[Contribution from the Chemical Institute, Faculty of Science, University of Zagreb]

A SYNTHESIS OF N^{ω}-PHTHALOYL DERIVATIVES OF BASIC AMINO ACIDS. AMINO ACIDS. VII[1]

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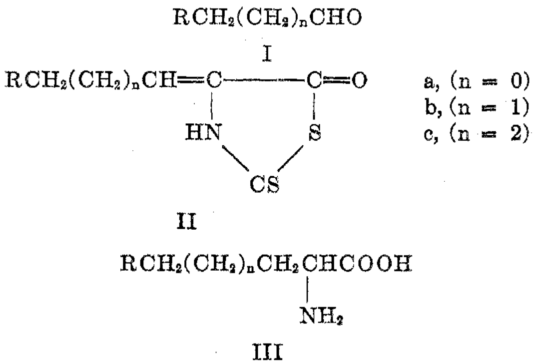
Many synthetic methods for the preparation of basic amino acids have been hitherto described (1). In this paper a general method is given for the preparation of basic amino acids from monoamino acids. The starting materials for these syntheses were the N-phthaloyl derivatives of aminoaldehydes obtained from glycine, β-alanine, and γ-aminobutyric acid.

Radde (2) first prepared phthalimidoacetaldehyde (Ia) from glycine by the Rosemund-Zetzsche reduction of N-phthaloylglycyl chloride. Following the same procedure we obtained in good yields β-phthalimidopropionaldehyde (Ib) from β-alanine, and γ-phthalimidobutyraldehyde (Ic) from γ-aminobutyric acid.

Applying the condensation of aldehydes with 2-mercaptothiazol-5-one as described by Billimoria and Cook (3), the condensation products (IIa–c) were obtained.

The compounds (IIa–c) were hydrolyzed and reduced with a mixture of 40% hydriodic acid and glacial acetic acid (1:6), and the following amino acids were obtained: α-amino-γ-phthalimidobutyric acid (IIIa), N^{δ}-phthaloyl-*d*,*l*-ornithine (IIIb), and N^{ϵ}-phthaloyl-*d*,*l*-lysine (IIIc).



$R = C_6H_4(CO)_2N$— in all cases

By further hydrolysis with concentrated hydrochloric acid, the corresponding diamino acids were obtained.

The N^{ω}-phthaloyl derivatives of these diamino acids (IIIb–c) are new compounds; they may prove to be useful for syntheses of peptides containing basic amino acids.

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[1] Paper VI, Balenović and Fleš, *J. Org. Chem.*, **17**, 347 (1952).

EXPERIMENTAL

All melting points are uncorrected.

Microanalyses were carried out by Dr. L. Filipović in our laboratory.

γ-Phthalimidobutyraldehyde (Ic). γ-Phthalimidobutyryl chloride was prepared by heating a mixture of γ-phthalimidobutyric acid (6.3 g.) (4) and thionyl chloride (11 ml.) at 70° during 1 hour. The excess thionyl chloride was removed under reduced pressure and the residue was dissolved in xylene and precipitated with petroleum ether (1:1). γ-Phthalimidobutyryl chloride was obtained (5.9 g., 87%) with m.p. 67°. Gabriel and Colman (4) gave m.p. 67–69°.

γ-Phthalimidobutyryl chloride (3.3 g.) was dissolved in 20 ml. of xylene and reduced following the Rosemund-Zetzsche method (5) with 0.8 g. of palladium on barium sulfate (palladium content 5%) at 135–140°; (the hydrogen was introduced through the sintered glass bottom of the reaction flask). During three hours, 85% of the theoretical amount of hydrogen chloride was evolved. After filtering, half of the volume of xylene was evaporated *in vacuo*, and the crude oily aldehyde (2.65 g., 91%) was obtained by precipitation with petroleum ether (1:2). It was distilled at 90–95°/0.02 mm., and had m.p. 72–73°. King, L'Ecuyer, and Openshaw (6) prepared γ-phthalimidobutyraldehyde from γ-phthalimidobutyronitrile by Stephen's method and described it as a colorless oil.

Anal. Calc'd for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10.

Found: C, 66.68; H, 5.01.

The *dinitrophenylhydrazone* had m.p. 183.5–184°; [Lit. (6) m.p. 184°].

