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On the Configuration of β-Amino-δ-Methyl Hexanoic Acid (β-Aminohomoleucine)*

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The configuration of (+)-β-amino-δ-methyl hexanoic acid (β-aminohomoleucine) (IIa), obtained by the application of the Arndt-Eistert synthesis[2] on L-leucine (I) was determined. β-Phthalimido-δ-methyl hexanoyl chloride (III) was converted *via* Rosenmund-Zetsche reaction into the corresponding aldehyde IV and ethylene mercaptal V. Raney nickel reduction of V gave (+)-4-phthalimido-2-methyl- hexane (VI). Hydrolysis of VI with hydrobromic acid yielded (—)-4-amino-2-methyl-hexane hydrobromide (VII). The compounds VI and VII were also obtained from 1-diazo-3-phthalimido-5-methyl hexan-2-one (VIII) by a different way, Wolff rearrangement being not applied. VIII was converted to the corresponding ketone (IX), resp. thioketal (X), which was desulphurized to VI. The compounds VI and VII, obtained by both ways, had the same signs of rotation.

The obtained results agree with the previous findings of other authors[3,6] that during Wolff rearrangement of diazoketones no Walden inversion occurs.

Optically active β-amino-δ-methyl hexanoic acid (β-aminohomoleucine) (IIa) was prepared from L-leucine (I) several years ago[1] by Balenović's application of Arndt-Eistert synthesis on the diazoketones of optically active amino acid.[2] It has been known from the literature[3] that Wolff rearrangement of the diazoketones which occurs at an asymmetrical centre proceeds with the retention of configuration and no Walden rearrangement occurs. Therefore we presumed that β-amino homologue of L-leucine belonged to the L-series of amino acids.

To obtain a direct proof of configuration of IIa, we intended first to carry out the Barbier-Wieland degradation[4] on some β-aminohomoleucine derivatives. However, these attempts failed because of the inertness of β-amino acid derivatives against the Grignard reagent.[5]

The next attempt was to convert the optically active methyl β-phthalimido-δ-methyl hexanoate (IIb) to 4-phthalimido-2-methyl-hexane (VI), which can be obtained also starting from 1-diazo-3-phthalimido-5-methyl hexan-2--one (VIII).

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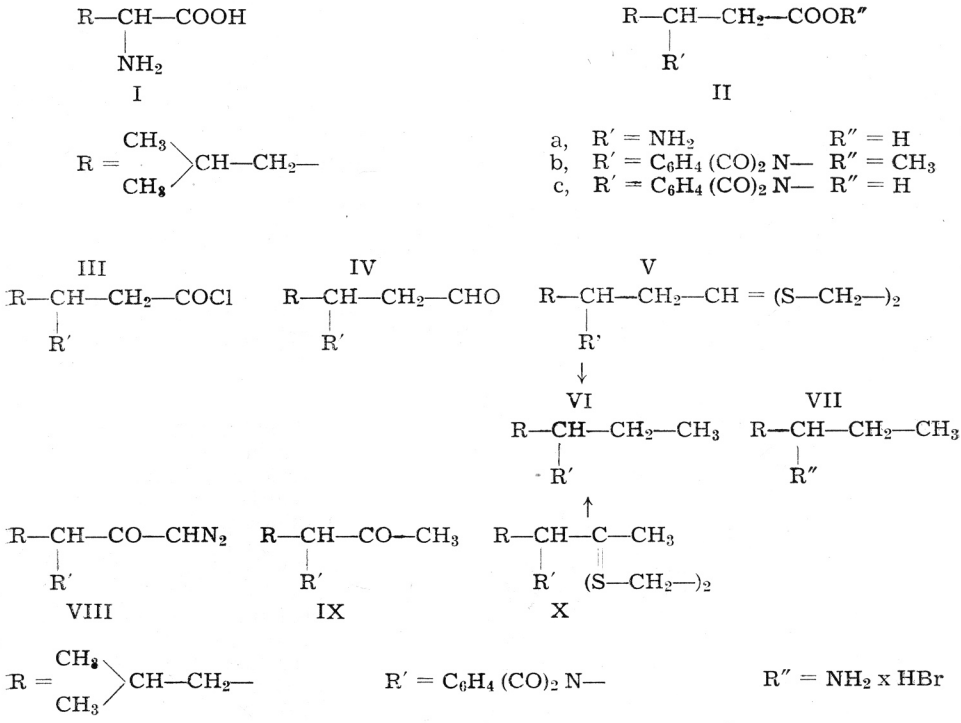

