PEPTIDES CONTAINING A NEOPENTYLGLYCINE RESIDUE

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Neopentylglycine (*III*, 2-amino-4,4-dimethylpentanoic acid) was synthesized in both enantiomeric forms. Using the conventional methods of peptide synthesis, L-prolyl-L-neopentylglycyl--glycine amide (*VII*), the diastereoisomeric cyclodipeptides cyclo(L-neopentylglycyl-L-prolyl) (*IXa*) and cyclo(D-neopentylglycyl-L-prolyl) (*IXb*) and also N-acetyl-L-neopentylglycine methylamide (*X*) were prepared as models for further studies on physical properties and conformation of peptides.

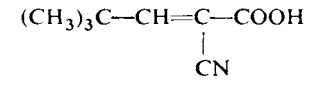
As part of our studies on peptides containing noncoded amino acids with extremely bulky side chains[1-3] and on relations between the structure of these peptides and their physical[4-6] and biological[7] characteristics we directed our attention to neopentylglycine* (*III*, 2-amino-4,4-dimethylpentanoic acid). The side chain of this α--amino acid contains the sterically demanding tert-butyl group as well as tert-leucine-(2-amino-3,3-dimethylbutanoic acid), yet separated from the main peptide chain by one methylene group. Hence, the structure relation between tert-leucine and neopentylglycine is similar to that encountered with the pair of two coded amino acids, valine (showing a marked steric effect of the side chain) and leucine (with a distinct hydrophobic side chain).

The aim of this study has been the preparation of amino acid *III* in optically pure form, its transformation to protected derivatives used in conventional peptide synthesis and the synthesis of several model peptides suitable for the examination of the effect of the neopentyl side chain on the conformation and chiroptical properties of the peptide backbone.

The recorded[9,10] procedures of preparation of amino acid *III* in optically active form have made use both of enantioselective synthesis and of enzymatic resolution. We have developed two novel procedures of synthesis of racemate *III* and its resolution with optically active bases. The first procedure starts with 2-cyano-4,4-dimethyl--2-pentenoic acid[11] which is converted into 2-cyano-4,4-dimethylpentanoic acid by hydrogenation using a palladium catalyst. The nitrile group is subsequently trans-

* Coded amino acids are represented by conventional symbols (*cf.*[8]); Tle stands for tert-leucine and Neo for neopentylglycine.

formed to the amide group by treatment with hydrogen peroxide in an alkaline medium. The half-amide *II* formed is degraded to α-amino acid *III* in alkaline hypobromite. The second procedure uses 3,3-dimethylbutanoyl chloride to start with which is converted into the aldehyde *via* Rosenmund reduction; the aldehyde is then transformed by cyanohydrin synthesis with subsequent hydrolysis in hydrochloric acid to DL-neopentylglycine (*III*). Racemic compound *III* obtained by one of the above procedures was converted into formyl derivative *IV* and resolved into enantiomers by crystallization of the brucine salts. The optically active amino acids D-(−)-*III* and L-(+)-*III* were prepared by hydrolysis in 10% hydrochloric acid. The absolute configuration of the amino acid prepared follows both from a comparison with recorded data and from circular dichroism measurements and finally also from X-ray diffraction analysis of the cyclopeptide prepared from D-enantiomer *III* and L-proline (*cf.*[12,13]).



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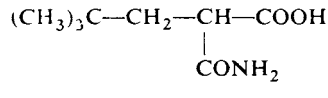
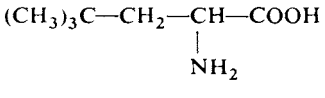
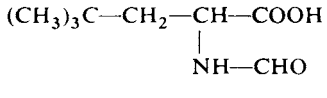


II



III



IV

N-Benzyloxycarbonyl-L-neopentylglycine, N-2-nitrobenzenesulfenyl-L-neopentylglycine and both enantiomers of N-tert-butyloxycarbonylneopentylglycine were prepared for further peptide synthesis by conventional procedures.

