To a solution of homoveratrylamine (0.05 mol) in methanol (4 ml) was added N-phthaloyl-L-alanine (3b) (0.05 mol) and heated in a glycerin bath at 140°-145°C for 40 minutes. The pale yellow solid mass was dissolved in petroleum ether (40 ml) by oxidative heating. The insoluble portion was filtered, the organic layer was washed in HCl solution (3%) and brought to a neutral medium with distilled water. The ether was distilled and the residue was crystallized in Me₂CO. Yield 78% (1.22 g), Rf/0.8 system: CH₃OH / C₆H₆ (1:12). White crystal, mp: 173-175°C; FT-IR (KBr) / cm⁻¹: 3456 (N-phthalimid); 2941 (C-H); 1765, 1711 (C = O); 1594, 1594, 1518 (Ar); 1396, 1333 (N-C). ¹H NMR (400 MHz, CDCl₃, δ, ppm, J / Hz): 2.88 (2H, t, J = 7.7, CH₂-O, 3.75 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 3.84 (2H, t, J = 7.7, CH₂-β), 6.68 (1H, d, J = 1.5, Ar-H₂), 6.7-6.75 (2H, m, Ar-H, 6), 7.63-7.66 (2H, m, H-phthalimid), 7.74-7.77 (2H, m, H-phthalimid).

### 2.2.1 General procedure for the preparation of 6a-g (Scheme 3)

#### Metod-A
5.5 mmol of chloroanhydride of N-phthaloyl acids was dissolved in 15 ml of dichloromethane (DCM) and (1.0 mL, 5.5 mmol) and homoveratraline along with triethylamine (TEA) (1.4 mL, 11 mmol) solution in 15 ml DCM was added dropwise at 0°C. The mixture was stirred at temperatures from 0°C to the room temperature for 0.5-2 hrs. The reaction mixture was washed in HCl (1 M) solution, and extracted with DCM. The organic phases were brought to a neutral medium with distilled water, and was dried using anhydrous Na₂SO₄. Na₂SO₄ was filtered and DCM drove. The residue was filtered and recrystallized in ethanol.

#### Metod-B
5.5 mmol of chloroanhydride of N-phthaloyl amino acids suspension in 20 ml of benzene were taken and (1.0 mL, 5.5 mmol) homoveratraline along TEA (1.4 mL, 11 mmol) solution in 15 ml DCM was added dropwise at 0°C. The mixture was stirred at temperatures from 0°C to the room temperature for 1-3 hrs. The course of the reaction was controlled using TLC. The resulting thick mass was filtered and recrystallized in ethanol.

2.2.2.1 N-(3,4-Dimethoxyphenethyl)-2-(1,3-dioxoisindolin-2-yl)acetamide (6a)
White powder, yield = 90% (Method B-84%), Mp: 193-196°C (ethanol), Rf/0.77 (system 2); FT-IR (KBr) / cm⁻¹: 3323 (N-H); 2391 (C-H); 1773, 1660 (N=C=O); 1595, 1417 (Ar); 1393, 1317 1270, 1235 (C-N). ¹H NMR (400 MHz, TFA + CD₃COOD, δ, ppm, J/Hz): 2.43 (2H t, J = 6.9, CH₂-α), 3.23 (2H, q, J = 6.5, CH₂-β), 3.45 (3H, s, OCH₃), 3.48 (3H, s, OCH₃), 4.15 (2H, s, CH₂-2a), 6.40 (1H, dd, J = 8.2, 1.9, Ar-H-6), 6.43 (1H, d, J = 1.9, Ar-H-2), 6.46 (1H, d, J = 8.2, Ar-H-5), 6.90 (1H, br.t, J = 5.9, NH), 7.42-7.45 (2H, m, H-phthalimid), 7.50-7.53 (2H, m, H-phthalimid).

