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Pseudoconhydrine; Direct Correlation of the Configuration at C(2) with that of α-Amino Acids*

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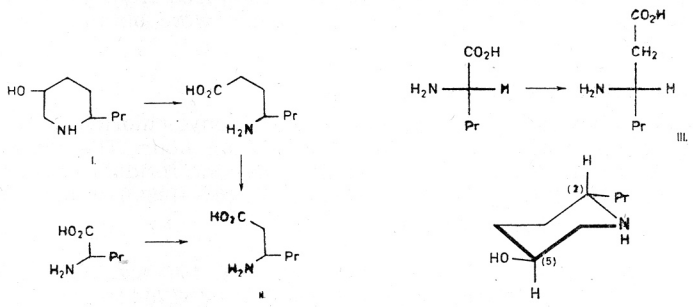
(+)-β-Amino-*n*-caproic acid, obtained by oxidation of pseudoconhydrine[1], was prepared by stereospecific synthesis from L-norvaline which showed that this acid is of the configuration III, and pseudoconhydrine of the configuration IV.

Among the oxidation products of pseudoconhydrine (I, Pr = *n*-propyl, a minor alkaloid from hemlock *(Conium maculatum),* Spaeth *et al.*[1] isolated an amino acid (m. p. 205—207°, $[\alpha]_D$ + 35.6°) which presumably was β-amino-*n*-caproic acid (II).

The configuration of β-amino-*n*-caproic acid is, evidently, of interest for the stereochemistry of pseudoconhydrine at C(2). Pseudoconhydrine has been earlier reduced to *d*-coniine[2]. On the other hand, conhydrine has been converted to *l*-coniine[3], and oxidized to (—)-piperidine-2-carboxylic acid. This acid was proven to be of the L-series[4] *(a)* by applying the principle of Lutz and Jirgensons[5] and, later *(b)*, by corellation with a derivative of L-aspartic acid[6]. The stereochemistry of pseudoconhydrine at C(2) can be, therefore, indirectly deduced from these results.

We have synthesized (+)-β-amino-*n*-caproic acid by applying the Arndt-Eistert reaction to (—)-1-diazo-3-phthalimidohexan-2-one. This diazoketone was



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prepared *via* *N*-phthaloyl-L-norvalinyl chloride from *N*-phthaloyl-L-norvaline. L-Norvaline was obtained by the enzymatic resolution of *N*-chloroacetyl norvaline[7]. The hydrolysis of methyl-(+)-β-phthalimido-*n*-caproate, $[\alpha]_D + 7^0$ (which was obtained by the Wolff rearrangement of (—)-1-diazo-3-phthalimidohexan-2-one) gave (+)-β-amino-*n*-caproic acid, which was identical with Spaeth's authentic specimen by m. p., mixed m. p., R_f values, and sign of optical rotation.

The Wolff rearrangement of diazoketones proceeds with retention of configuration[8]; Spaeth's β-amino acid II can be, therefore, represented by the projection formula III, and consequently, the conformation and stereochemistry depicted in formula IV[a] may be assigned to pseudoconhydrine, carrying the generalizations of cyclohexane chemistry over to the heterocyclic analogues[9].

Our results from the present direct correlation of the stereochemistry of pseudoconhydrine at C(2) (formula IV) agree with earlier stereochemical studies of hemlock alkaloids[2–6].

EXPERIMENTAL

The melting points are uncorrected unless otherwise stated.

N-*Phthaloyl-L-norvaline*

A finely ground mixture of L-norvaline (16.3 g., 0.13 mole, prepared according to Greenstein *et al.*[7]) and phthalic anhydride (21.6 g., 0.15 mole) was heated at 125—130° during two hours. N-*Phthaloyl-L-norvaline* remained as a pale yellow oil, yield 29.5 g. (88.7%), showing $[\alpha]_D^{24}$ —20.0° ± 0.5° (c, 3.5 in ethanol). After standing at room temperature for several days, the oil solidified. The analytical sample was recrystallized from benzene-petroleum ether and had the m. p. 97° and $[\alpha]_D^{21}$ —22,1° ± 1° (c, 1.06 in ethanol).

Anal. 10.44 mg. subst.: 24.13 mg. CO_2, 4.83 mg. H_2O
$C_{13}H_{13}O_4N$ (247.24) calc'd.: C 63.15; H 5.30%
found: C 63.06; H 5.18%

The whole amount of *N*-phthaloyl-L-norvaline was purified for the next reaction stage by treating it with benzene, filtering, and evaporating the filtrate to dryness. The residue (27.2 g., 81.9%) was recrystallized from carbon tetrachloride — petroleum ether, and 24.5 g. (73.5%) of crystals were obtained, with the m. p. 93—97°.

N-*Phthaloyl-L-norvalinyl Chloride*

N-Phthaloyl-L-norvaline (9.88 g., 0.04 mole), thionyl chloride (30 ml.) and benzene (20 ml.) were heated under reflux for half an hour. The excess of thionyl chloride was then removed under reduced pressure; the residual crude N-*phthaloyl-L-norvalinyl chloride* (10.3 g., 97.3%) distilled at 105—108°/0.04 mm. and showed $[\alpha]_D^{16}$ —45.5° ± 1° (c, 0.34 in benzene).