N-2-Nitrobenzenesulfenyl-L-neopentylglycine afforded the corresponding dipeptide *V* by condensation with glycine methyl ester using N,N'-dicyclohexylcarbodiimide. Dipeptide *V* from which the amino-protecting group had been removed was converted into 2-nitrobenzenesulfenyl-L-prolyl-L-neopentylglycyl-glycine methyl ester (*VI*) by reaction with N-2-nitrobenzenesulfenyl-L-proline. The ester group of tripeptide *VI* was transformed to the amide group in methanolic ammonia and the removal of the 2-nitrobenzenesulfenyl group afforded the terminal oxytocin tripeptide amide *VII* with L-neopentylglycine replacing L-leucine[14]. The enantiomers of N-tert-butyloxycarbonylneopentylglycine yielded after condensation with L-proline methyl ester using N,N'-dicyclohexylcarbodiimide the corresponding dipeptides *VIIIa* and *VIIIb* from which diastereoisomeric cyclodipeptides *IXa* and *IXb* were prepared by removal of the amino-protecting groups. To prepare N-acetyl-L-neopentylglycine methyl amide (*X*), free L-neopentylglycine was acetylated first with acetyl chloride, the N-acetyl derivative formed was converted into the activated ester (*p*-nitrophenyl) and the latter subjected to ammonolysis in methanolic methylamine solution.

Nps-L-Neo-Gly-OMe
V

Nps-L-Pro-L-Neo-Gly-OMe
VI

H-L-Pro-L-Neo-Gly-NH_2
VII

Boc-L-Neo-L-Pro-OMe
VIIIa

Boc-D-Neo-L-Pro-OMe
VIIIb

c(L-Neo-L-Pro)
IXa

c(D-Neo-L-Pro)
IXb

Ac-L-Neo-$NHCH_3$
X

EXPERIMENTAL

The melting points were determined in a Kofler block. The optical rotation measurements were carried out in Perkin–Elmer 141 polarimeter using concentrations of 0·2—0·5. The samples for elemental analysis were dried at room temperature *in vacuo* (130 Pa) over phosphorus pentoxide. The purity of the compounds was examined by thin layer chromatography on silica gel (Kieselgel G, Merck) in the systems 2-butanol–25% aqueous ammonia–water, 85 : 7·5 : 7·5, and 2-butanol–90% formic acid–water, 75 : 13·5 : 11·5. The compounds were detected by ninhydrin staining and chlorination. The samples in organic solvents were dried over magnesium sulfate and rotary evaporated.

2-Carbamoyl-4,4-dimethylpentanoic acid (*II*)

2-Cyano-4,4-dimethyl-2-pentenoic acid[11] (*I*, 3·9 g) was dissolved in 80 ml of glacial acetic acid and hydrogenated in the presence of palladium black. The hydrogen uptake after 11·5 h was 725 ml. The catalyst was filtered off, washed with acetic acid and the filtrate was taken to dryness. The residue (3·8 g, 98%) of oily 2-cyano-4,4-dimethylpentanoic acid was used in the subsequent step. The evaporated residue (2·5 g) in a solution of 2·1 g of potassium hydroxide in 6·3 ml of water was treated with 85 ml of 3% hydrogen peroxide at room temperature. The mixture was stirred 2 h, acidified with dilute (1 : 1) hydrochloric acid and concentrated to half its volume *in vacuo*. The crystals which had separated were filtered off; yield 1·4 g (50%), m.p. 150—151°C. For $C_8H_{15}NO_3$ (173·2) calculated: 55·47% C, 8·73% H, 8·09% N; found: 55·68% C, 8·56% H, 8·21% N.

D,L-Neopentylglycine (D,L-*III*)

A) Bromine (14·6 ml) was added at −5 to 0°C to a solution of 31·6 g of sodium hydroxide in 360 ml of water. The mixture was treated dropwise with a solution of 5·6 g of acid *II* in 40 ml of 1 mol l^{-1} sodium hydroxide. The mixture was stirred 2 h at 30—40°C, then coled down to room temperature, acidified with concentrated hydrochloric acid and taken to dryness *in vacuo*. The residue was evaporated twice with water, dissolved in the minimal volume of water and passed

over a Dowex-50 column. After the acidic effluents had emerged the column was eluted by 5% aqueous ammonia. The eluate was evaporated *in vacuo*; yield 4·7 g (100%) of *III*, m.p. 235–237°C (decomp.). For $C_7H_{15}NO_2$ (145·2) calculated: 57·90% C, 10·41% H, 9·65% N; found: 57·82% C, 10·62% H, 9·32% N.