### 2.2.2 N-(3,4-Dimethoxyphenethyl)-2-(1,3-dioxoisindolin-2-yl)propanamide (6b)
White powder, yield = 87% (Method B-78%), Mp: 118-121°C (ethanol), Rf/0.72 (system 2); FT-IR (KBr) / cm⁻¹: 3323 (N-H); 2939, 2836 (C-H); 1778, 1646 (C=O); 1590, 1419 (Ar); 1384, 1295, 1235 (C-N). ¹H NMR (400 MHz, CDCl₃, δ, ppm, J/Hz): 1.58 (3H, d, J = 7.3, CH₃-3a), 2.67 (2H, dt, J = 1.5, 7.1, CH₂-α), 3.38 (2H, m, CH₂-β), 3.69 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 4.78 (1H q, J = 7.3, CH₂-β), 6.52 (1H, t, J = 5.6, NH), 5.68-6.62 (3H, m, Ar-H=2, 5, 6), 7.62-7.65 (2H, m, H-phthalimid), 7.69-7.72 (2H, m, H-phthalimid).

### 2.2.3 N-(3,4-Dimethoxyphenethyl)-2-(1,3-dioxoisindolin-2-yl)butanamide (6c)
White powder, yield = 75% (Method B-69%), Mp: 173-176°C (ethanol), Rf/0.75 (system 2); ¹H NMR (400 MHz, CD₃OD-CDCl₃ (1:1), δ, ppm, J/Hz): 0.89 (3H, t, J = 7.4, CH₃-4a), 2.14-2.30 (2H, m, CH₂-3a), 2.74 (2H, td, J = 7.2, 3.39, CH₂-α), 3.42 (2H, q, J = 6.4, CH₂-β) 3.79 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 4.66 (1H, dd, J = 5.4, 9.9, CH₂-2a), 6.71 (1H, dd, J = 8.1, 1.9, Ar-H-6), 6.76 (1H, d, J = 8.2, Ar-H-5), 6.78 (1H, d, J = 2, Ar-H-2), 7.79-7.82 (2H, m, H-phthalimid), 7.84-7.87 (2H, m, H-phthalimid).

### 2.2.4 N-(3,4-Dimethoxyphenethyl)-2-(1,3-dioxoisindolin-2-yl)pentanamide (6d)
White powder, yield = 78% (Method B-78%), Mp: 167-170°C (ethanol), Rf/0.75 (system 2); ¹H NMR (400 MHz, CD₃OD-CDCl₃ (1:1), δ, ppm, J/Hz): 0.77 (system 2); 1.39 (21), 85 (100). Calc. for C₂₀H₂₀N₂O₈: 368.38
2.2.4. N-(3,4-Dimethoxyphenethyl)-2-(1,3-dioxygenoindolin-2-yl)-3-methylbutanamide (6d)

White powder, yield = 72% (Method B-60%), Mp: 181-184°C (ethanol), Rf/0.68 (system 2); FT-IR (KBr) / cm−1: 3335 (N-H); 2963, 1862 (C=O); 1772, 1714, 1643 (C=O); 1540, 1464, 1417 (Ar); 1335, 1257, 1236 (C=N). 1H NMR (400 MHz, CDCl3, δ, ppm, J/Hz): 0.84 (3H, t, J = 7.3, CH3-5a), 1.2 (2H, m, CH2-4a), 1.96 (1H, m, CH2-3a), 2.18 (1H, m, CH2-3a), 2.69 (2H, t, J = 6.9, CH2-α), 3.44 (2H, q, J = 6.8, CH2-β), 3.71 (3H, s, OCH3), 3.77 (3H, s, OCH3), 4.71 (1H, dd, J = 10.7, 5.4, CH2-6a), 2.62 (1H, t, J = 5.8, NH), 6.58 (2H, overlap, ArH-2, 6), 6.62 (1H, overlap, ArH-5), 7.67-7.70 (2H, m, H-phthalimido), 7.75-7.78 (2H, m, H-phthalimido). 13C NMR (100 MHz, CDCl3, δ, ppm): 13.5 (C-5a), 19.73 (C-4a), 30.78 (C-3a), 35.05 (C-α), 41.01 (C-β), 54.79 (C-2), 55.84 (OCH3), 55.87 (OCH3), 111.18 (C-2), 111.93 (C-5), 120.67 (C-6), 123.51 (C-2), 123.62 (C-5’), 131.23 (C-1’), 131.61 (C-6’), 134.39 (C-1), 147.6 (C-OR), 148.99 (C-OR), 168.21 (2CO-NPh), 169.18 (CO-NH). ESI-MS (+ESI TIC Scan Frag=125.0 V) m/z = 433.30 [M+N+Na]+ (9), 410.60 [M+H]+ (33), 88 (100). Calc. for C24H23N2O3: 410.18.

