CCA - 59 547.466.2:547.584

Introduction of the *N*-Phthaloyl Group into Heat-Sensitive Amino Acid Derivatives; *N*-Phthaloyl-L-Aspartic Acid*

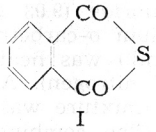
K. Balenović, B. Gašpert and N. Štimac

Chemical Laboratory, Faculty of Science, University of Zagreb, Strossmayerov trg 14 Zagreb, Croatia, Yugoslavia

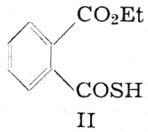
Received May 27, 1957

A method is described by which heat-sensitive amino acid derivatives can be converted to unracemized *N*-phthaloyl amino acids using *o*-carbethoxythiobenzoic acid (II) or its sodium salt. In this manner *N*-phthaloyl-L-aspartic acid was prepared.

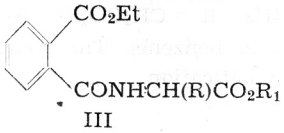
The preparation of *N*-phthaloyl derivatives of optically active amino acids has been accomplished readily, and with no racemization, by fusion.[1] Difficulties arose, however, in the preparation of optically active *N*-phthaloyl derivatives of those amino acids which contained additional functional groups. Whereas in the case of the former amino acids the temperature of fusion can rise to 130—150°, the temperature of fusion should not rise above 110°, during the preparation of *S*-benzyl-*N*-phthaloyl-L-cysteine and even under these optimal conditions yields of the optically pure compound are small (7—10%)[2]. The same is the case with *o*-ethyl-*N*-phthaloyl-L-serine, L-aspartic and L-glutamic acids. In the preparation of the *N*-phthaloyl derivatives of these compounds we used[4] *o*-carbethoxythiobenzoic acid (II) obtained from phthaloyl sulphide (I) according to Reissert and Holle[3].



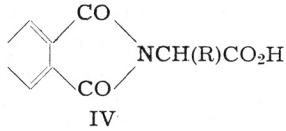
I



II



III



IV

We have now applied this method to the preparation of *N*-phthaloyl-L-aspartic acid, which has been prepared earlier using phthalic anhydride and diethyl L-aspartate[5]. In our procedure sodium *o*-carbethoxythiobenzoate reacted smoothly with diethyl-L-aspartate hydrochloride in *N* : *N*-dimethyl-

* Communication No. 65 from this Laboratory. 42nd Contribution on Amino Acids; 41st: *Croat. Chem. Acta* **29** (1957) 87—92.

formamide, by heating at 80°, affording high yields of optically active *N*-(*o*-carbethoxybenzoyl) diethyl-L-aspartate (III, R = CH_2CO_2Et; R_1 = Et)[4]. Subsequent refluxing of this compound with 4% ethanolic hydrochloric acid gave *N*-phthaloyl diethyl-L-aspartate (yield 91%), and by further heating with a mixture of hydrochloric and glacial acetic acids optically pure *N*-phthaloyl-L-aspartic acid was obtained.

EXPERIMENTAL

All melting points are uncorrected unless otherwise stated.

Sodium o-Carbethoxythiobenzoate

To a cold solution of sodium (2.3 g., 0.1 g. atom) in absolute ethanol (80 ml.) phthaloyl sulphide (17.5 g., 0.105 mole, prepared according to Reissert and Holle[3]) was added gradually during three hours. After standing overnight the reaction mixture was filtered, and the filtrate evaporated to dryness *in vacuo* (below 30°). The crystalline residue was triturated with ether (50 ml.) and filtered. Trituration and filtration was repeated with the same quantity of ether, and the crystals of *sodium o-carbethoxythiobenzoate* collected and dried. Yield 17.5 g. (71%). The analytical sample was recrystallized from absolute ethanol; the compound is very hygroscopic, and showed the m. p. 178—183° (decomp., in vacuum-sealed capillary tube).

Anal. 9.57 mg. subst.: 2.99 mg. Na_2SO_4
$C_{10}H_9O_3SNa$ (232.23) calc'd.: Na 9.91%
found: Na 10.10%

Diethyl-L-aspartate hydrochloride

This compound was prepared according to Fischer and Koenigs[6], only using L-aspartic acid (13.3 g.), and 4% ethanolic hydrochloric acid (200 ml.). After refluxing, the reaction mixture was evaporated to dryness *in vacuo*, completely freed of hydrochloric acid, dissolved in absolute ethanol (60 ml.), and precipitated with ether (200 ml.). The crystalline, hygroscopic *diethyl-L-aspartate hydrochloride* (17.5 g., 78%) thus obtained showed $[\alpha]_D^{16}$ + 14.5° (c, 1.21 in ehanol).

Reaction of Sodium o-Carbethoxythiobenzoate with Diethyl-L-aspartate Hydrochloride.