In the same manner we prepared phthalimidoacetaldehyde (Ia) (2) and β-phthalimidopropionaldehyde (Ib) (7) in 75% and 90% yields respectively.

2-Thio-4-(phthalimidoethylidene)thiazolid-5-one (IIa). To a solution of 2-mercaptothiazol-5-one (8) (0.5 g., 0.0037 mole) in hot acetic acid (5 ml.) were added phthalimidoacetaldehyde (Ia, 0.95 g., 0.005 mole) and piperidine (2 drops). This procedure was carried out without heating. After standing for a short time, separation of yellow crystals occurred. The reaction mixture was left at room temperature for 24 hours, and the crystals were collected. Yield 1.05 g. (92%), m.p. 195°. After two recrystallizations from glacial acetic acid, the compound had m.p. 213° (decomp.).

Anal. Calc'd for $C_{13}H_8N_2O_3S_2$ (304.33): C, 51.30; H, 2.65.

Found: C, 51.13; H, 2.48.

2-Thio-4-(2'-phthalimidopropylidene)thiazolid-5-one (IIb). To a solution of 2-mercaptothiazol-5-one (1.0 g., 0.007 mole) in boiling acetic acid (10 ml.) β-phthalimidopropionaldehyde (Ib, 1.6 g., 0.008 mole) and piperidine (2 drops) were added. After proceeding in the same manner as with IIa, 2.1 g., (89%) of yellow crystals, m.p. 197° (decomp.) remained. After two recrystallizations from acetic acid, the compound had m.p. 202–203° (decomp.).

Anal. Calc'd for $C_{14}H_{10}N_2O_3S_2$ (318.36): C, 52.82; H, 3.17.

Found: C, 52.72; H, 3.36.

2-Thio-4-(3'-phthalimidobutylidene)thiazolid-5-one (IIc). To a solution of 2-mercaptothiazol-5-one (0.3 g., 0.002 mole) in boiling acetic acid (5 ml.) γ-phthalimidobutyraldehyde (Ic, m.p. 72°, 0.3 g., 0.001 mole) and piperidine (2 drops) were added. After proceeding in the same manner as with IIa, crystals of m.p. 175–177° (0.4 g., 87%) were obtained. Recrystallized from glacial acetic acid they showed m.p. 183–185°.

Anal. Calc'd for $C_{15}H_{12}N_2O_3S_2$ (332.38): C, 54.20; H, 3.64.

Found: C, 54.58; H, 3.70.

α-Amino-γ-phthalimidobutyric acid (IIIa). To a solution of the thiazolidone (IIa, 1.2 g., 0.004 mole) in boiling acetic acid (50 ml.), red phosphorus (3 g.) and 40% hydriodic acid (7 ml.) were added. This mixture was refluxed for 4 hours. The phosphorus was filtered off and the reaction mixture evaporated to dryness. The excess hydriodic acid was removed by adding water to the residue, and by evaporating again to dryness. The dry residue was dissolved in water and extracted with ether. By evaporating the water layer a syrup remained which crystallized on standing for a short time. These crystals were collected and

washed with the smallest possible quantity of cold ethanol. Pale yellow prisms of α-amino-γ-phthalimidobutyric acid hydriodide were obtained; yield 1.34 g. (90%), m.p. 175° (decomp.). Recrystallized from absolute ethanol-ether, the m.p. was 183° (decomp.).

Anal. Calc'd for $C_{12}H_{13}IN_2O_4$ (376.16): C, 38.31; H, 3.48.
Found: C, 38.06; H, 3.86.

The hydriodide (0.65 g.) was dissolved in ethanol (4 ml.) and water (8 ml.), cooled to 0°, pyridine (exactly 0.5 ml.) was added, and the mixture left overnight at 0°. The crystals were collected, yield 0.34 g. (80%), m.p. 194–195°. Recrystallized from water, they had m.p. 197° (decomp. at 200°). Fischer (9) reported m.p. 197°.

Anal. Calc'd for $C_{12}H_{12}N_2O_4$ (248.23): C, 58.06; H, 4.87.
Found: C, 57.68; H, 5.09.

