CCA-322

547.747:541.63

Original Scientific Paper.

The Absolute Configuration of 3-Carboxypyrrolidine (β-Proline)*

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Received December 6, 1963

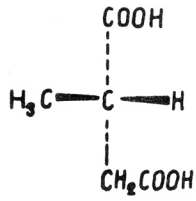
(+)-3-Carboxypyrrolidine was synthesized from (+)-1-benzyl--4-carboxy-2-pyrrolidone, and its configuration correlated with (+)-2-methyl-4-phthalimidobutyric acid of known configuration. The configuration of carbon-3 atom of (+)-β-proline is shown to be *S*.

The objective of this investigation was the preparation of an optically active β-carboxypyrrolidine (I) of known configuration and its correlation to β-proline.

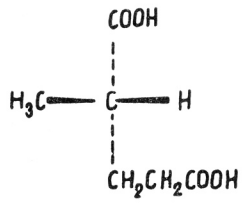
Inactive β-proline was first synthesized by Myamoto[1] from 1,3-dicarbethoxy-4-pyrrolidone, which was prepared *via* the Dieckmann condensation of the corresponding tricarboxylic acid. This synthesis, however, was not suitable for determination of the absolute configuration of β-proline and intermediates.

In this communication (+)-β-proline (I) was synthesized from (+)-1--benzyl-4-carboxy-2-pyrrolidone and its configuration correlated with (+)--2-methyl-4-phthalimidobutyric acid (II), the configuration of which was established by Adams and Fleš[2].

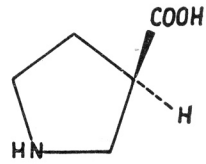
By means of chemical interconversion they related the configuration of (+)-2-methyl-4-phthalimidobutyric acid (II) and (+)-2-methyl-4-aminobutyric acid (III) to (—)-2-methylsuccinic acid (IV), the configuration of which is known to be *S*[3,4]. The configuration of C-3 of (+)-β-proline is thus shown to be *S*.



(—) IV



(+) III



(+) I

The structural formula of β-proline I is drawn in such a way that the five-membered ring is placed in the plane of the paper.

* Presented at the I. Yugoslav Congress of Pure and Applied Chemistry, Zagreb, June 1960; Abstract of Papers, p. 42

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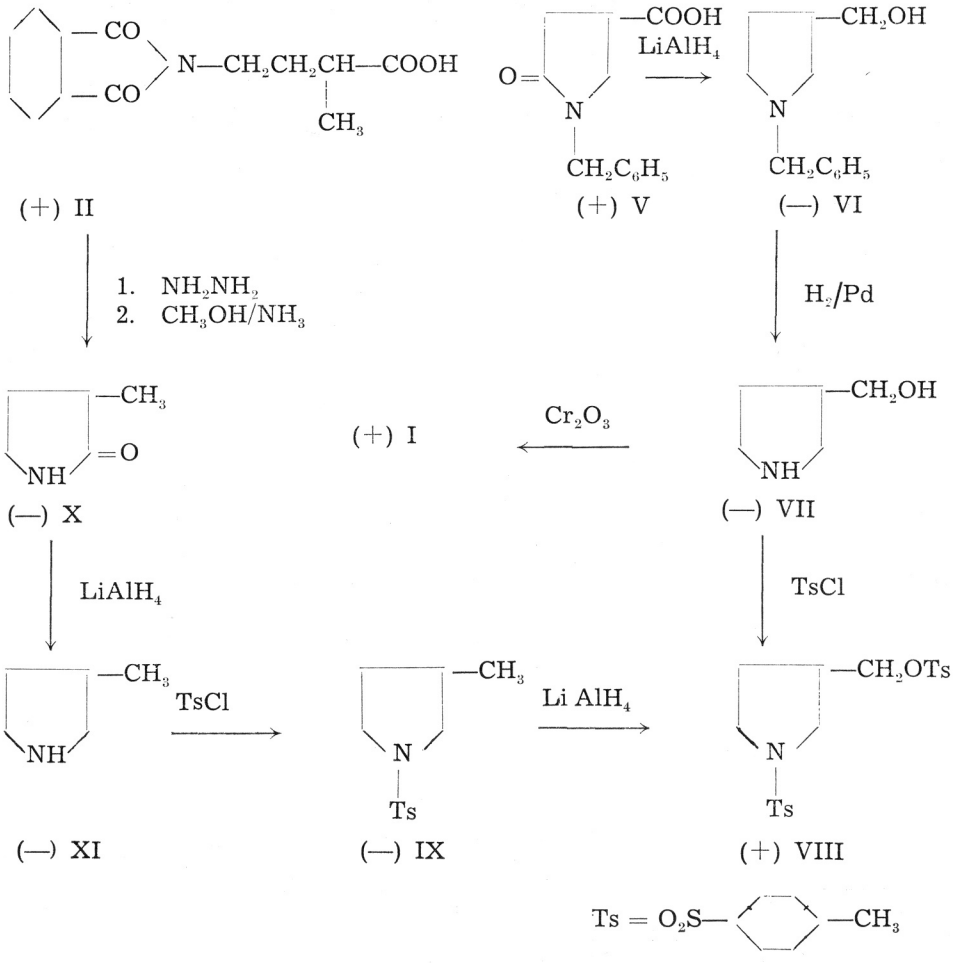
The key compound in this work was optically active 1-benzyl-4-carboxy--2-pyrrolidone (V) which was prepared by resolution of the inactive acid, obtained by condensation of itaconic acid with benzylamine, following the procedure described by Paytash *et al.*[5].