To a solution of diethyl-L-aspartate hydrochloride (9.03 g., 0.04 mole) in *N* : *N*-dimethylformamide (60 ml.) a solution of sodium *o*-carbethoxy-thiobenzoate (9.3 g., 0.04 mole) in *N* : *N*-dimethylformamide (60 ml.) was heated. The mixture was heated to 80—85° (preferably in a stream of nitrogen). After 4 hours the evolution of hydrogen sulphide ceased. The reaction mixture was poured onto ice (300 g.), and extracted with benzene (3 × 60 ml.). The combined extracts were washed with water and dried (Na_2SO_4). After evaporating the solvent, 12.0 g. (82.3%) of N-(*o-carbethoxybenzoyl*)-*diethyl-L-aspartate* (III, R = CH_2CO_2Et, R_1 = Et) remained as a yellow oil, with $[\alpha]_D^{17}$ — 40.8° (c, 2.5 in benzene). The compound was used for the following reaction without further purification.

N-Phthaloyl Diethyl-L-aspartate

N-(*o*-Carbethoxybenzoyl) diethyl-L-aspartate (12.0 g., 0.03 mole) was heated under reflux for 2 hours with 4% ethanolic hydrochloric acid (130 ml.). The reaction mixture was evaporated to dryness *in vacuo* (below 40°). *N-Phthaloyl diethyl-L-aspartate* remained as a light-brown oil (91%) which distilled at 110°/0.01 mm., and showed $[\alpha]_D^{17}$ — 40° (c, 0.52 in ethanol). (Reported b. p. 180—190/0.05 mm.[5]).

Anal. 9.74 mg. subst.: 21.52 mg. CO_2, 4.71 mg, H_2O
$C_{16}H_{17}O_6N$ (319.30) calc'd.: C 60.18; H 5.37%
found: C 60.29; H 5.42%

N-Phthaloyl-L-aspartic Acid

A solution of *N*-phthaloyl diethyl-L-aspartate (9.93 g., 0.03 mole) in glacial acetic acid (85 ml.) and concentrated hydrochloric acid (23 ml.) was heated under reflux for 2 hours. The reaction mixture was evaporated *in vacuo* to the volume of about 15 ml. After standing overnight the crude *N-phthaloyl-L-aspartic acid* was collected, in a yield of 5.0 g. (68%). It was dissolved in water (25 ml.), treated with charcoal, filtered, and the filtrate left standing overnight at room temperature. A small amount of crystals separated (0.9 g.) which showed $[\alpha]_D^{15} -12.5^0 \pm 0.6^0$ (c, 1.23 in methanol). The filtrate was evaporated *in vacuo* to half its volume, and left for 24 hours at 0°. *N*-Phthaloyl-L-aspartic acid was obtained in a yield of 3.9 g. (53%); overall yield from diethyl-L-aspartate hydrochloride 42%), and showed the m.p. 197° and $[\alpha]_D^{17} -58^0$ (c, 0.39 in methanol). [Reported m.p. 193° and $[\alpha]_{20}^{D} -59.5^0$ (in ethanol)[5].] The analytical sample was recrystallized from water.

Anal. 8.32 mg. subst.: 16.72 mg. CO_2, 2.59 mg. H_2O
$C_{12}H_9O_6N$ (263.20) calc'd.: C 54.76; H 3.45%
found: C 54.81; H 3.48%

N-Phthaloyl-L-Aspartic Acid Anhydride

N-Phthaloyl-L-aspartic acid (2.63 g., 0.01 mole) and acetic anhydride (25 ml.) were heated for 3—4 minutes at 100°. On cooling, the *N-phthaloyl-L-aspartic acid anhydride* separated, yield 1.2 g. (49%). The analytical sample was recrystallized from a mixture of *N* : *N*-dimethylformamide and ether, and showed the m.p. 210—213° and $[\alpha]_D^{15} -60^0$ (c, 0.27 in *N* : *N*-dimethylformamide). (Reported m.p. 209—211°, but without $[\alpha]_D$ values[5].)

Anal. 7.92 mg. subst.: 17.13 mg. CO_2, 2,13 mg. H_20
$C_{12}H_7O_5N$ (245.18) calc'd.: C 58.78; H 2.88%
found: C 59.02; H 3.02%

Acknowledgment. The authors are indebted to Mrs. Z. Štefanac for the microanalyses.

REFERENCES

1. cf. J. C. Sheehan, D. W. Chapman and R. W. Roth, *J. Am. Chem. Soc.* **74** (1952) 3822.
2. K. Balenović, N. Bregant, B. Gašpert, I. Jambrešić and V. Tomašić, *Arhiv kem.* **27** (1955) 207.
3. A. Reissert and H. Holle, *Ber.* **44** (1911) 3027.
4. K. Balenović and B. Gašpert, Chemistry & Industry **1957**, 115.
5. F. E. King and D. A. A. Kidd, *J. Chem. Soc.* **1951**, 2976.
6. E. Fischer and E. Koenigs, *Ber.* **37** (1904) 4599.

IZVOD

Uvođenje *N*-ftaloilne grupe u derivate aminokiselina osjetljive na povišenu temperaturu

K. Balenović, B. Gašpert i N. Štimac

Opisana je metoda kojom se može, polazeći od o-karbetoksitiobenzoeve kiseline (II), odnosno njezine Na-soli, i derivata aminokiselina koji racemiziraju kod povišene temperature, prirediti neracemizirane *N*-ftaloil aminokiseline. Služeći se tom metodom opisana je preparacija *N*-ftaloil-L-asparaginske kiseline.

KEMIJSKI INSTITUT
PRIRODOSLOVNO-MATEMATIČKI FAKULTET
ZAGREB

Primljeno 27. svibnja 1957.