Meanwhile Balenović, Bregant and Cerar[6] have established by a direct chemical method the correlation of configuration of (+)-β-aminobutyric acid with L-α-aminobutyric acid and have thus confirmed that the homologization of β-amino acids by Arndt-Eistert synthesis proceeds without Walden inversion.

This paper describes the preparation of β-phthalimido-δ-methyl hexanoic acid (IIc) in two ways: *a)* by hydrolysis of IIb, and *b)* by fusion of IIa with phthalic anhydride. As the resulting IIc obtained by both methods had the same optical activity, we can conclude that hydrolysis of phthaloyl group of IIb with hydriodic acid in the preparation of IIa,[1] as well as the fusion of IIa with phthalic anhydride, proceeds without racemization.

IIc was then converted to the chloride (III). The Rosenmund-Zetsche reduction used already by Balenović and his collaborators[7] on several phthaloyl amino acid chlorides was applied also in this case, and 3-phthalimido-5-methyl hexanal (IV) was obtained. Ethanedithiol gave with IV the corresponding mercaptal V, which on desulphurisation with Raney nickel yielded the 4-phthalimido-2-methyl hexane (VI) as a colourless oil .By hydrolysis with hydrobromic acid[8] VI was converted into 4-amino-2-methyl hexane hydrobromide (VII).

Following the other way, we started from 1-diazo-3-phthalimido-5-methyl hexan-2-one (VIII).[1] Reaction of VIII with hydriodic acid[9] yielded the ketone IX, which was then converted into the corresponding mercaptal X.

Desulphurization of X with Raney nickel gave the already mentioned 4-phthalimido-2-methyl hexane (VI), and after hydrolysis the hydrobromide VII respectively.

The fact that VI as well as VII obtained by both methods had the same signs of rotation, confirmes that IIa belongs to the L-series of amino acids.

EXPERIMENTAL

All melting points are uncorrected.

β-Phthalimido-δ-methyl hexanoic acid (IIc)

A. By hydrolysis of IIb. — To a solution of methyl β-phthalimido-δ-methyl hexanoate (IIb, 9.0 g., 0.031 mole, $[\alpha]_D^{20}$ + 9.0°, in methanol) in glacial acetic acid (30 ml.), 34% hydrobromic acid (20 ml.) was added and the solution kept at 50—55° during four hours. Water (50 ml.) was added, the reaction mixture extracted several times with ether, the ethereal extracts washed with 5% sodium bicarbonate, then with water and dried (Na_2SO_4). After evaporating the ether, IIc was obtained as a yellow viscous oil, which crystallized on addition of benzene. Yield 7.3 g., (85.6%), m. p. 82—84°. For analysis the compound was distilled at 150°/0.010 mm. as a colourless oil which solidified. $[\alpha]_D^{20}$ + 7.0 (±1) (c, 4.11, in ethanol).

Anal. 7.925 mg. subst.: 18.920 mg. CO_2, 4.387 mg. H_2O
5.486 mg. subst.: 0.2528 ml. N_2 (19.8°, 755 mm.)
$C_{15}H_{17}NO_4$ (275.29) calc'd.: C 65.43; H 6.23; N 5.09%
found: C 65.15; H 6.20; N 5.34%

S-Benzyl-isothiuronium salt of IIc was prepared by standard technique. White needles from ethanol-water (1 : 1), m. p. 163—164°.