The racemic form of V was resolved by fractional crystallization of its cinchonine salt. (+)-1-Benzyl-4-carboxy-2-pyrrolidone was then converted through compounds VI and VII, as represented on Chart I, to (+)-β-proline [(+) I]. (—)-3-Methylpyrrolidine (XI), identified as the tosyl derivative (—) IX, was synthesized in two ways: the first, by the pathway compound X, and the second, from compound V, through compounds VI, VII, and VIII to the same tosyl derivative (—) IX. The configurations of all the intermediates, which correlate the configuration of (+)-2-methyl-4-phthalimidobutyric acid (II) with that of (+)-β-proline (I), have thus been established.

Chart I



It is worth mentioning that while (+)-1-benzyl-4-carboxy-2-pyrrolidone V could be easily prepared from the less soluble cinchonine salt, its antipode was obtained only with a very low degree of optical purity from the more soluble salt. The (—) acid however could be obtained from the partly resolved cinchonine salt by treatment with 10% hydrochloric acid. Of the resulting (—) acid and racemic acid, the (—) acid is much more soluble in dilute hydrochloric acid. When the two crystallize out, the (±) acid crystallizes in the form of small crystals, while the (—) acid forms very large prismatic crystals, which may be separated mechanically from the racemic acid.

EXPERIMENTAL

Melting points are uncorrected.

Resolution of 1-benzyl-4-carboxy-2-pyrrolidone (V)

To a solution of 14.1 g. (0.064 mole) of (±)-1-benzyl-4-carboxy-2-pyrrolidone and 17.7 g. (0.06 mole) of cinchonine in 60 ml. of 96% ethanol was added 450 ml. of ether, and the clear solution left overnight at room temperature. After cooling for 5 hrs. at 0—5°, the crystalline product was separated by filtration and recrystallized from ethanol-ether (4 ml. of ethanol and 24 ml. of ether per 1 g. of salt). This procedure was repeated twice, yielding 13.2 g. (42.5%) of the salt, melting at 143—144° and with a rotation $[\alpha]_D^{20}$ + 117° (*c* 2.02% in ethanol). The less soluble fraction (13.2 g.) was treated with 26 ml. of 10% hydrochloric acid and left overnight in a refrigerator. The crystalline precipitate was thoroughly washed with diluted hydrochloric acid and water, dried on air and recrystallized from benzene. Yield 3.9 g. (27.6%, based on (±) acid), of needless m.p. 99—99.5°; $[\alpha]_D^{22}$ + 15.7° (*c* 2.98% in abs. ethanol).

Anal. $C_{12}H_{13}NO_3$ (219.232) calc'd: C 65.74; H 5.98; N 6.23%
found: C 65.71; H 5.66; N 6.39%

The solvent of the first mother liquor from which the less soluble cinchonine salt was isolated was evaporated *in vacuo*, yielding 13.5 g. of a yellow viscous oil. The crude salt was dissolved in 27 ml. of 10% hydrochloric acid and allowed to stand at room temperature for about 2 weeks. The racemic acid crystallized in very small crystals on the bottom of the flask, while the (—) acid formed large prismatic crystals. The crystalline product was filtered, washed with cooled 10% hydrochloric acid, then with ice cooled water, and the large prismatic crystals representing pure (—) acid were separated mechanically. Yield 1.6 g. (11.4% based on (±)-acid), m. p. 99—100°; $[\alpha]_D^{22}$ —15.7° (*c* 2.042% in abs. ethanol). A mixture of equal parts of (+) and (—) acid melted at 142—144° (reported[5] m.p. for racemic acid 143—144°).