2.2.5. N-(3,4-Dimethoxyphenethyl)-2-(1,3-dioxygenoindolin-2-yl)-1-methylpentanamide (6e)

White powder, yield = 81% (Method B-74%), Mp: 133-136°C (ethanol), Rf/0.70 (system 2); FT-IR (KBr) / cm−1: 3335 (N-H); 2963, 1862 (C=O); 1772, 1714, 1643 (C=O); 1540, 1464, 1417 (Ar); 1335, 1257, 1236 (C=N). 1H NMR (400 MHz, CDCl3, δ, ppm, J/Hz): 0.84 (3H, t, J = 7.3, CH3-5a), 1.2 (2H, m, CH2-4a), 1.96 (1H, m, CH2-3a), 2.18 (1H, m, CH2-3a), 2.69 (2H, t, J = 6.9, CH2-α), 3.44 (2H, q, J = 6.8, CH2-β), 3.71 (3H, s, OCH3), 3.77 (3H, s, OCH3), 4.71 (1H, dd, J = 10.7, 5.4, CH2-6a), 2.62 (1H, t, J = 5.8, NH), 6.58 (2H, overlap, ArH-2, 6), 6.62 (1H, overlap, ArH-5), 7.67-7.70 (2H, m, H-phthalimido), 7.75-7.78 (2H, m, H-phthalimido). 13C NMR (100 MHz, CDCl3, δ, ppm): 13.5 (C-5a), 19.73 (C-4a), 30.78 (C-3a), 35.05 (C-α), 41.01 (C-β), 54.79 (C-2), 55.84 (OCH3), 55.87 (OCH3), 111.18 (C-2), 111.93 (C-5), 120.67 (C-6), 123.51 (C-2), 123.62 (C-5’), 131.23 (C-1’), 131.61 (C-6’), 134.39 (C-1), 147.6 (C-OR), 148.99 (C-OR), 168.21 (2CO-NPh), 169.18 (CO-NH). ESI-MS (+ESI TIC Scan Frag=125.0 V) m/z = 433.30 [M+N+Na]+ (9), 410.60 [M+H]+ (33), 88 (100). Calc. for C24H23N2O3: 410.18.

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SYNTHESIS OF NEW AMIDES BASED ON N-PHTHALOYL-A-AMINO ACIDS

2.3.1. N\textsuperscript{α}-(3,4-Dimethoxyphenethyl)-N\textsuperscript{α}-(1-(3,4-dimethoxy-phenethylamino)-1-oxopropan-2-yl)phthalalamide (7b)

