

CCA-399

547.517.02

Original Scientific Paper

The Absolute Configuration of γ -Methyl- ϵ -caprolactam (5-Methyl-azacycloheptanon-2)

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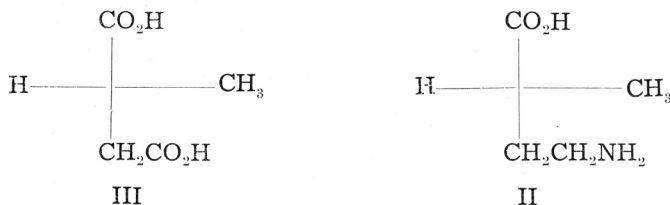
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Received October 29, 1965

(+)- γ -Methyl- ϵ -caprolactam was synthesized from optically active α -methyl- γ -phthalimidobutyric acid by two successive Arndt-Eistert syntheses. The configuration of the title compound was thus proved to be (S) (+).

Very little has as yet been published about the properties of optically active polymers other than those prepared from optically active amino acids. Information now available in the literature indicates that optically active polymers have higher melting points and greater crystallinity than the corresponding racemic modifications. An example is poly *D*-(-)- β -methyl- ϵ -caprolactam whose melting point is 90° above that of the racemic polymer. This polymer was prepared by Overberger and Jabloner¹ from *D* (-)- β -methyl- ϵ -caprolactam, the configuration of which was derived from the known *D*-configuration of pulegone. It is the only optically active methyl substituted ϵ -caprolactam that has been prepared and polymerized.

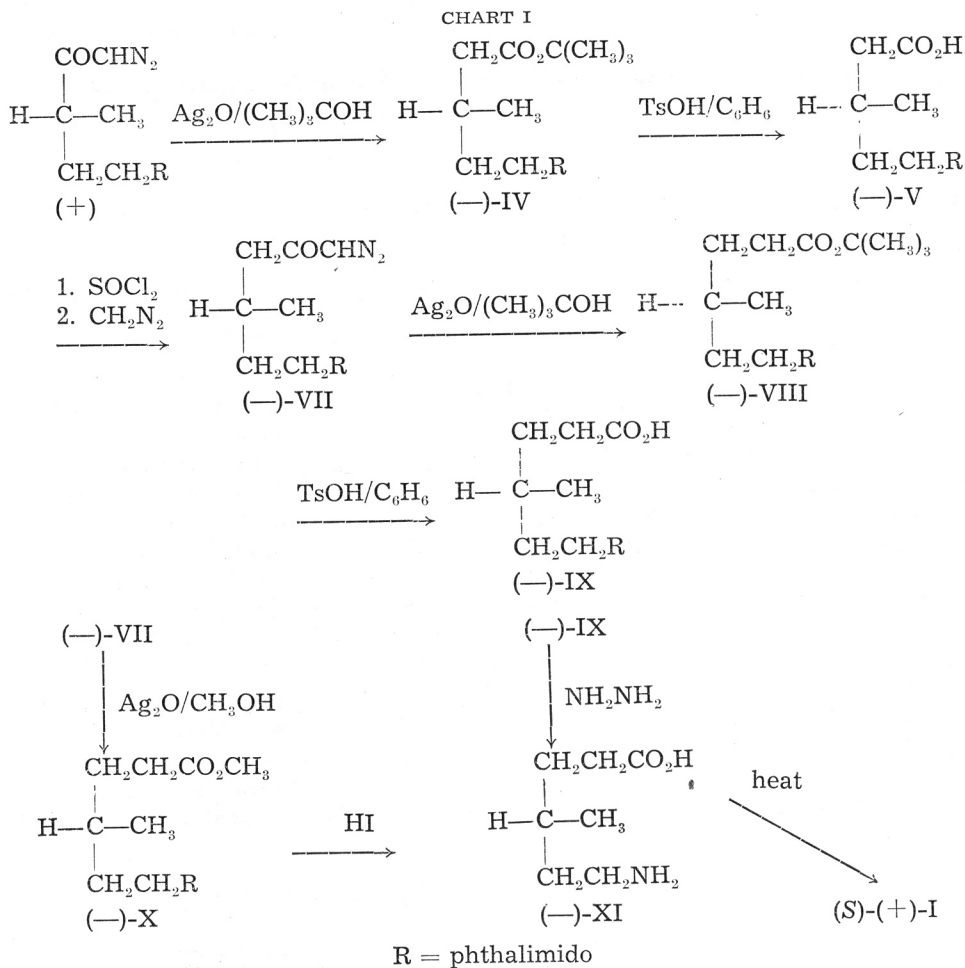
The purpose of the present investigation has been the preparation of both the (*R*) (-) and (*S*) (+)-isomers of γ -methyl- ϵ -caprolactam. α -Methyl- γ -phthalimidobutyric acid was used as starting material and as the stereochemical reference compound. Adams and Fleš² have, by chemical interconversion, correlated the configuration of α -methyl- γ -aminobutyric acid (II) with that of methylsuccinic acid (III).