B) 3,3-Dimethylbutanoyl chloride (10 g) was dissolved in 200 ml of toluene. To the solution 10 g of $Pd/BaSO_4$ was added and hydrogen was passed through the stirred mixture in a bath (temperature 120°C) for 5 h as long as hydrogen chloride was emerging from the mixture. The catalyst was removed from the mixture by filtration, then washed with toluene and the pooled toluene solutions used in the next reaction. To determine the yield one tenth of the toluene solution was used for the preparation of 2,4-dinitrophenylhydrazone, m.p. 131–133°C. For $C_{12}H_{16}N_4O_4$ (280·3) calculated: 51·42% C, 5·75% H, 19·99% N; found: 51·30% C, 5·79% H, 20·64% N. Judging by this yield the reduction of the chloride proceeded to 81%. A saturated aqueous solution of 10 g of potassium cyanide and 12 ml of concentrated aqueous ammonia solution were added to the main portion of the toluene solution. The mixture was heated 3 h at 50°C, cooled down and extracted with benzene. The benzene extract was dried and evaporated to dryness. The residue (5 g) was heated with 55 ml of concentrated hydrochloric acid 2 h in a boiling water bath. The mixture was then evaporated *in vacuo*, the residue dissolved in water and passed over a Dowex 50 column. The latter was eluted with 5% aqueous ammonia and the eluate evaporated *in vacuo*. The yield was 3·4 g (32%) of *III*, chromatographically homogeneous and identical with the compound prepared as described under *A*).

N-Formyl-D,L-neopentylglycine (D,L-*IV*)

Acid *III* (5·0 g) was dissolved in 70 ml of anhydrous formic acid and the solution was slowly treated with 24·1 g of acetic anhydride at 0–5°C. The mixture was stirred 2 h until its temperature went up to room temperature. Water (27 ml) was added afterwards and the mixture was evaporated *in vacuo*. The residue was crystallized from a mixture of ethanol and benzene; yield 5·6 g (93%), m.p. 162–163°C. For $C_8H_{15}NO_3$ (173·2) calculated: 55·47% C, 8·72% H, 8·08% N; found: 55·73% C, 8·71% H, 8·14% N.

Resolution: Formyl derivative *IV* (5 g) was dissolved in 16 ml of ethanol with heating and the solution was mixed with a hot brucine solution (13·3 g in 100 ml of ethanol). The mixture was allowed to stand in the refrigerator overnigh, the crystals which had separated were filtered off; portion A, 9·6 g, m.p. 145–146°C, $[\alpha]_D$ −10·6° (water), was purified by three-fold crystallization from ethanol till constant rotation $[\alpha]_D$ −8·0° (water), m.p. 159–161°C. The mother liquor remaining after filtration of portion A was evaporated to dryness; portion B, 8·24 g, m.p. 129 to 130°C, $[\alpha]_D$ −36·0° (water).

N-*Formyl*-L-*neopentylglycine* (L-IV): The brucine salt (8·2 g) of portion B was dissolved in 20 ml of water and 25 ml of 1 mol l^{-1} sodium hydroxide was added. Brucine which had separated was filtered off, was washed with water, the aqueous solution was evaporated to approximately 10 ml, was acidified with dilute (1 : 1) hydrochloric acid and set aside in a refrigerator for 0·5 h. The crystals which had separated were filtered off and washed with water; yield 1·4 g (56%), m.p. 175–177°C, $[\alpha]_D$ −13·0° (ethanol). For $C_8H_{15}NO_3$ (173·2) calculated: 55·47% C, 8·72% H, 8·08% N; found: 55·76% C, 8·76% H, 8·20% N.