Anal. 8.277 mg. subst.: 18.99 mg. CO_2, 4.728 mg. H_2O
$C_{23}H_{27}N_3O_4S$ (441.53) calc'd.: C 62.56; H 6.16%
found: C 62.61; H 6.39%

B. From IIa. — β-Amino-δ-methyl hexanoic acid (IIa, 1.0 g., 6.9 mMoles, $[\alpha]_D^{20}$ + 28°, in water) and phthalic anhydride (1.1 g., 7.4 m Moles) were mixed and heated on an oil bath (bath temp. 135—140°) for one hour. The reaction mixture was dissolved in benzene, treated with charcoal, filtered and precipitated with petroleum ether. 1.25 g., (65.8%) of β-phthalimido-δ-methyl hexanoic acid was obtained, which after two recrystallizations from benzene-petroleum ether had m. p. 82—84°, $[\alpha]_D^{20}$ + 7.4° (±1) (c, 3.82, in ethanol). The analytical sample distilled at 160°/0.016 mm. as a colourless oil which solidified.

Anal. 9.720 mg. subst.: 23.28 mg. CO_2, 5.45 mg. H_2O
$C_{15}H_{17}NO_4$ (275.29) calc'd.: C 65.43; H 6.23%
found: C 65.36; H 6.28%

β-Phthalimido-δ-methyl hexanoyl chloride (III)

To 5.5 g. (0.02 mole) of the acid IIc, thionyl chloride (10 ml.) was added and the mixture heated on an oil bath (bath temp. 50°) for one hour. The excess of thionyl chloride was removed under reduced pressure, and the resulting viscous oil, was used without further purification for the preparation of the aldehyde.

An other sample was distilled twice at 140—150°/0.025 mm. A colourless oil was obtained.

Anal. 8.164 mg. subst.: 18.328 mg. CO_2, 3.925 mg. H_2O
$C_{15}H_{16}NO_3Cl$ (293.74) calc'd.: C 61.33; H 5.49%
found: C 61.26; H 5.38%

3-Phthalimido-5-methyl hexanal (IV)

A solution of the chloride III (obtained from 5.5 g. of IIc) in xylene (40 ml.) was reduced with palladium (5%) on barium sulphate[7] at 150° (oil bath temp.), during four hours. 3.9 g. (75% calc'd on IIc) of IV as a pale yellow oil, showing $[\alpha]_D^{19}$ — 8.9° (c, 3.52 in ethanol) was obtained. For analysis a sample was distilled at 122—125°/0.012 mm. and a colourless oil obtained, $[\alpha]_D^{19}$ — 10.8° (± 0.7) (c, 3.05, in ethanol).

Anal. 7.664 mg. subst.: 19.555 mg. CO_2, 4.719 mg. H_2O
$C_{15}H_{17}NO_3$ (259.29) calc'd.: C 69.47; H 6.61%
found: C 69.63; H 6.89%

Semicarbazone was precipitated from a methanolic solution of IV and recrystallized from methanol-water. White needles, m. p. 197—199°.

Anal. 8.090 mg. subst.: 18.000 mg. CO_2, 4.622 mg. H_2O
$C_{16}H_{20}N_4O_3$ (316.35) calc'd.: C 60.74; H 6.37%
found: C 60.72; H 6.39%

3-Phthalimido-5-methyl hexanal ethylene mercaptal (V)

The aldehyde IV (2.6 g., 0.01 mole, $[\alpha]_{18}^{D}$ — 10.2°) was dissolved in a 3% solution of anhydrous hydrochloric acid in dioxane (10 ml.), ethanedithiol (2 ml.) added and the solution kept at room temp. for two days. The solvent was removed *in vacuo*, and the remaining oil subjected to chromatography (benzene as solvent and eluent) over alumina (80 g., Riedel de Haën). From the eluates 2.5 g. of V (yield 75%) was obtained as a pale yellow oil which crystallized. The analytical sample was twice recrystallized from methanol; white plates, m. p. 81—82.5°, $[\alpha]_D^{19}$ +18.9° (± 1) (c, 4.42, in benzene).