The optically active (+)- γ -methyl- ϵ -caprolactam *I* (5-methyl-azacycloheptanon-2) was prepared by two methods. The first was by the conversion of optically active α -methyl- γ -phthalimidobutyric acid to γ -methyl- ϵ -phthalimidocaproic acid by two successive Arndt-Eistert syntheses as represented in Chart I, and the second by the resolution of γ -methyl- ϵ -phthalimidocaproic acid

* Part of the thesis submitted by V. Seke in partial fulfilment for the requirements of the degree of Doctor of Chemistry (Ph. D.) at the University of Zagreb.

via the diastereomeric quinine salt. The first pathway was used for the determination of the absolute configuration of γ -methyl- ϵ -caprolactam while the second one was applied as a convenient preparative method for the preparation of optically active caprolactam.



As described in the paper by Adams and Fleš² the methyl ester of β -methyl- δ -phthalimidovaleric acid was prepared from its lower homologue by applying the Arndt-Eistert synthesis. An attempt to hydrolyse the methyl ester group without affecting the phthaloyl group failed, and in order to perform the second Arndt-Eistert synthesis it was necessary to prepare β -methyl- δ -aminovaleric acid, phthaloylate it, and then convert to the higher homologue. This difficulty was avoided when Wolff rearrangement was performed during the Arndt-Eistert synthesis in tertiary butyl alcohol, since tertiary butyl esters are easily saponified in benzene containing a catalytic amount of *p*-toluenesulfonic acid.^{3,4} Under the mild conditions used, the ester was saponified without affecting the imide linkage.

The termination of the saponification reaction was determined by both the disappearance of isobutylene from the off gases, and by the disappearance of the tertiary butyl group from the NMR spectrum of the reaction mixture.

After removal of the phthaloyl group from the compound (—)-IX, the obtained (—) γ -methyl- ϵ -aminocaproic acid was converted to (S)-(+)- γ -methyl- ϵ -caprolactam by heat distillation in a vacuum.

Optically inactive γ -methyl- ϵ -caprolactam was prepared from 4-methylcyclohexanone oxime *via* the Beckmann rearrangement, following the procedure of Marvel and Eck⁵ and Schäffler and Ziegenbein.⁶ The lactam was then hydrolyzed with aqueous hydrochloric acid, converted to its *N*-phthaloyl derivative and resolved by fractional crystallization of its diastereomeric quinine salts.

Since the reactions used for the correlation of the configuration of γ -methyl- ϵ -caprolactam with that of α -methyl- γ -aminobutyric acid do not involve the asymmetric carbon atoms of the intermediate compounds, the (+)- γ -methyl- ϵ -caprolactam has the (S) configuration.

EXPERIMENTAL*

Tert-butyl (+)-3-methyl-5-phthalimidovalerate (IV)

To a solution of 6.3 g. (0.0233 mole) of (—)-1-diazo-3-methyl-5-phthalimido-2-pentanone in 100 ml. of boiling *tert*-butyl alcohol a suspension of freshly prepared silver oxide in *tert*-butanol was added gradually until the evaluation of nitrogen had ceased (about 5 hrs). The silver oxide was removed by filtration, washed with two 15-ml. portions of *tert*-butanol, the solvent evaporated and the residue dissolved in 60 ml. of ether. After filtering from the precipitated silver oxide, the ether was evaporated and the 4.8 g. residue was distilled, b. p. 140—160° (air bath temperature) at 0.025 mm., yielding 4.52 g. (61.5%) of a slightly yellow oil, which crystallizes on standing, m. p. 42°, $[\alpha]_D^{20} + 8.98^{\circ}$ (c, 4.016% in benzene). Redistillation indicated a b. p. of 135—140° at 0.025 mm.