White powder, yield = 58%. Mp: 169-171°C (ethanol), Rf/0.43 (system 2); FT-IR (KBr) / cm\textsuperscript{-1}: 3296 (N-H); 2962 (C-H); 1717, 1642 (C=O); 1544, 1467, 1419 (Ar); 1318, 1283, 1234 (C-N).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, δ, ppm, J/Hz): 1.36 (3H, d, J = 7.1, CH\textsubscript{3}-3a), 2.77 (4H, dt, J = 7.1, 7.1, 2CH\textsubscript{2}-α, α'), 3.43 (2H, q, J = 7.8, CH\textsubscript{2}-β), 3.53 (2H, m, CH\textsubscript{2}-β'), 3.72 (6H, s, 2OCH\textsubscript{3}), 3.74 (3H, s, OCH\textsubscript{3}), 3.76 (3H, s, OCH\textsubscript{3}), 4.45 (1H, m, CH-2a), 6.61-6.63 (7H, m, NH-β, ArH-2', 2'; ArH-5', 5', ArH-6, 6'), 6.85 (1H, br.s, NH-C-2a), 7.29 and 7.34 (each 2H, m, ArH-2', 3',4', 5'), 7.43 (1H, br. t, NH-C-β'). 13C NMR (100 MHz, CDCl\textsubscript{3}, δ, ppm). 17.68 (3Aa, 34.89 (Cα-a'), α), 41.15 (C-β), 41.47 (C-β'), 49.59 (C-2a), 55.65, 55.68, 55.72, 55.75 (4OCH\textsubscript{3}), 111.17 (C-1', 2', 2'), 111.88 (C-5', 5'), 120.50, 120.53 (C-6, 6'), 127.22 (C-5'), 127.71 (C-2'), 129.91 (C-6'), 130.40 (C-1''), 131.00 (C-3'), 131.61 (C-4'), 134.30, 135.56 (C-1', 1'), 147.44 (C-OR), 148.77 (C-OR), 168.55 (CO-1c), 169.08 (CO-1a), 171.61 (CO-1b). ESI-MS (+ESI TIC Scan Frag=125.0 V) m/z = 564.50 [M+H]+. Calc. for C\textsubscript{32}H\textsubscript{31}N\textsubscript{3}O\textsubscript{8}: 563.64

2.3.2. N\textsuperscript{α}-(3,4-Dimethoxyphenethyl)-N\textsuperscript{α}-(1-(3,4-dimethoxy-phenethylamino)-1-oxobutan-2-yl)phthalalamide (7c)

White powder, yield = 70%. Mp: 158-160°C (ethanol), Rf/0.44 (system 2); FT-IR (KBr) / cm\textsuperscript{-1}: 3423, 3277 (N-H); 2932 (C-H); 1695, 1644 (C=O); 1624, 1590, 1418 (Ar); 1321, 1261, 1238 (C-N).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, δ, ppm, J/Hz): 1.04 (3H, t, J = 2.8, 7.3, 3H, CH\textsubscript{3}-2a), 2.35 (1H, dq, J = 2.8, 7.3, CH\textsubscript{3}-3a), 2.96 (2H, m, CH\textsubscript{2}-α, α'), 3.06 (2H, m, CH\textsubscript{2}-β, β'), 3.56 (9H, s, 3OCH\textsubscript{3}), 3.58 (3H, s, OCH\textsubscript{3}), 3.74 (2H, m, CH\textsubscript{2}-β, β'), 3.81 (2H, dd, J = 9.6, 4.2, CH\textsubscript{2}-β', β'), 4.96 (1H, dd, J = 9.3, 8.0, 4.5, CH-2a), 6.70 (2H, dd, J = 8.1, 3.8, ArH-5, 5'), 6.81 (2H, dd, J = 8.2, 3.4, 1.9, ArH-6, 6'), 6.89 (2H, dd, J = 4.6, 1.9, ArH-2', 2'), 7.18 (1H, td, J = 7.5, 1.4, ArH-3'), 7.24 (1H, td, J = 7.5, 1.4, ArH-4'), 7.61 (1H, dd, J = 7.6, 1.4, ArH-2'), 7.68 (1H, dd, J = 7.6, 1.4, ArH-5'), 9.02 (1H, t, J = 5.6, NH-C-β'), 9.45 (1H, t, J = 5.7, NH-C-β'), 9.68 (1H, d, J = 8.0, NH-C-2a), 127.94 (C-1, 2, 2'), 129.68 (C-3', 4'), 130.56 (C-1', 2'), 139.74 (C-6), 139.67 (C-6'), 140.31 (C-2'), 147.34, 147.58 (C-OR), 148.74, 148.87 (C-OR), 168.54 (CO-1c), 169.49 (CO-1b), 170.43 (CO-1a). ESI-MS (+ESI TIC Scan Frag=125.0 V) m/z = 1185.5 [2M+H]+ (7c), 592.40 [M+H]+ (55), 63.8 (100). Calc. for C\textsubscript{34}H\textsubscript{33}N\textsubscript{3}O\textsubscript{8}: 591.69

Results and discussion

The process of synthesis of N-phthaloyl amino acids on the basis of N-carboxyphthalimide at room temperature and in aqueous solution is ecologically important [20, 25]. However, in most cases the synthesis of N-phthaloyl amino acids is carried out on the basis of phthalanhydride, which is relatively available and inexpensive.