N-*Formyl*-D-*neopentylglycine* (D-IV): Using the same procedure as for the L-enantiomer 6·5 g of the brucine salt of portion A afforded 1·55 g (62%) of D-*IV*, m.p. 176–178°C, $[\alpha]_D$ +14·9° (ethanol). Found: 55·40% C, 8·76% H, 7·97% N.

D-*Neopentylglycine* (D-III): A suspension of 1·59 g of derivative D-*IV* in 16 ml of 10% hydrobromic acid was heated 2 h in a boiling water bath, then taken to dryness, the residue evaporated

twice with water, dissolved in a small volume of water and passed over a Dowex 50 column. After the acidic effluents had emerged amino acid D-*III* was eluted by 5% aqueous ammonia and the eluate was evaporated *in vacuo*; yield 1·3 g (100%), m.p. 259–260°C, $[\alpha]_D$ −14·9° (acetic acid). For $C_7H_{15}NO_2$ (145·2) calculated: 57·90% C, 10·41% H, 9·65% N; found: 57·67% C, 9·80% H, 9·77% N.

L-*Neopentylglycine* (L-III): Using the same procedure as for the D-enantiomer 1·33 g of L-*IV* afforded 1·1 g of L-*III* (100%), m.p. 258–259°C, $[\alpha]_D$ +14·7° (acetic acid). Found: 57·65% C, 10·64% H, 9·40% N. CD spectrum, 0·01 mol l^{-1} HCl (*c* 0·01): λ_{max} 207 nm ($\Delta\varepsilon$ +1·37).

N-Benzyloxycarbonyl-L-neopentylglycine

L-Neopentylglycine (L-*III*) (0·6 g) was dissolved in a solution of 0·5 g of sodium hydroxide in 12 ml of water and 0·9 ml of benzyloxycarbonyl chloride was added with stirring. The mixture was stirred 2 h at room temperature, extracted with ether, the aqueous layer was acidified with dilute (1 : 1) hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated. The oily residue was dissolved in ether and the dicyclohexylammonium salt was precipitated; m. p. 154–155°C, $[\alpha]_D$ −12·5° (methanol), yield 0·9 g (55%). For $C_{27}H_{44}N_2O_4$ (460·6) calculated: 70·39% C, 9·62% H, 6·08% N; found: 70·53% C, 9·83% H, 6·06% N.

N-2-Nitrobenzenesulfenyl-L-neopentylglycine

2-Nitrobenzenesulfenyl chloride (0·6 g) was added stepwise to a solution of L-*III* (0·5 g) in 1·5 ml of 2 mol l^{-1} sodium hydroxide and 4 ml of dioxane at pH 8·8. The mixture was then stirred 30 min, diluted with 30 ml of water and extracted with ether. The mixture was acidified with 0·5 mol l^{-1} sulfuric acid and again extracted with ether, the extract was dried and evaporated. The residue (0·9 g, 87%) was dissolved in ether and the dicyclohexylammonium salt was precipitated; m.p. 163–165°C, $[\alpha]_D$ −49·7° (dimethylformamide). For $C_{25}H_{40}N_3O_4S$ (478·7) calculated: 62·73% C, 8·42% H, 8·78% N; found: 62·75% C, 8·62% H, 8·55% N.

N-Tert-butyloxycarbonyl-L-neopentylglycine

A solution of 0·9 g of sodium hydrogen carbonate in 3·5 ml of water and 0·9 g of ditert-butyl dicarbonate were added to a solution of 0·5 g of L-*IV* in 7 ml of dioxane and 3·5 ml of water. The mixture was stirred at room temperature 2 h, then extracted with ether, the aqueous layer was acidified with citric acid and again extracted with ether. This ether extract was dried and evaporated. The residue crystallized after the addition of petroleum ether; yield 0·76 g (90%), m.p. 102–103°C, $[\alpha]_D$ +14·0° (methanol). For $C_{12}H_{23}NO_4$ (245·3) calculated: 58·75% C, 9·45% H, 5·71% N; found: 58·96% C, 9·32% H, 5·82% N.

N-Tert-butyloxycarbonyl-D-neopentylglycine was prepared by the same procedure as the L-enantiomer in an almost quantitative yield, m.p. 102–103°C, $[\alpha]_D$ −12·2° (methanol). Found: 58·52% C, 9·72% H, 5·52% N.