Anal. $C_{18}H_{23}NO_4$ (317) calc'd.: C 68.14%; H 7.25%; N 4.25%
found: C 67.87%; H 7.43%; N 4.68%

In the same way *tert*-butyl (\pm) 3-methyl-5-phthalimidovalerate was prepared, b. p. 189—195° (air bath temperature) at 0.02 mm.

Anal. $C_{18}H_{23}NO_4$ (317) found: C 68.02%; H 7.60%; N 4.52%

(+)-3-Methyl-5-phthalimidovaleric acid (V)

A mixture of 4.45 g. of distilled ester and 0.22 g. of *p*-toluenesulfonic acid in 36 ml. of benzene was refluxed for about 3 hours, after which time there was no band corresponding to the *tert*-butyl group in its NMR spectrum. In some experiments the end of reaction was determined by the disappearance of *iso*-butylene from the off-gases by gas chromatography. The benzene solution was washed with water to remove *p*-toluene sulfonic acid, the solvent dried over magnesium sulfate and evaporated *in vacuo*, yielding 3.8 g. of an oily product. The crude acid was dissolved in a saturated solution of sodium bicarbonate, decolorized with charcoal and precipitated with concentrated hydrochloric acid. The crystalline precipitate was separated by filtration, washed with water and recrystallized from a mixture of benzene-petroleum ether (1 : 1); yield 2.46 g., (67.2%); m. p. 32—3°; $[\alpha]_D^{20} + 13.22^{\circ}$ (c, 1.96% in ethanol).

Anal. $C_{14}H_{15}NO_4$ (261) calc'd.: C 64.37%; H 5.75%; N 5.36%
found: C 64.62%; H 6.08%; N 5.20%

* The melting points are uncorrected.

The racemic 3-methyl-5-phthalimidovaleric acid was prepared in the same way, m. p. 105.5—106°.

Anal. C₁₄H₁₅NO₄ (261) found: C 64.53%; H 6.01%; N 5.19%

(—)-3-Methyl-5-phthalimidovaleryl chloride (VI)

A mixture of 2.4 g. of (+)-3-methyl-5-phthalimidovaleric acid and 16 ml. of thionyl chloride was heated for one hour with the bath temperature not allowed to rise above 80°. The excess of thionyl chloride was distilled *in vacuo*, the residue dried overnight in a desiccator over potassium hydroxide and the oily residue extracted with six 20-ml. portions of warm petroleum ether (b. p. 40—60°). Evaporation of the petroleum ether gave 2.4 g. (93.7%) of a colorless oil, $[\alpha]_D^{20} - 8.25$ (c, 1.945% in benzene). A sample was distilled for analysis, b. p. 148—156° at 0.01 mm, whereas the rest of the chloride was used without further purification in the next step.

Anal. C₁₄H₁₄ClNO₃ (279.46) calc'd.: C 60.12%; H 5.01%; N 5.01%
found: C 60.41%; H 4.72%; N 5.26%

The racemic chloride had b. p. 148—168° at 0.012 mm.

Anal. C₁₄H₁₄ClNO₃ (279.46) found: N 5.25%

(+)-1-Diazo-4-methyl-6-phthalimido-2-hexanone (VII)

A solution of 2.3 g. of (—)-3-methyl-5-phthalimidovaleryl chloride in 50 ml. of dry ether was added slowly to 650 ml. of an ethereal solution of diazomethane prepared from 34 g. of nitrosomethylurea. The reaction mixture was left overnight in a refrigerator, filtered from any precipitate and the ether evaporated. The residue which crystallized was used in the next step without further purification. Yield 2.2 g. (95%) of yellow crystals, m. p. 69—70°. A sample was recrystallized twice from a mixture of ether and petroleum ether and analyzed; m. p. 83—4°, $[\alpha]_D^{20} + 18$ (c, 3.16% in ethyl acetate).