Anal. 9.298 mg. subst.: 20.780 mg. CO_2, 5.255 mg. H_2O
$C_{17}H_{21}NO_2S_2$ (335.47) calc'd.: C 60.86; H 6.31%
found: C 60.99; H 6.32%

4-Phthalimido-2-methyl-hexane (VI) via *IIc*

The thioacetal V (1.70 g., 5.07 mMoles $[\alpha]_D^{19}$ + 18°) in abs. ethanol (15 ml.) was desulphurized with Raney nickel[10] (W-2 activity in abs. ethanol) under reflux with stirring during two hours. After removing the catalyst the obtained oil was filtered through alumina (50 g., Riedel de Haën) and the benzene eluates evaporated. A colourless oil (870 mg., 70%) remained. The analytical sample distilled at 81—84°/0.03 mm, $[\alpha]_D^{19}$ + 7.2° (± 1) (c, 4.04, in benzene).

Anal. 9.138 mg. subst.: 24.570 mg. CO_2, 6.600 mg. H_2O
$C_{15}H_{19}NO_2$ (245.31) calc'd.: C 73.43; H 7.81%
found: C 73.37; H 8.08%

4-Amino-2-methyl hexane hydrobromide (VII) via *IIc*

VI (600 mg., 2.45 mMoles) was refluxed with glacial acetic acid (5 ml.) and 66% hydrobromic acid (4 ml.) for ten hours[8]. The reaction mixture was evaporated to dryness and extracted with chloroform. After evaporation of the solvent, the residue was crystallized from ethyl acetate, and VII (480 mg., 58.4%) obtained as white needles. For analysis the compound was recrystallized from ethyl acetate, m. p. 229.5—230.5° $[\alpha]_D^{20}$ — 7.5° (± 1) (c, 3.34, in ethanol).

Anal. 6.952 mg. subst.: 10.892 mg. CO_2, 5.884 mg. H_2O
$C_7H_{18}NBr$ (196.14) calc'd.: C 42.86; H 9,25%
found: C 42.75; H 9.47%

3-Phthalimido-5-methyl hexan-2-one (IX)

To a solution of 1-diazo-3-phthalimido-5-methyl hexan-2-one (VIII, 8.55 g., 0.03 mole, $[\alpha]_D^{21}$ —98,6°, ethyl acetate) in chloroform (25 ml.), 47% hydriodic acid[9] (15 ml.) was gradually added over a period of half an hour. The mixture was shaken with sodium thiosulphate, then with water and dried over Na_2SO_4 sicc. After evaporating the solvent *in vacuo*, the yellow oil was extracted several times with petroleum ether. The eluates were combined, evaporated *in vacuo* and IX as a clear oil obtained (7.1 g., 91%, $[\alpha]_D^{22}$ —40.7° (c, 3.81, in benzene). For analysis the compound was distilled twice at 95—110°/0.03 mm and obtained as a viscous oil, which crystallized from petroleum-ether, m. p. 38—39°. $[\alpha]_D^{22}$ —50.2 (± 0.5) (c, 3.48 in benzene).

Anal. 12. 574 mg. subst.: 31.970 mg. CO_2, 7.448 mg. H_2O
$C_{15}H_{17}O_3N$ (259.29) calc'd.: C 69.48; H 6.61%
found: C 69.38; H 6.63%

2,4-Dinitrophenyl hydrazone of IX, yellow needles from ethanol, m. p. 161—162°.

Anal. 8.896 mg. subst.: 18.757 mg. CO_2, 3.822 mg. H_2O
$C_{21}H_{21}N_5O_6$ (439.42) calc'd.: C 57.39; H 4.82%
found: C 57.54; H 4.81%

Semicarbazone of IX, white prisms from methanol, m. p. 207—208° (sealed capillary).