(+) 1-Benzyl-4-carbomethoxy-2-pyrrolidone

To a solution of diazomethane prepared from 15 g. of nitrosomethylurea in 150 ml. of ether was added gradually 2.5 g. (0.011 mole) of (+)-1-benzyl-4-carboxy--2-pyrrolidone, and the solution left 30 minutes at room temperature. Ether was evaporated *in vacuo* and the residue crystallized from a mixture of 6 ml. of ether and 1 ml. of petroleum ether (b.p. 40—60°). Yield 2 g. (75.2%), m.p. 57°. A sample was recrystallized for analysis from ether and melted at 55.5—57°; $[\alpha]_D^{22}$ + 18.9° (*c* 2.88% in methanol).

Anal. $C_{13}H_{15}NO_3$ (233.14) calc'd: C 66.93; H 6.48; N 6.01%
found: C 67.08; H 6.24; N 6.25%

(—) 1-Benzyl-3-hydroxymethyl-pyrrolidine (VI)

The (+) ester (1.5 g., 0.0064 mole) was dissolved in 75 ml. of ether and added under vigorous stirring into 45 ml. of a 2.9% solution of lithium aluminum hydride

in ether. The reaction mixture was refluxed for 6 hrs. The excess of reducing agent was hydrolyzed by dropwise addition of 50 ml. of wet ether, followed by 2 ml. of water. The slurry was refluxed for one hour, the inorganic material removed by suction filtration and thoroughly washed with ether. The combined ether layers were dried over magnesium sulfate, the solvent evaporated *in vacuo* and the residue distilled at 113—123° (0.08 mm), yielding 1.2 g. (98%) of colorless oil. $[\alpha]_D^{20}$ —2.55° (*c* 3.98% in ethanol).

Anal $C_{12}H_{17}NO$ (191.26) calc'd: C 75.34; H 8.96; N 7.33%
found: C 75.17; H 8.72; N 7.35%

The same compound was prepared from (+) acid (1.5 g.) which was suspended in 150 ml. of ether and gradually added into a solution of lithium aluminum hydride. The reaction mixture was worked up as previously described. A sample of carbinol was converted to the oxalate which was recrystallized from ethanol and finally from a mixture of ethanol and ether; m.p. 106.5—108°. $[\alpha]_D^{20}$ + 2.1° (*c* 7.165% in water).

Anal. $C_{14}H_{19}NO_5$ (281.30) calc'd: C 59.77; H 6.81; N 4.98%
found: C 59.82; H 6.49; N 5.04%

The inactive oxalate was similarly prepared and melted at 101—103°.

found: C 59.83; H 6.62; N 5.06%

(—)-3-Hydroxymethylpyrrolidine (β-prolinol) (VII)

A solution of 1.53 g. (0.008 mole) of(—)-1-benzyl-3-hydroxy-methylpyrrolidine VI was hydrogenolyzed in EtOH at room temperature with 179 ml. of hydrogen in the presence of 250 mg. of 10% palladium on charcoal catalyst. After the absorption of hydrogen had ceased, the catalyst was removed by suction filtration, washed with ethanol, and the solvent evaporated *in vacuo* yielding 0.71 g. (87.7%) of colorless oil which was used without further purification in the next step. A sample was distilled for analysis at 90° (air bath temperature) and a pressure of 4 mm. $[\alpha]_D^{20}$ —19.1° (*c* 4.554% in ethanol). A sample was converted to the oxalate, which was recrystallized twice from ethanol and melted at 100—101°; $[\alpha]_D^{20}$ —6.8° (*c* 3.075% in water).

Anal. $C_7H_{13}NO_5$ (191.18) calc'd: C 43.97; H 6.85; N 7.33%
found: C 43.76; H 6.65; N 7.31%

(+)-3-Carboxypyrrolidine [(+)-β-Proline] (I)