Anal. C₁₅H₁₅N₃O₃ (285) calc'd.: C 63.16%; H 5.26%; N 14.74%
found: C 63.28%; H 5.43%; N 14.88%

In the same way racemic diazomethyl ketone was prepared, m. p. 69—70°.

Anal. C₁₅H₁₅N₃O₃ (285) found: C 63.14%; H 5.43%; N 14.78%

Tert-butyl (+)-4-methyl-6-phthalimido caproate (VIII)

A solution of 0.4 g. of (+)-1-diazo-4-methyl-6-phthalimido-2-hexanone in 20 ml. of boiling *tert*-butanol was treated with a freshly prepared suspension of silver oxide in *tert*-butanol and the reaction mixture worked up in the same manner as described for the preparation of *tert*-butyl (+)-3-methyl-5-phthalimido valerate. The crude ester (0.28 g.) was distilled at 120—130° (air bath temperature) and 0.02 mm; yield 0.23 g. (49.4%); $[\alpha]_D^{20} - 7.2$ (c, 3.52% in benzene)

Anal. C₁₉H₂₅NO₄ (331) calc'd.: C 68.88%; H 7.55%; N 4.23%
found: C 69.14%; H 7.88%; N 4.49%

The racemic *tert*-butyl ester was prepared in the same way, b. p. 160—170° at 0.025 mm, yield 53.8%.

Anal. C₁₉H₂₅NO₄ (331) found: C 69.08%; H 7.75%; N 4.54%

(+)-4-Methyl-6-phthalimidocaproic acid (IX)

Tert-butyl ester (0.36 g.) was saponified with 20 mg. of *p*-toluene sulfonic acid in the manner as described for the preparation of (+)-3-methyl-5-phthalimidovaleric acid. (+)-4-Methyl-6-phthalimidocaproic acid was recrystallized for analysis from a mixture of benzene-petroleum ether, yield 0.12 g. (40.4%), m. p. 60—1°; $[\alpha]_D^{20} + 6.3$ (c, 3.02% in ethanol).

Anal. C₁₅H₁₇NO₄ (275) calc'd.: C 65.45%; H 6.18%; N 5.10%
found: C 65.50%; H 6.43%; N 5.42%

In the same way (\pm) 4-methyl-6-phthalimidocaproic acid was prepared, m. p. 74—5°.

Anal. C₁₅H₁₇NO₄ (275) found: C 65.28%; H 6.53%; N 5.05%

Methyl (—)-4-methyl-6-phthalimidocaproate (X)

To 2.75 g. of (+) diazomethyl keton VII in 50 ml. of boiling methanol, a methanolic suspension of freshly prepared silver oxide was added gradually until the evolution of nitrogen had ceased (about 6 hours). The silver oxide was removed by filtration, washed with two 20 ml. portions of methanol, the solvent evaporated *in vacuo* and the oily residue dissolved in 30 ml. of ether. After filtering from the precipitated silver oxide, the ether was evaporated, yielding 2.31 g. (82.5%) of a pale light yellow oil, which was used in the next step without further purification, $[\alpha]_D^{25}$ — 6.6° (c, 4.92% in benzene).

A 200 mg. sample was twice distilled for analysis, b. p. 170—5° (air bath temperature) at 0.02 mm.

Anal. C₁₆H₁₉NO₄ (289) calc'd.: C 66.42%; H 6.62%; N 4.84%
found: C 66.13%; H 7.04%; N 5.07%

(—)-4-Methyl-6-aminocaproic acid (XI)

a) From (+)-4-methyl-6-phthalimidocaproic acid — A mixture of 0.42 g. of (+)-4-methyl-6-phthalimidocaproic acid and 2.36 ml. of *M*-hydrazine hydrate solution in ethanol was refluxed for one hour. The residue remaining after evaporation of the ethanol was dissolved in 5 ml. of water, adjusted to pH 5 with acetic acid and allowed to stand 10 min. at 50°, and one hour at room temperature. The phthaloyl hydrazide was filtered and washed with five 3 ml. portions of water. The combined water and washings were evaporated *in vacuo*, to a volume of about 2 ml., treated with charcoal and then evaporated to dryness. Traces of water were removed by repeated evaporation from absolute ethanol. The semicrystalline residue was dissolved in 2 ml. of absolute ethanol and 1 ml. of ether added to aid crystallization. After standing overnight in a refrigerator the amino acid crystallized as fine needles, yield 0.19 g. (80%), m. p. 173—5°. Recrystallization from ethanol-ether yielded a product with m. p. 178—9°, $[\alpha]_D^{20}$ — 1.18° (c, 7.62% in water).