2-Nitrobenzenesulfenyl-L-neopentylglycyl-glycine methyl ester (*V*)

The dicyclohexylammonium salt of 2-nitrobenzenesulfenyl-L-neopentylglycine (0·6 g) in dichloromethane (10 ml) was mixed with glycine methyl ester hydrochloride (0·13 g), cooled down to −10°C and 0·25 g of N,N'-dicyclohexylcarbodiimide was added. The mixture was stirred 15 min at −10°C and set aside overnight in a refrigerator. N,N'-Dicyclohexylurea which had separated

was filtered off, the solution was washed with 0·5 mol l^{-1} sulfuric acid and with saturated sodium hydrogen carbonate solution, then with water, was dried afterwards and evaporated. The residue was dissolved in ether and petroleum ether was added to precipitate the product. The latter was filtered off; yield 0·45 g (99%), m.p. 74–75°C, $[\alpha]_D$ −37·7° (dimethylformamide). For $C_{16}H_{23}N_3O_5S$ (369·4) calculated: 52·02% C, 6·27% H, 11·37% N; found: 52·05% C, 6·29% H, 11·41% N.

2-Nitrobenzenesulfenyl-L-prolyl-L-neopentylglycyl-glycine methyl ester (*VI*)

To a solution of ester *V* (0·8 g) in methanol (10 ml) 10 ml of 3 mol l^{-1} hydrogen chloride in ether was added. The mixture was evaporated after 5 min, the residue was digested with petroleum ether and the remaining oil was dried in a desiccator over potassium hydroxide. Yield 0·57 g (99%) of L-neopentylglycyl-glycine methyl ester hydrochloride. The product is homogeneous when subjected to TLC and was used for the subsequent reaction. In the latter it was dissolved (0·53 g) in dichloromethane (60 ml), the solution was treated with 0·92 g of the dicyclohexylammonium salt of N-2-nitrobenzenesulfenyl-L-proline and, after being cooled down to −10°C, with 0·44 g of N,N′-dicyclohexylcarbodiimide. The mixture was stirred 15 min at −10°C and then set aside overnight in a refrigerator. N,N′-Dicyclohexylurea which had separated was filtered off, the solution was extracted with 0·5 mol l^{-1} sulfuric acid, then with a saturated solution of sodium hydrogen carbonate and water. It was dried and evaporated afterwards. The residue had crystallized from dichloromethane–petroleum ether. Yield 1·0 g (100%) m.p. 163–164°C, $[\alpha]_D$ −15·7° (dimethylformamide). For $C_{21}H_{30}N_4O_6S$ (466·6) calculated: 54·06% C, 6·48% H, 12·01% N; found: 54·57% C, 6·54% H, 12·23% N.

2-Nitrobenzenesulfenyl-L-prolyl-L-neopentylglycyl-glycine amide

Methyl ester *VI* (1·0 g) was dissolved in methanolic ammonia (25 ml, 2 mol l^{-1}) and the solution was let standing 24 h at room temperature. The mixture was evaporated afterwards and the residue was allowed to crystallize from a mixture of ethanol and ether. Yield 0·75 g (77%), m.p. 101–103°C, $[\alpha]_D$ −12·8° (dimethylformamide). For $C_{20}H_{29}N_5O_5S$ (451·5) calculated: 53·20% C, 6·47% H, 15·51% N; found: 53·53% C, 6·26% H, 15·29% N.

L-Prolyl-L-neopentylglycyl-glycine amide hydrochloride (*VII*)

The preceding tripeptide amide (0·6 g) was dissolved in 20 ml of methanol and 10 ml of 0·6 mol . . l^{-1} hydrogen chloride in methanol was added. The reaction was complete after 5 min according to TLC. The mixture was evaporated, the residue was dissolved in water, the solution was filtered over active charcoal and lyophilized. Yield 0·4 g (90%) of *VII*, $[\alpha]_D$ +54° (water). For $C_{14}H_{27}N_4O_3 \cdot H_2O$ (352·9) calculated: 47·65% C, 8·28% H, 15·87% N; found: 48·02% C, 8·25% H, 15·26% N.