A more effective method is to dilute phthalanhydride in a closed container and add the appropriate amino acid to it and obtain N-phthaloyl amino acid in a short time with good yield [26]. However, even if less time is spent in this method, a temperature above 140°C can lead to racemization [27].

Synthesis of N-phthaloyl amino acids was also performed by heating a reaction mixture consisting of phthalanhydride and the corresponding amino acid at low pressure (40 mmHg) without solvent [28]. Carrying out the synthesis of N-phthaloyl amino acid in toluene solvent allows the reaction to take place at normal pressure and at a relatively low temperature. However, this requires the addition of a proton acceptor (TEA) and a relative
increase in reaction time [12, 15, 17, 29]. Conducting the practice in an acetic acid environment makes the method relatively efficient and economical [30, 31]. In a toluene and acetic acid environment, the synthesis of N-phthaloyl amino acids can be avoided, although it takes some time to synthesize.

Reactions of phthalanhydride and amino acids in TEA or 4-DMAP [10] and acetic acid [32] were carried out by microwave method in the production of N-phthaloyl amino acids. This method can overcome the shortcomings of other methods with the short time spent on the reaction, high yield and, most importantly, does not lead to racemization.

In order to compare the methods in practice and apply them for the next step, we carried out the synthesis of N-phthaloyl amino acids (3a-b) thermally in an acetic acid medium (scheme 1). The results obtained for the synthesis of N-phthaloyl amino acids (3a-b) are given in Table 1.

![Scheme 1. Synthesis of N-phthaloyl amino acids (3a-g).](image)

Table 1. The results obtained for the synthesis of N-phthaloyl amino acids (3a-g)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino acids</th>
<th>Product</th>
<th>M.p./°C found/reported</th>
<th>Rf (sysa)</th>
<th>Time (hr.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Gly</td>
<td>3a</td>
<td>199-202/196-198 [28]</td>
<td>0.5</td>
<td>5.5</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Ala</td>
<td>3b</td>
<td>147-150/149-151 [28]</td>
<td>0.45</td>
<td>6.5</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>Abu</td>
<td>3c</td>
<td>78-80</td>
<td>0.47</td>
<td>6</td>
<td>90.5</td>
</tr>
<tr>
<td>4</td>
<td>Val</td>
<td>3d</td>
<td>106-108/110 [29]</td>
<td>0.53</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Nva</td>
<td>3e</td>
<td>88-91</td>
<td>0.6</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>Ile</td>
<td>3f</td>
<td>123-125/123-125 [28]</td>
<td>0.4</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>Leu</td>
<td>3g</td>
<td>138-141/143 [29]</td>
<td>0.55</td>
<td>6</td>
<td>82</td>
</tr>
</tbody>
</table>

As in our previously published study [33], the reaction of N-phthaloyl-L-alanine with homoveratrylamine was performed. We observed the formation of a suspension (even when heated) when dissolved in petroleum ether (40-60°C) for the purpose of processing the reaction mixture. The solid mass obtained by filtration of the suspension was purified by recrystallization in water. From the clear filtrate, we separated the second product by performing processing in a solution of hydrochloric acid and other purification operations. The melting points of the obtained compounds and the conducted polarimetric, IR and 1H NMR analyzes showed that they were DL-alanine and the amine phthalimide 5 [34]. Then the reaction of these substrates was carried out in m-xylene under reflux at the boiling point. But dehydrative amidation reaction did not occur, however, a transmitted reaction was observed. To bypass this barrier in the synthesis of N-phthaloyl amino acid amides, the carboxyl group had to be activated in an alternative way. In this case, acyl chloride of N-phthaloyl amino acids 3a-g were obtained using known methods [16, 35] and were used for 6a-g synthesis of targeted amides without excessive