Anal. 10.43 mg. subst.: 22.50 mg. CO_2, 4.36 mg. H_2O
$C_{13}H_{12}O_3NCl$ (265.69) calc'd.: C 58.76; H 4.55%
found: C 58.89; H 4.68%

(—)-*1-Diazo-3-phthalimidohexan-2-one*

To a solution of *N*-phthaloyl-L-norvalinyl chloride (10 g., 0.04 mole) in ether (50 ml.) a solution of diazomethane (prepared from 30 g. of nitrosomethylurea) was

[a] With hypothetical stereochemistry at C(5).

added dropwise, with stirring. After standing at 0° for 24 hours, the ether was evaporated *in vacuo* and *(—)-1-diazo-3-phthalimidohexan-2-one* remained (10.0 g., 97%), showing $[\alpha]_D^{17}$ —70° ± 1° (c, 1.08 in benzene). The compound was used for the following reaction without further purification.

*Methyl-(+)-β-phthalimido-*n*-caproate*

A freshly prepared alkali-free suspension of silver oxide in methanol (obtained from 1.5 g. of silver nitrate) was added in four portions during 3 hours to a refluxing solution of (—)-1-diazo-3-phthalimidohexan-2-one (5.4 g., 0.02 mole) in methanol (40 ml.), and the suspension heated under reflux for 4 more hours. The hot suspension was treated with charcoal, filtered and evaporated to dryness. The residue (4.03 g. 73.3%) was extracted with petroleum ether (6×60 ml.), and the solvent from the combined extracts evaporated to dryness under reduced pressure. Yield 3.53 g. (64.2%) of crude *methyl-(+)-β-phthalimido-*n*-caproate,* which distilled at 125—127°/0.01 mm. and showed $[\alpha]_D^{16}$ + 7.1° ± 1° (c, 0.35 in methanol).

Anal. 8.02 mg. subst.: 19.18 mg. CO_2, 4.50 mg. H_2O
$C_{15}H_{17}O_4N$ (275.29) calc'd.: C 65.44; H 6.22%
found: C 65.24; H 6.27%

*(+)-β-Amino-*n*-caproic Acid;* [(+)-β-*Norleucine*] (III)

A solution of methyl-(+)-β-phthalimido-*n*-caproate (2.75 g., 0.01 mole) in glacial acetic acid (15 ml.) and 48% hydriodic acid (18 ml.) was heated under reflux for 10 hours. After cooling the phthalic acid was filtered off, washed with glacial acetic acid, and the combined filtrate and washings evaporated to dryness under reduced pressure. The residue was dissolved in water, the solution extracted with ether (2 × 20 ml.) and the aqueous layer again evaporated to dryness. The residue was dissolved in water (20 ml.), treated with charcoal, filtered and evaporated to dryness. The residual hydriodide of (+)-β-amino-*n*-caproic acid was dissolved in water (500 ml.) and passed through a column of Amberlite IR-4B (20—50 mesh, 35 g.) at 50 ml./hr. The column was washed with water (1000 ml.) and the washings evaporated *in vacuo.* (+)-β-*Amino-*n*-caproic acid* remained (1.10 g., 84.4%), which was recrystallized from ethanol-acetone (yield 0.91 g., 69.5%). The analytical sample was recrystallized from ethanol, and sublimed at 155°/0.01 mm., m. p. 203.5°. The following $[\alpha]_D$ values were obtained $[\alpha]_D^{15}$ +61° ± 1° (c, 0.4 in water); $[\alpha]_D^{15}$ + 36° ± 0.5° (c, 0.29 in 5*N* HCl); $[\alpha]_D^{15}$ + 13° ± 1° (c, 0.35 in 2*N* NaOH).

Anal. 5.19 mg. subst.: 10.47 mg. CO_2, 4.66 mg. H_2O
$C_6H_{13}O_2N$ (131.17) calc'd.: C 54.93; H 9.99%
found: C 55.10; H 10.06%

Paper chromatography of (+)-β-amino-*n*-caproic acid on Whatman No. 1 paper, at 20°, with butanol-acetic acid-water (10:3:9) as mobile phase, gave a violet spot, R_f 0.51, with a 0.1% ninhydrin solution. The authentic specimen of Spaeth's (+)-β-amino-*n*-caproic acid [m. p. 205—207°, $[\alpha]_D^{17}$ + 35.6 (in water)] obtained from the oxidation products of pseudoconhydrine[1] gave the identical R_f value in the solvent system used, and on admixture of our synthetic compound [m. p. 204° (corr.) $[\alpha]_D^{15}$ + 61°[b] (in water)] gave no depression of m. p., [mixed m. p. 204—205° (corr.)].

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[b] Spaeth's specimen was evidently slightly racemized.

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IZVOD

Pseudokonhidrin; direktna korelacija konfiguracije na C(2) s konfiguracijom α-aminokiselina

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(+)-β-amino-*n*-kapronska kiselina, dobivena oksidacijom pseudokonhidrina, priređena je stereospecifičnom sintezom iz L-norvalina, te je time za tu kiselinu utvrđena konfiguracija III, a za pseudokonhidrin konfiguracija IV.

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