(—)β-Prolinol (1.28 g., 0.013 mole) was dissolved in a cold solution of 0.3 ml. concentrated sulfuric acid and 7.1 ml of water (*p*H of the mixture 4.5) and the resulting solution was added at once into a solution of 1.08 g. chromic acid and 0.7 ml. concentrated sulfuric acid in 14.2 ml. of water. During the addition and for the next 5 min. the temperature was kept at 0°. The reaction mixture was heated with stirring in a boiling water-bath for 2 min., cooled to 0° and treated with a cold solution of 1.08 g. chromic acid in 0.68 ml. sulfuric acid and 14.2 ml. water. The dark colored solution was heated for 30 min. in a boiling water bath, and the resulting green solution was cooled to room temperature. Sulfur dioxide was bubbled through the solution for 10 min. causing the color to change to green-blue. The solution was then heated to 40° and powdered barium hydroxide was gradually added until the reaction mixture was alkaline to phenolphthalein. After a total of 19. g. of barium hydroxide was added, the reaction mixture was cooled to room temperature and the precipitate was filtered off and washed with 80 ml. of boiling water. The excess of barium hydroxide was removed with CO_2, which was bubbled through the almost colorless solution for several minutes. Water was removed *in vacuo*, yielding a brown oil which solidified into white crystals. β-Proline was separated from the remaining inorganic material by extraction with 160 ml. absolute ethanol. Evaporation of ethanol furnished 1.09 g. (75.2%) of crude product

which was sufficiently pure for preparative work; m.p., 182—184°. For analysis a sample was dissolved in water, decolorized with charcoal, water evaporated *in vacuo* and the residue recrystallized from ethanol; m.p., 188—190°; $[\alpha]_D^{20}$ + 18.5° (*c* 3.135% in water).

Anal. $C_5H_9NO_2$ (115.13) calc'd: C 52.16; H 7.88; N 12.17%
found: C 51.88; H 7.32; N 12.28%

(+)-*1*-p-*Toluenesulfonyl-3*-p-*toluenesulfonyloxymethylpyrrolidine* (N,O--*Ditosyl-β-prolinol)* (VIII)

To a cold solution of 0.55 g. (0.0054 mole) of crude β-prolinol (VII) in 2 ml. of pyridine was added a solution of 2.8 g. (0.015 mole) of *p*-toluenesulfonyl chloride in 4 ml. of pyridine, and the reaction mixture was kept for 1 hr. at 0° and then 48 hours at room temperature. Pyridine was evaporated *in vacuo*, the residue suspended in 5 ml. of water, extracted with three 10-ml. portions of chloroform, and the extract washed succesively with two 5-ml. portions of 2% hydrochloric acid, and 10 ml. of water. The chloroform solution was dried with magnesium sulfate and evaporated *in vacuo*, yielding 1.8 g. of dark brown oil. The crude tosylate was recrystallized from 2 ml. of ethanol yielding 1 g. of red crystalline product, which was dissolved in 5 ml. of ethyl acetate, decolorized with charcoal and recrystallized by addition of 5 ml. of petroleum ether; yield 700 mg. (31.4%), m.p. 78—79°; $[\alpha]_D^{25}$ + 4.8° (*c* 8.765% in ethyl acetate).

Anal. $C_{19}H_{23}NO_5S_2$ (409.38) calc'd: C 55.74; H 5.66; N 3.42%
found: C 55.79; H 5.37; N 3.67%

(—)-*3-Methyl-2-pyrrolidone* (X)

A mixture of 4.2 g. (0.017 mole) of (+)-2-methyl-4-phthalimidobutyric acid and 6.5 ml. of *M*-hydrazine hydrate solution in ethanol was heated under reflux for one hour. The residue after evaporation of ethanol was treated with 5 ml. of 10% hydrochloric acid and allowed to stand 10 min. at 50° and one hour at room temperature. The phthaloyl hydrazide was filtered and washed with three 5-ml. portions of water. The combined filtrates were evaporated *in vacuo* and the residue allowed to stand 2 days at room temperature with 18 ml. of absolute ethanol saturated with hydrochloric acid.

The crude ester hydrochloride obtained on evaporation of the ethanol was dissolved in 10 ml. of chloroform, cooled in ice and treated for 5 min. with a stream of dry ammonia. The ammonium chloride was filtered, washed with chloroform and the filtrate evaporated *in vacuo*. The oily ester was allowed to stand in a pressure bottle for 72 hours with 25 ml. of methanol saturated with dry ammonia at 0°. The semicrystalline residue was extracted with ether, yielding 0.417 g. (26.6%) of crystalline product upon evaporation of ether. A sample was distilled at 100—110° (0.1 mm) to give a colorless oil which solidified on cooling. The product was recrystallized from ether for analysis; m.p. 45°; $[\alpha]_D^{20}$ —58.3° (*c* 3.975% in benzene).