![Scheme 2. Thermal condensation of N-phthaloyl amino acids with homoveratrylamine.](image)

(i) 1: Homoveratrylamine in CH3OH, 2: ϑ° 140-145°C; (ii) Homoveratrylamine in m-xylene, reflux

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purification. In this process, unrefined acyl chloride was added dropwise to the DCM solution, homoantranilic amine in an equimolar ratio, and TEA to the dissolved DCM solution. The reaction was carried out by stirring from 0°C to room temperature, and by processing the corresponding amides were isolated in pure form at 6a-g (Scheme 3). We also repeated the acylation process for all compounds by converting the solvent to non-polar benzene, the proton acceptor to pyridine. Modification of the method resulted in the accumulation of the product mixture, and to obtain purification. We carried out the reaction system. This observation of our team led to the conclusion that the chlorohydride production stage was less productive and the amino equimolar amount used in the acylation process was excessively high, leading to the formation of a second product.

Scheme 3. Synthesis amides of N-phthaloyl amino acids (6a-g) and unsymmetric diamides of phthalic acid (7b-d).

(iii) 1: SOCl₂, reflux, 1.5 h to 2 h, or PCl₅, DCM, mixing, 1.5 h, 2: a) homoantranilic amine, TEA, DCM, 0°C to rt, 30 min to 2 h, or b) homoantranilic amine, Py, C₆H₆, 0°C to rt, 1 h to 3 h; (iv) 1: SOCl₂, reflux, 1.5 h to 2 h, 2: homoantranilic amine (4 equiv.), DCM, 0°C to rt, 11-12 h;

Table 2. Physicochemical Characteristics of the Synthesized Compounds (10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Solvent (method A or B)</th>
<th>Time (h) (method A or B)</th>
<th>Yield % (method A or B)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>6a</td>
<td>DCM or Benzene</td>
<td>0.5 or 1</td>
<td>90 or 84</td>
<td>193-196</td>
</tr>
<tr>
<td>3b</td>
<td>CH₃</td>
<td>6b</td>
<td>DCM or Benzene</td>
<td>2 or 3</td>
<td>87 or 78</td>
<td>118-121</td>
</tr>
<tr>
<td>3c</td>
<td>CH₂CH₂</td>
<td>6c</td>
<td>DCM or Benzene</td>
<td>2 or 2</td>
<td>75 or 69</td>
<td>173-176</td>
</tr>
<tr>
<td>3d</td>
<td>(CH₃)₂CH</td>
<td>6d</td>
<td>DCM or Benzene</td>
<td>3 or 3</td>
<td>72 or 60</td>
<td>181-184</td>
</tr>
<tr>
<td>3e</td>
<td>CH₂CH₂CH₂</td>
<td>6e</td>
<td>DCM or Benzene</td>
<td>2.5 or 3</td>
<td>81 or 74</td>
<td>133-136</td>
</tr>
<tr>
<td>3f</td>
<td>CH₂CH₂(CH₃)CH</td>
<td>6f</td>
<td>DCM or Benzene</td>
<td>3 or 3</td>
<td>80 or 59</td>
<td>154-157</td>
</tr>
<tr>
<td>3g</td>
<td>CH(CH₃)₂CH₂</td>
<td>6g</td>
<td>DCM or Benzene</td>
<td>2.5 or 3</td>
<td>79 or 72</td>
<td>140-143</td>
</tr>
<tr>
<td>3h</td>
<td>CH₃</td>
<td>7b</td>
<td>DCM</td>
<td>11</td>
<td>63</td>
<td>135-137</td>
</tr>
<tr>
<td>3c</td>
<td>CH₂CH₂</td>
<td>7c</td>
<td>DCM</td>
<td>12</td>
<td>59</td>
<td>158-160</td>
</tr>
<tr>
<td>3d</td>
<td>(CH₃)₂CH</td>
<td>7d</td>
<td>DCM</td>
<td>12</td>
<td>74</td>
<td>169-171</td>
</tr>
</tbody>
</table>