Anal. C₇H₁₅NO₂ (145.19) calc'd.: C 57.90%; H 10.41%; N 9.65%
found: C 57.62%; H 10.52%; N 9.73%

b) From methyl (—)-4-methyl-6-phthalimidocaproate — A mixture of 2.21 g. of crude ester (0.008 moles), 13.5 ml. of glacial acetic acid and 7.2 ml. of hydriodic acid (47%) was refluxed for 10 hours and then allowed to stand overnight in a refrigerator. Phthalic acid was removed by filtration, washed with 5 ml. of acetic acid and the filtrate evaporated under reduced pressure. The traces of acids were removed by repeated evaporation from water. The residue was dissolved in 30 ml. of water, extracted with ether, and the aqueous layer evaporated *in vacuo*. The crude iodide was dried overnight *in vacuo* over potassium hydroxide, dissolved in 100 ml. of water, treated with charcoal and the solution made up to 1 l. This was then passed through a column of Amberlite IR-4B (66 × 2.5 cm), and the column washed with 2 l. of water. The effluent was evaporated *in vacuo* and the residue was dissolved repeatedly in absolute ethanol and the solvent evaporated until the product crystallized. Crude amino acid (0.37 g.) was treated with 6 ml. of boiling ethanol and crystallized overnight in a refrigerator yielding 0.26 g. of white needles, m. p. 176—7°, $[\alpha]_D^{20}$ — 1.35° (c, 16.3% in water). The product was, in all of its properties, identical with (+)-4-methyl-6-aminocaproic acid obtained from a) as indicated by their melting points and mixed melting points, and their identical IR spectra.

(±)-4-Methyl-6-aminocaproic acid (XI)

(\pm)-4-Methyl-6-caprolactam^{5,6} (40 g.) was refluxed for 7 hours with 280 ml. of 20% hydrochloric acid, the reaction mixture was cooled, evaporated to dryness and the oily residue dissolved in 800 ml. of water. This solution was treated with charcoal and passed through a column of Amberlite IR-4B (4 × 60 cm). The column was washed with 2 l. of water and the effluent evaporated *in vacuo* yielding 40 g. of crude yellow

crystals. Crystallization from 200 ml. of 96% ethanol and 40 ml. of ether afforded 37 g. (81%) of 4-methyl-6-aminocaproic acid, m. p. 179—180°.

Anal. $C_7H_{13}NO_2$ (145.2) calc'd.: C 57.9%; H 10.41%; N 9.65%
found: C 58.12%; H 10.58%; N 9.59%

(±)-4-Methyl-6-phthalimidocaproic acid (IX)

A finely powdered mixture of 33 g. of (±)-4-methyl-6-aminocaproic acid and 33.6 g. of phthalic anhydride was heated in an oil bath with a thermometer immersed in the reaction mixture. The temperature was maintained for 2 hours at 130°. The water formed during the reaction was removed *in vacuo* and the residue dissolved in 180 ml. of benzene. The insoluble part was removed by suction filtration and discarded. Addition of 150 ml. of petroleum ether (b. p. 30—60°) promoted the crystallization of 4-methyl-6-phthalimidocaproic acid, yield 51.65 g. (90.5%) m. p. 74.5°.