Anal. C_5H_9NO (99.13) calc'd.: C 60.58; H 9.19; N 14.13%
found: C 60.33; H 9.05; N 13.93%

(—)-*3-Methylpyrrolidine* (XI)

A solution of 0.8 g (0.008 mole) of (—)-3-methyl-2-pyrrolidone in 15 ml. of ether was added slowly with stirring to 19 ml. (0.002 mole) of a normal ethereal solution of lithium aluminum hydride. The reaction mixture was stirred while heating under reflux for 6 hours, after which 50 ml. of wet ether and 2 ml. of water was added. The inorganic precipitate was filtered, and washed with five 50-ml. portions of ether. The combined filtrate and ether washings were dried over magnesium sulfate and the solvent evaporated *in vacuo*. A sample was distilled at 92—94° to give a colorless oil; $[\alpha]_D^{20}$ —15.5° (*c* 0.586% in ethanol).

The crude base was dissolved in ether and treated with a saturated solution of oxalic acid, yielding 450 mg. of oxalate. A sample was recrystallized from ethanol-ether (1 : 3) and melted at 81—82°; $[\alpha]_D^{20}$ —6.7° (*c* 2.798% in ethanol).

Anal. $C_7H_{13}NO_4$ (175.18) calc'd: C 47.99; H 7.48; N 8.00%
found: C 47.83; H 7.26; N 8.20%

(—)-*1*-p-*Toluenesulfonyl-3-methyl-pyrrolidine* (IX)

A. From (+)-1-p-toluenesulfonyl-3-p-toluenesulfonyloxy-methylpyrrolidine. — A solution of 1.17 g. (0.0028 mole) of (+)-*N,O*-ditosylderivative VIII in 30 ml. of tetrahydrofuran was added with stirring to a solution of 0.5 g. lithium aluminum hydride. The reaction mixture was stirred for three hours, after which the excess of reducing agent was destroyed by the addition of 4 ml. of water, the inorganic precipitate removed by filtration and thoroughly washed with ether. The ethereal solution was dried and the solvent evaporated *in vacuo* yielding 750 mg. of crystalline product melting at 88—89°. After two crystallizations from ethanol the melting point was constant at 90—91°; $[\alpha]_{21}^{D}$ —7.8° (*c* 2.050% in ethanol).

Anal. $C_{12}H_{17}NO_2S$ (239.28) calc'd: C 60.24; H 7.16%
found: C 60.27; H 6.89%

B. From (—)-3-methylpyrrolidine. — Into a solution of 1.43 g. (0.017 mole) of (—)-3-methylpyrrolidine in 10 ml. of pyridine cooled with ice, was added at once 4.29 g. (0.022 mole) of *p*-toluenesulfonyl chloride. The reaction mixture was left overnight at room temperature, after which time pyridine was evaporated *in vacuo*. The residue was suspended in 10 ml. of water and extracted with three 30-ml. portions of ether. The extract was washed with 20 ml. of 5% hydrochloric acid, followed by two 10 ml. portions of water, and dried with magnesium sulfate. Evaporation of ether gave 2.7 g. of a crystalline product which melted at 50—56°. The product was very carefully heated to 100° (air bath temperature) (0.1 mm.) to remove the excess of *p*-toluenesulfonyl chloride. After the sublimation ceased, the residue (0.7 g.) was recrystallized from 2 ml. of ethanol; m.p. 84—85°. A sample was recrystallized for analysis from a mixture of benzene-petroleum ether (b.p. 40—60°) (1 : 3), and finally sublimed at 120—130° (air bath temperature) (0.1 mm); m.p. 91—92°; $[\alpha]_D^{20}$ —8.8° (*c* 1.952% in ethanol).

Anal. $C_{12}H_{17}NO_2S$ (239.28) calc'd: C 60.24; H 7.16; N 5.85%
found: C 60.00; H 6.94; N 5.85%

The product was identical with the one previously described, as indicated by mixed m.p. and identical IR spectra.

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IZVOD

Apsolutna konfiguracija 3-karboksipirolidina (β-prolina)

D. Fleš i T. Ghyczy

(+)-β-Prolin sintetiziran je iz (+)-1-benzil-4-karboksi-2-pirolidina, čija je konfiguracija određena uspoređivanjem sa (+)-2-metil-4-ftalimidomaslačnom kiselinom poznate konfiguracije. Na taj način je pokazano da je konfiguracija C-3 atoma u (+)-β-prolinu *S*.

ZAVOD ZA ORGANSKU KEMIJU S TEHNOLOGIJOM
TEHNOLOŠKI FAKULTET
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Primljeno 6. prosinca 1963.