N^{δ}-Phthaloyl-d,l-ornithine (IIIb). To a solution of the thiazolidone (IIb, 2 g., 0.006 mole) in boiling acetic acid (60 ml.) red phosphorus (5 g.) and 40% hydriodic acid (11 ml.) were added. This mixture was refluxed for 4 hours. Following the same procedure as with IIIa, 2.23 g. (91%) of pale yellow prisms of N^{δ}-phthaloyl-*d,l*-ornithine hydriodide remained, with m.p. 111°. After recrystallization from absolute ethanol-ether the compound had m.p. 215° (decomp.).

Anal. Calc'd for $C_{13}H_{15}IN_2O_4$ (390.19): C, 40.01; H, 3.88.
Found: C, 39.98; H, 4.37.

A solution of the hydriodide (2.2 g.) in ethanol (25 ml.) was cooled to 0°, pyridine (1 ml.) was added, and the mixture was left overnight at 0°. White crystals of N^{δ}-phthaloyl-*d,l*-ornithine separated, yield 1.5 g. (91%), m.p. 225°. Recrystallized from 25% aqueous ethanol, they had m.p. 233–235° (decomp.).

Anal. Calc'd for $C_{13}H_{14}N_2O_4$ (262.26): C, 59.53; H, 5.38.
Found: C, 58.92, 59.15; H, 5.70, 6.04.[2]

N^{α},N^{δ}-Dibenzoyl-d,l-ornithine. N^{δ}-Phthaloyl-*d,l*-ornithine (IIIb, 0.5 g.) was heated with concentrated hydrochloric acid (4 ml.) in a sealed tube at 100° for 12 hours. After cooling, water (20 ml.) was added to the reaction mixture from which phthalic acid had previously separated, and the crystals were filtered off. The hydrochloric acid was removed from the filtrate by evaporation and the residue was diluted with water (10 ml.) and extracted with ether. The water layer was evaporated to dryness and the crude *d,l*-ornithine dihydrochloride was converted into the dibenzoyl derivative following Fischer's procedure (10). Recrystallized from ethanol, the crystals had m.p. 185°. Fischer (10) reported m.p. 185°.

Anal. Calc'd for $C_{19}H_{20}N_2O_4$ (340.37): C, 67.04; H, 5.92.
Found: C, 67.04; H, 5.98.

N^{ϵ}-Phthaloyl-d,l-lysine (IIIc). The thiazolidone (IIc, 0.8 g.) was dissolved in acetic acid (45 ml.). Red phosphorus (2 g.) and 40% hydriodic acid (8 ml.) were added, and the mixture was refluxed for 4 hours. By the same procedure as given for IIIa, a mixture of crystals and syrupy liquid was obtained, which was dissolved in ethanol (10 ml.). Then pyridine (2 ml.) was added and the mixture was left in an ice-box overnight. Crystals of m.p. 229–232°, yield 0.6 g., (89%) were obtained. Recrystallized from ethanol they had m.p. 248–250° (with darkening at 138°).

Anal. Calc'd for $C_{14}H_{16}N_2O_4$ (276.28): C, 60.86; H, 5.84.
Found: C, 60.85; H, 5.82.

d,l-Lysine dipicrate. N^{ϵ}-Phthaloyl-*d,l*-lysine (IIIc, 0.4 g.) was hydrolyzed in a sealed tube with concentrated hydrochloric acid (6 ml.) at 100° for 12 hours. After proceeding in the same manner as in the preparation of *d,l*-ornithine dihydrochloride, 0.3 g., (94%) of *d,l*-lysine dihydrochloride remained. By Adamson's procedure (11) this hydrochloride (0.22 g.) was converted into *d,l-lysine dipicrate*. Yield, 0.56 g. (92%). Recrystallized from water the compound showed m.p. 188–190°. Adamson also reported (11) m.p. 188–190°.

[2] This compound was dried at 100°/0.05 mm. for 10 hours; Fischer (6) encountered similar difficulties with the elemental analysis of α-amino-γ-phthalimidobutyric acid.

Anal. Calc'd for $C_{18}H_{20}N_8O_{16}$ (604.40): C, 35.77; H, 3.33.
Found: C, 35.54; H, 3.60.

SUMMARY

With α-, β-, and γ-phthalimido acids as starting material we obtained N^{ω}-phthaloyl-diamino acids (IIIa-c) through the reaction stages I–III.

By this procedure glycine, β-alanine, and γ-aminobutyric acid yielded α,γ-diaminobutyric acid, *d,l*-ornithine, and *d,l*-lysine respectively.

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