After that, we continued the reactions in excess equimolar amounts of the amine in order to avoid the method of column chromatography, which is tedious in the separation of the product mixture, and to obtain compounds with a small Rₚ-value. We carried out the reactions from 0°C to room temperature for 3–12 h, in benzene and DCM solvents, with a proton acceptor and without a proton acceptor. Our studies showed that diamides are optimally effective in 7b-d DCM solvents, absence of additional proton acceptors, when using 4 equivalents of amine, and ending in 10-12 hours. We also observed that in this selected method, N-phthaloylglycine 3a does not form diamide, but produces amide 6a. The results obtained for the synthesis of amides (6a-g) and diamides (7b-d) given in Table 2.
The structure of all synthesized amides and diamides was confirmed by spectrophotometric methods (IR, \textsuperscript{1}H NMR, and \textsuperscript{13}C NMR), mass spectrometry, and determination of melting points. In the IR spectra, characteristic absorption bands in the strong range belonging to the N-H bonds of amides and diamides were observed in the ranges 3373–3323 cm\(^{-1}\) and 3423–3277 cm\(^{-1}\). Intensive absorption bands belonging to carboxyl groups occur in the range 1778–1643 cm\(^{-1}\) and 1721–1640 cm\(^{-1}\), as well as in amide and diamides, respectively, stretching vibrations for the C-N bond in the absorption poles 1393-1214 cm\(^{-1}\) and 1326-1234 cm\(^{-1}\). Absorption bands belonging to aliphatic C-H bonds were recorded in the range of 2993–2931 cm\(^{-1}\) and 2962–2837 cm\(^{-1}\), and relatively intense absorption bands of the aromatic ring were recorded in the range of 1595–1417 cm\(^{-1}\) and 1624–1418 cm\(^{-1}\).

