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SYNTHESIS OF N^4-DIALKYL-L-ASPARAGINE AND N^5-DIALKYL-L-GLUTAMINE DERIVATIVES

APPLICATION TO THE SYNTHESIS OF RELATED PEPTIDES[1]

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Abstract—A general and convenient method for the preparation of N^4-dialkyl-L-asparagine and N^5-dialkyl-L-glutamine derivatives is described. The applicability of these derivatives in the preparation of related peptides is illustrated by the syntheses of N^2 - carbobenzoxy - (N^4 - dimethyl) - L - asparaginyl - (S - benzyl) - L - cysteinyl - L - prolyl - L - leucylglycine amide and N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutaminyl - L - asparaginyl - (S - benzyl) - L - cysteinyl - L - prolyl - L - leucylglycine amide in satisfactory yields.

While [glutamic acid^4] oxytocin[2] exhibits an extremely low level of activities of the parent hormone, [N^4-methyl-L-asparagine^4] oxytocin, a glutamine isomer of oxytocin, retains a high potency as compared with the former.[3] As the study of the structure-activity relationships of neurohypophyseal hormones is reaching the long-standing goal of predicting the effects of changes, it is clear that positions 4 and 5 are of crucial importance[4] for biological activity. Hence we became interested in analogs of glutamine and asparagine, bearing modified carboxamide groups and derivatives of N^4-dialkyl-L-asparagine and N^5-dialkyl-L-glutamine have been synthesised and used successfully for the preparation of related peptides.

RESULTS AND DISCUSSION

Several years ago Meister[5] reported that condensation of N^2-carbobenzoxy-L-γ-glutamylhydrazide, via its azide, with dimethylamine afforded a colorless oil, which upon catalytic hydrogenation gave N^5-dimethyl-L-glutamine in 30% yield (based on the hydrazide used). Its structure was confirmed by microanalytical data, but no m.p. and optical value of the aforementioned product was given.

In an other communication we described the coupling of N-trityl or N-carbobenzoxyglycine with alkylamine hydrochlorides, via the mixed anhydride method, to yield the corresponding N-alkylamido derivatives in good yields.[6] We now wish to establish the potential utility of this procedure for the synthesis of the desired N-dialkylcarboxamide derivatives of L-glutamine and L-asparagine. Accordingly, α-benzyl N^2-carbobenzoxy-L-glutamate[7] was coupled by the mixed anhydride method with dimethylamine hydrochloride, in the presence of triethylamine, to give crystalline α-benzyl N^2-carbobenzoxy-(N^5-dimethyl)-L-glutaminate (**1**) in 70% yield. Its structure was confirmed by microanalytical and spectral data.

Treatment of **1** with dilute lithium hydroxide hydrolysed the α-benzyl group to afford, after acidification, N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutamine (**2**), which was isolated in crystalline form. Proof that saponification occurred only at the α-carboxyl group, was established spectroscopically.

As the next step, the incorporation of **2** into a peptide chain either by the *p*-nitrophenyl active ester[8] or the N-hydroxybenzotriazole method[9] was investigated. Thus, treatment of **2** with *p*-nitrophenol and DCCI in the usual way, produced *p*-nitrophenyl N^2-carbobenzoxy-(N^5-dimethyl)-L-glutaminate (**3**) in crystalline form, which was coupled to H-Asn-Cys (Bzl)-Pro-Leu-Gly-NH_2 to give N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutaminyl - L - asparaginyl - (S - benzyl) - L - cysteinyl - L - prolyl - L - leucylglycine amide (**4**) in 62% yield. Alternatively, the same coupling product **4** was secured, using the N-hydroxy-benzotriazole method for the condensation of N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutamine (**2**) with H-Asn-Cys(Bzl) - Pro - Leu - Gly - NH_2, in 75% yield. Both hexapeptide derivatives behaved as single, homogeneous compounds, when checked by thin layer chromatography in several solvent systems; furthermore, they gave the expected amino acid values following acid hydrolysis. The ^{1}H NMR spectra of these derivatives show characteristically a doublet at δ 2.99 for the Me_2N group.

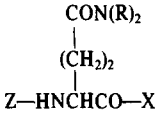
Other dialkylamido derivatives of L-glutamine and L-asparagine, prepared in an analogous fashion, are listed in Tables 1 and 2. As the N^2 - carbobenzoxy - (N^4 - dialkyl) - L - asparagine derivatives were oils, brief treatment of them with dicyclohexylamine afforded crystalline salts (Table 2).

Condensation of N^2 - carbobenzoxy - (N^4 - dimethyl) - L - asparagine either by the N - hydroxybenzotriazole or the *p* - nitrophenyl ester method, with H-Cys(Bzl)-Pro-Leu-Gly-NH_2, provided the desired N^2 - carbobenzoxy - (N^4 - dimethyl) - L - asparaginyl - (S - benzyl) - L - cysteinyl - L - leucylglycine amide (**5**) in pure form and satisfactory yields.