Anal. 10.810 mg. subst.: 18.000 mg. CO_2, 4.622 mg. H_2O
$C_{16}H_{20}N_4O_3$ (316.35) calc'd.: C 60.74; H 6.37%
found: C 60.65; H 6.28%

3-Phthalimido-5-methyl hexan-2-one ethylene mercaptal (X)

The ketone IX (5.2 g., 0.02 mole, $[\alpha]_D^{20}$ —41°) was dissolved in a 3% solution of anhydrous hydrochloric acid in dioxane (20 ml.), ethanedithiol (2 ml.) added, and the solution kept at +5° for five days. The solvent was removed *in vacuo*, the remaining oil dissolved in hot benzene, treated with charcoal and filtered. After evaporation of the solvent the yellow-reddish oil was dissolved in hot acetone: water (2 : 1). On cooling, white crystals of X separated (4.5 g., yield 67%) m. p. 108—113°. After two recrystallizations from acetone: water (2 : 1) white prisms of the pure compound, m. p. 115—116°, $[\alpha]_D^{22}$ —41° (±1) (c, 4.69, in benzene) were obtained.

Anal. 8.040 mg. subst.: 17.932 mg. CO_2, 4.580 mg. H_2O
$C_{17}H_{21}NO_2S_2$ (335.47) calc'd.: C 60.86; H 6.31%
found: C 60.86; H 6.38%

4-Phthalimido-2-methyl hexane (VI) via *VIII*

The thioketal X (1.3 g., 3.9 mMoles, $[\alpha]_D^{21}$ —39.3°) in abs. ethanol (10 ml.) was desulphurized with Raney nickel[10] (W-2 activity in abs. ethanol) under reflux with stirring during six hours. After removing the catalyst, the obtained oil was filtered through alumina (50 g., Riedel de Haën) and the benzene eluates evaporated. A colourless oil (735 mg., 77%, $[\alpha]_D^{22}$ +7.9° (±1) (c, 2.15, in benzene) was obtained. The analytical sample distilled at 82—86°/0.03 mm.

Anal. 12.842 mg. subst.: 34.560 mg. CO_2, 8.820 mg. H_2O
$C_{15}H_{19}NO_2$ (245.31) calc'd.: C 73.43; H 7.81%
found: C 73.44; H 7.69%

4-Amino-2-methyl-hexane hydrobromide (VII) via *VIII*

VI (870 mg., 3.5 mMoles) was refluxed with glacial acetic acid (5 ml.) and 66% hydrobromic acid (4 ml.) for ten hours.[8] The reaction mixture was evaporated to dryness, extracted with chloroform and then evaporated *in vacuo*. The residue was crystallized from ethyl acetate and VII (400 mg., 57.5%) obtained as white needles. For the analysis the compound was twice recrystallized from ethyl acetate, m. p. 229.5—230.5°, $[\alpha]_D^{23}$ —8.3 (± 1) (c, 1.25, in ethanol).

Anal. 7.130 mg. subst.: 11.250 mg. CO_2, 5.869 mg. H_2O
$C_7H_{18}NBr$ (196.14) calc'd.: C 42.86; H 9.25%
found: C 43.06; H 9.21%

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IZVOD

O konfiguraciji β-amino-δ-metil heksanske kiseline (β-aminohomoleucina)

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Optički aktivni 4-ftalimido-2-metil heksan (VI), te njegov hidrobromid VII, priređeni su na dva različita načina. Prvi (I—VI) polazi od β-amino-δ-metil heksanske kiseline (β-homoleucina) (IIa), koja je dobivena iz L-leucina putem Wolffovog premještaja; kod druge pak metode (VIII—VI) nije upotrebljen Wolffov premještaj.

Kako VI i VII, priređeni po objema metodama, pokazuju isti smjer skretanja, potvrđeno je, da IIa ima konfiguraciju L-amino kiselina, što je i u skladu s istraživanjima drugih autora[3,6] o Wolffovom premještaju.

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