Cyclo(D-neopentylglycyl-L-prolyl) (*IXb*)

L-Proline methyl ester di(*p*-toluenesulfone)imide (2·5 g), 0·6 ml of triethylamine and 1·3 g of N,N′-dicyclohexylcarbodiimide were added at −10°C to 0·8 g of N-tert-butyloxycarbonyl-D--neopentylglycine dissolved in 20 ml of dichloromethane. The mixture was stirred 15 min and set aside for 2 days in the refrigerator. N,N′-Dicyclohexylurea which had separated was filtered off, the dichloromethane solution was extracted with 20% aqueous citric acid, then with a saturated solution of sodium bicarbonate and water. The solution was dried and evaporated afterwards.

The residue was dissolved in 25 ml of trifluoroacetic acid, set aside for 10 min and then evaporated. The residue was dissolved in methanolic ammonia (25 ml, 2 mol l^{-1}), set aside overnight, evaporated and then passed in 50% aqueous methanol over columns of Dowex 50 and Amberlite IR-4B. The eluate was evaporated; yield 0·3 g (39%), $[\alpha]_D$ −54·2° (dimethylformamide), m.p. 158—160°C. For $C_{12}H_{20}N_2O_2$ (224·3) calculated: 64·25% C, 8·99% H, 12·49% N; found: 64·50% C, 9·15% H, 12·12% N.

Cyclo(L-neopentylglycyl-L-prolyl) (*IXa*)

Using 0·43 g of N-tert-butyloxycarbonyl-L-neopentylglycine and the same procedure as for compound *IXb* the linear dipeptide ester was prepared. Its cyclization afforded 0·15 g of cyclopeptide *IXa*, $[\alpha]_D$ −36·8° (dimethylformamide), m.p. 193—195°C. For $C_{12}H_{20}N_2O_2$ (224·3) calculated: 64·25% C, 8·99% H, 12·49% N; found: 64·70% C, 8·91% H, 12·01% N.

Acetyl-L-neopentylglycine

Acetyl chloride (0·15 g) was added with stirring at −10°C to L-neopentylglycine (0·25 g) dissolved in 3 ml of 2 mol l^{-1} sodium hydroxide. The mixture was stirred 2 h at room temperature; it solidified afterwards. It was then acidified with 1 mol l^{-1} hydrochloric acid and extracted with ethyl acetate. The extract was dried and evaporated. The residue (0·2 g) was allowed to crystallize from ethanol–ether; m.p. 224—225°C, yield 0·12 g (37·5%), $[\alpha]_D$ 0° (dimethylformamide). For $C_9H_{17}NO_3$ (197·2) calculated: 57·73% C, 9·15% H, 7·48% N; found: 57·63% C, 9·27% H, 7·63% N.

N-Acetyl-L-neopentylglycine methyl amide (*X*)

A solution of 0·1 g of the preceding acetyl derivative in 10 ml of dichloromethane was treated 10 min with stirring at −10°C with 0·08 g of 4-nitrophenol and with 0·12 g of N,N'-dicyclohexylcarbodiimide. The mixture was then stirred 15 min at −10°C and set aside overnight at 5°C. N,N'-Dicyclohexylurea which had separated was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in methanol and a methanolic solution of methylamine (0·4 g in 10 ml) was added. The mixture was set aside overnight in refrigerator, evaporated *in vacuo* and the residue dissolved in dichloromethane. The solution was stepwise extracted with 1 mol l^{-1} hydrochloric acid, with a saturated solution of sodium hydrogen carbonate (as long as the extract was yellow-tinged) and with water. The extract was then dried and evaporated. The residue was allowed to crystallize from dichloromethane–petroleum ether; yield 0·09 g (90%), m.p. 158—159°C, $[\alpha]_D$ −15·8° (dimethylformamide). For $C_{10}H_{20}N_2O_2$ (200·3) calculated: 59·97% C, 10·06% H, 13·99% N; found: 60·36% C, 10·33% H, 13·53% N.

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