Anal. $C_{15}H_{17}NO_4$ (275.038) calc'd.: C 65.45%; H 6.18%; N 5.16%
found: C 65.47%; H 6.47%; N 5.41%

Resolution of 4-methyl-6-phthalimidocaproic acid

A mixture of 30 g. of 4-methyl-6-phthalimidocaproic acid and 35.4 g. of quinine was dissolved under reflux in 435 ml. of ethyl acetate and left overnight in a refrigerator at +5°. The crystalline product was separated by filtration and recrystallized from ethyl acetate (5 ml. of ethyl acetate per 1 g. of quinine salt) until a yield of 50% by weight of quinine salt was obtained (4—7 crystallizations). The quinine salt melted at 75—6° and had a rotation of $[\alpha]_D^{20} - 104^\circ$ (c, 3.58% in benzene).

In a separating funnel 35.9 g. of the less soluble salt was treated with 90 ml. of 10% hydrochloric acid in the presence of 350 ml. of benzene. The aqueous layer was separated and extracted with two 30-ml. portions of benzene, and the combined benzene solutions were washed with three 25-ml. portions of water. The benzene fractions were combined, dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo*, yielding 16.0 g. of partly resolved product $[\alpha]_D^{20} - 1.85^\circ$ (c, 11.87% in ethanol). This product was dissolved in 48 ml. of benzene and 18 ml. of petroleum ether (b. p. 30—60°), inoculated with racemic 4-methyl-6-phthalimidocaproic acid and allowed to stand overnight in a refrigerator. The mother liquor was decanted from the crystalline part. This weighed 11.3 g. and had a rotation of $[\alpha]_D^{20} - 0.59^\circ$ (c, 10.17% in ethanol). Addition of 3 ml. of petroleum ether to the mother liquor caused further crystallization, and 1 g. of product m. p. 71—4°, $[\alpha]_D^{20} - 0.93^\circ$ (c, 10.98 in ethanol) was separated. The mother liquor was evaporated under reduced pressure and gave 3.15 g. of product melting at 61—3°, $[\alpha]_D^{20} - 5.22^\circ$ (c, 9.79% in ethanol). After recrystallization from a mixture of benzene-petroleum ether the product had a m. p. 60—2°, $[\alpha]_D^{20} - 6.38^\circ$ (c, 9.73% in ethanol). This product was, in all of its properties identical with (—)-4-methyl-6-phthalimidocaproic acid prepared *via* the Arndt-Eistert synthesis, as proved by their m. p. mixed m. p. and identical IR spectra.

(+)-4-Methyl-6-caprolactam (I)

(—)-4-Methyl-6-aminocaproic acid (1.16 g.) was heated to 180° under a reduced pressure of 15 mm. until the evolution of water had ceased. The product was then distilled at 95—100° (air bath temperature) and 0.025 mm. as colorless oil, yield 0.35 g. (34.5%), $[\alpha]_D^{20} + 18.9^\circ$ (c, 10.45% in ethanol), $[\alpha]_D^{20} + 22.9^\circ$ (c, 18.10% in benzene) $[\alpha]_D^{20} + 49.2^\circ$ (c, 12.61% in *m*-cresol).

Anal. $C_7H_{13}NO$ (127.18) calc'd.: C 66.14%; H 10.24%; N 11.02%
found: C 66.00%; H 10.67%; N 10.86%

In the same way (±)-4-methyl-6-caprolactam was prepared.

Anal. $C_7H_{13}NO$ (127.18) found: C 66.22%; H 10.46%; N 11.23%

Acknowledgment. We wish to thank Miss Lj. Znika for help in much of the experimental work and Dr. B. Černicki for the determination and interpretation of the NMR spectra. The authors are indebted to Mr. Z. Šlipečević for the microanalyses and to Mrs. Z. Burić for the determination of the infrared spectra.

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IZVOD

**Apsolutna konfiguracija γ -metil- ϵ -kaprolaktama
(5-metil-azacikloheptanon-2)**

V. Seke i D. Fleš

Apsolutna konfiguracija (+) γ -metil- ϵ -kaprolaktama utvrđena je korelacijom sa 2-metil-4-ftalimidomaslačnom kiselinom, koja je upotrebljena kao ishodni i referentni spoj. 2-Metil-4-ftalimidomaslačna kiselina je pomoću dvije sukcesivne Arnt-Eistert-ove sinteze prevedena u 4-metil-6-ftalimidokapronsku kiselinu.

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ORGANSKO KEMIJSKA INDUSTRIJA
ZAGREB

Primljeno 29. listopada 1965.