Extension of the peptide chains of **4** and **5** from the N-terminal end would require removal of the N^2-carbobenzoxy group; therefore, the stability of the dimethylcarboxamide moiety under the conditions used for cleavage of the N-carbobenzoxy group with HBr/AcOH was examined. Thus, treatment of N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutamine with 2N HBr/AcOH afforded N^5 - dimethyl - L - glutamine hydrobromide almost in theoretical yield.

As expected, the γ- and β-dialkylamido groups of

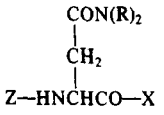
Table 1. N^2 - carbobenzoxy - (N^5 - dialkyl) - L - glutamine derivatives[a]



R	X	Mp, °C	$[a]_D^{24}$ [b]	Yield%
C_2H_5	OBzl	62-63[c]	-21.1°	70
C_2H_5	OH	129-130[d]	-6.7°	60
C_3H_7	OH[e]	84-85[c]	-7.9°	57
C_2H_5	ONp	87-88[d]	+2.3°	77

[a]Analytical data were within ±0.4% for C, H, N. [b]As 2% solution in DMF. [c]Recrystallised from ether. [d]Recrystallised from ethyl acetate. [e]This compound was obtained from the correspond oily benzyl ester.

Table 2. N^2 - carbobenzoxy - (N^4 - dialkyl) - L - asparagine derivatives[a]



R	X	Mp, °C	$[a]_D^{24}$	Yield%
CH_3	OH[b]	117-118[c]	-45.1°[d]	70
C_2H_5	OH[b]	128-129[e]	+13.2°[d]	75
CH_3	ONp	122-123[f]	-3.1°[g]	63

[a]Analytical data were within ±0.4% for C, H, N. [b]Isolated as the dicyclohexylammonium salt. [c]Recrystallised from ethyl acetate-ether. [d]As 1% solution in EtOH. [e]Recrystallised from aceton. [f]Recrystallised from ethyl acetate. [g]As 2% solution in DMF.

L-glutamine and L-asparagine, respectively, are stable under reductive conditions with sodium in liquid ammonia.[10] Indeed, the reduced compound **1**, provided N^5-dimethyl-L-glutamine (**6**) identical with that obtained by catalytic hydrogenolysis of **1** over palladium black. Also, it should be mentioned that N^5-dimethyl-L-glutamine remained unaffected, when it was exposed to trifluoroacetic acid for 1 hr at room temperature.

In an effort to provide derivatives suitable for the preparation of N-terminal N^5-dialkyl-L-glutamine and N^4-dialkyl-L-asparagine peptides, α-benzyl N^2-trityl-L-aspartate[11] and α-benzyl N^2-trityl-L-glutamate[12] were condensed with dimethylamine, as previously described. In both cases the resulting products were oils not homogeneous according to thin layer chromatography. As repeated trials for crystallisation failed, chromatographic separation on silica gel secured a high degree of purity of the desired products. Although, α-benzyl N^2 - trityl - (N^4 - dimethyl) - L - asparaginate (**7**) and α-benzyl N^2 - trityl - (N^5 - dimethyl) - L - glutaminate (**8**) were obtained finally in rather low yields, they constitute, however valuable intermediates for the synthesis of C-terminal N^4-dimethyl-L-asparagine and N^5-dimethyl-L-glutamine peptides. Indeed, detritylation of **7** and **8** with *p*-toluenesulfonic acid afforded α-benzyl N^4-dimethyl-L-asparaginate (**9**) and α-benzyl N^5-dimethyl-L-glutaminate (**10**) p-*toluenesulfonates* in good yields (Experimental).

EXPERIMENTAL

M.ps were taken on a Buchi SMP-20 capillary m.p. apparatus and are uncorrected. Microanalyses were performed by the Laboratory of Microanalysis of National Hellenic Research Foundation, Athens, Greece. Optical rotations were determined with a Carl Zeiss precision polarimeter (0.005°). NMR spectra were obtained with a Hitachi Perkin-Elmer R-24 (60-MHz) spectrometer in $CDCl_3$. Chemical shifts are reported in δ units using TMS as the internal standard. IR spectra were recorded with a Hitachi Perkin-Elmer 457 Grating Infrared spectrophotometer. Tlc was carried out on silica gel SiF chromatogram sheets with the solvent system I (BAW), 1-butanol-acetic acid-water (4:1:5) and II (BE), benzene-ethanol (8:2) and visualised by UV, ninhydrin and chlorine-tolidine reagent.

α - Benzyl - N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutaminate (**1**)

To a chilled soln of α - benzyl - N^2 - carbobenzoxy - L - glutamate (5.56 g, 15 mmol) and triethylamine (1.5 g, 15 mmol) in THF (30 ml) was added 1.65 g (15 mmol) of ethylchlorocarbonate. After 2 min a soln of dimethylamine hydrochloride

(3.67 g, 200% excess) and triethylamine (4.5 g) in 10 ml of THF–H_2O (7:3) was added with vigorous shaking. The mixture was kept at room temp for 30 min and the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc, washed with 5% $NaHCO_3$, H_2O, and dried (Na_2SO_4). The solvent was removed and the remaining oily product was solidified from petroleum ether and cooling. Recrystallisation from EtOH gave 4.2 g (70%) of product; m.p. 68–70°; $[\alpha]_D^{22}$ −22.3° (*c*, 2, DMF); IR (KBr), 3320 (NH), 1750 (ester C–O), 1690 (carbobenzoxy C–O), 1640 (N-alkylamido C–O), 1530 cm^{-1}; NMR ($CDCl_3$) δ 2.9 (d, 6H, $N(CH_3)_2$), 5.1–5.2 (two singlets, 4H, $ArCH_2OCON$, $ArCH_2OCO$), 7.3 (s, 10H, $2C_6H_5$). (Found: C, 66.59; H, 6.55; N, 7.19. Calc. for $C_{22}H_{26}N_2O_5$: C, 66.33; H, 6.53; N, 7.04%).