NMR spectra of amide and phthalic acid diamides were recorded in CDCl\(_3\), TFA + CD\(_3\)COOD, CD\(_3\)OD, and Pyridine-d\(_5\). Aliphatic, aromatic and -NH proton signals according to \textsuperscript{1}H NMR spectra were observed with integration and broadening in the expected domains. Separate resonance of proton pairs in the 2\(''\), 5\(''\) and 3\(''\), 4\(''\) positions of the aromatic ring of the phthaloyl fragment in amides was recorded in the form of a multiplet signal in the ranges \(\delta \ 7.42–7.82\) ppm and \(\delta \ 7.50–7.84\) ppm. The 2, 5, 6 proton signals in the second aromatic ring were observed separately and in the added field in a relatively lower field due to the electron donor effect. In particular, the proton in position 6 was recorded in the form of a doublet-doublet signal in the range \(\delta \ 6.40-6.71\) ppm in compounds 6a, 6c, 6g, and in the form of a doublet signal in the range \(\delta \ 6.40\) ppm in compounds 6d, 6f. In the 5th position, the proton signal resonated in the form of a doublet in the 6a, 6g compounds in the \(\delta \ 6.46-6.73\) ppm range, in the 6d, 6f compounds in the singlet form in the \(\delta \ 6.68\) ppm area, and in the 6c compound in the \(\delta \ 6.78\) ppm area in the triplet form. Resonance of proton signals in three position in compounds 6b and 6e was recorded in multiplet form in the range \(\delta \ 6.62–6.58\) ppm. Proton signals belonging to the NH group were observed to resonate in the triplet form in the range \(\delta \ 6.22–6.94\) ppm field in compounds 6a, 6b, 6d, and 6e. In the 6f compound, the signal characterizing the NH group proton was observed as a multiplet in the range \(\delta \ 6.92–6.99\) ppm. Protons in the 2a-positions were observed in the form of singlet (6a), doublet (6a, 6f), doublet-doublet (6e, 6g) and quartet (6b, 6c) in the range \(\delta \ 4.78–4.15\) ppm. It was observed that the proton triads in the methoxy groups observe as separate singletons in the field range \(\delta \ 3.45–3.84\) ppm. It was noted that the two protons in the \(\beta\)-state bound to the nitrogen atom resonate in the form of quartets (6a, 6c, 6d and 6f), triplet-doublet (6g) and multiplet (6b, 6e) in the range \(\delta \ 3.52-3.23\) ppm, which is stronger than alkyl protons. The two protons in the \(\alpha\)-state observed in the \(\delta \ 2.43–2.83\) ppm field as triplets (6a, 6b, 6e), triplet-doublets (5c), and multiplets (6d, 6f, 6g). The signals of aliphatic protons appeared in the expected weak domain ranges. The NMR spectrum of the 6s compound was recorded in Pyridine-d\(_5\), where, unlike other diamides, the signals pertaining to the NH-\(\beta\), NH-\(\beta'\), and NH-protons resonated in the triplet and doublet range in the strong range \(\delta \ 9.02-9.68\) ppm, respectively. It was noted that the protons bound to nitrogen in compound 6d resonated as triplets and duplicates in the range \(\delta \ 6.67-7.28\) ppm in separate fields in the order given. In compound 7b, NH-\(\beta\) protons appeared with phenethyl aromatic ring protons in the \(\delta \ 6.61–6.63\) ppm region as a multiplet of the integration of seven protons, while NH-2a and NH-\(\beta'\) protons in the \(\delta \ 6.85\) ppm and \(\delta \ 7.43\) ppm regions were singlet, and triplet-shaped resonance was observed. In compounds 7b and 7d, the proton pairs of the aromatic nucleus of phthalic acid 2\(''\), 5\(''\) and 3\(''\), 4\(''\) appeared in the form of multiplets in the range \(\delta \ 7.29-7.34\) ppm and \(\delta \ 7.31-7.37\) ppm, as in amides. It was noted that 3\(''\), 4\(''\) and 2\(''\), 5\(''\) protons in the 6s compound appeared as triplet-doublet and doublet-doublet, respectively, in the field ranges \(\delta \ 7.18–7.68\) ppm. In 7b–d compounds, twelve protons of four methoxy groups resonated in singlet form by integrating 9H and 3H and 6H and 6H in the \(\delta \ 3.56-3.78\) ppm or \(\delta \ 3.72-3.76\) ppm regions. Two protons in the b- and g-positions were observed to appear in the quartet and multiplet (7b), multiple and doublet-doublet (7s) and multiplet (7d) in the \(\delta \ 3.43-3.81\) ppm field. The integration of the four protons in the \(\alpha\) and \(\alpha'\) positions in the \(\delta \ 2.77\) ppm and \(\delta \ 2.78\) ppm fields in the form of a doublet triplet (7b) and a quartet (7d), and the integration of two separate protons in the \(\delta \ 2.96–3.06\) ppm multiplet (7c) resonance was observed. It was noted that signals related to aliphatic protons resonate in the expected weak \(\delta \ 0.80–2.42\) ppm range.

**Conclusion**

In conclusion, we note that it is not possible to synthesize amides of N-phthaloyl-\(\alpha\)-amino acids thermally (to > 140°C). Based on the activation of the carboxyl group of N-phthaloyl-\(\alpha\)-amino acids, it is possible to carry out the synthesis of their amides (6a-g). However, diamides (7b-g) are also formed according to the basic power of the amine, the presence of the proton acceptor in the reaction system, the duration of the reaction, and the nature of the acid-holding \(R\).
SYNTHESIS OF NEW AMIDES BASED ON N-PHTHALOYL-A-AMINO ACIDS

We are currently conducting pharmacological investigations of the obtained amide and symmetric phthalic acid diamides, as well as intramolecular cyclization reactions of amides.

Acknowledgment The corresponding author is sincerely grateful to his supervisor prof. Valentina Ivanovna Vinogradova.

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