N^2 - *Carbobenzoxy* - (N^5 - *dimethyl*) - L - *glutamine* (**2**)

To a soln of **1** (1.99 g, 5 mmol) in 20 ml MeOH was added LiOH (130 mg, 5% excess) in 5 ml water with stirring for 4 hr at room temp. The MeOH was removed *in vacuo*, the residue diluted with 50 ml water and washed twice with EtOAc. The aqueous phase was further diluted to 100 ml, cooled to 0° and acidified with N HCl to pH 1.5. The product, which separated as an oil, was extracted with EtOAc. The organic phase was washed repeatedly with water, dried (Na_2SO_4) and the solvent was evaporated *in vacuo* leaving an oil, which solidified upon addition of ether. Recrystallisation from EtOAc gave 1.06 g (69%) of product; m.p. 118–120°; $[\alpha]_D^{20}$ −4.8° (*c*, 2, DMF); IR (KBr), 3320 (NH), 2800–3000 (carboxylic OH), 1730 (carboxylic C–O), 1690, 1640 (N-alkylamido C–O), 1530 cm^{-1}; NMR ($CDCl_3$, δ 2.95 (d, 6H, $N(CH_3)_2$), 5.1 (s, 2H, $ArCH_2OCON$), 6.1 (br d, 1H, OCONH, D_2O exchangeable), 7.3 (s, 5H, C_6H_5), 8.25 (br s, 1H, COOH, D_2O exchangeable). (Found: C, 58.12; H, 6.18; N, 8.83. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.44; H, 6.49; N, 9.09%).

p-Nitrophenyl N^2 - *carbobenzoxy* - (N^5 - *dimethyl*) - L - *glutaminate* (**3**)

To a soln of N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutamine (4.0 g, 13 mmol) in EtOAc (25 ml), *p*-nitrophenol (2.0 g, 15% excess) and N,N'-dicyclohexylcarbodiimide (2.6 g, 13 mmol) were added. The mixture was kept at room temp for 2 days. The N,N'-dicyclohexylurea, which separated out, was filtered off and washed with EtOAc. The combined filtrates were evaporated to dryness, leaving an oil, which was crystallised from EtOAc-ether. Recrystallisation from EtOH gave 4.2 g (76%); m.p. 103–104°; $[\alpha]_D^{20}$ −2.9° (*c*, 2, DMF); IR (KBr), 3300, 1765, 1720, 1640, 1520 cm^{-1}; NMR ($CDCl_3$), δ 2.9 (d, 6H, $N(CH_3)_2$), 5 (s, 2H, $ArCH_2$), 6.1 (br d, 1H, OCONH, D_2O exchangeable) 7.2 (s, 5H, C_6H_5), 8.1 (d, J ~ 10 Hz, 2H, ortho to NO_2). (Found: C, 58.56; H, 5.10; N, 9.73. Calc. for $C_{21}N_{23}N_3O_7$: C, 58.74: H, 4.90;d N, 9.80%)

N^2 - *Carbobenzoxy* - (N^5 - *dimethyl*) - L - *glutaminyl* - L - *asparaginyl* - (*S* - *benzyl*) - L - *cysteinyl* - L - *prolyl* - L - *leucylglycine amide* (**4**)

(A) In 5 ml CF_3COOH, containing 1 ml anisole was added N - t - Boc - Asn - (S - bzl)Cys - Pro - Leu - Gly - NH_2 (4.15 g, 6 mmol), m.p. 213–215°, $[\alpha]_D^{20}$ −54° (*c*, 1, DMF), and the resulting soln kept for 1 hr at room temp. The volatile components were removed *in vacuo* and the oily residue solidified by addition of ether. The product was filtered, washed with ether and dried over P_2O_5; yield 4.1 g (97%). To a soln of N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutamine (2.0 g, 6.5 mmol) and 1-hydroxybenzotriazole (0.88 g, 6.5 mmol) in DMF (5 ml) cooled at 0° for 0.5 hr, was added N,N'-dicyclohexylcarbodiimide (1.34 g, 6.5 mmol). The mixture was kept for 0.5 hr at 0° and then mixed with 3.53 g (5 mmol) of the above peptide trifluoroacetate and N-methylmorpholine (0.5 g) in DMF (10 ml). After 10 hr at room temp the mixture was filtered from the precipitated N,N'-dicyclohexylurea and the solvent evaporated *in vacuo*. The remaining oily residue solidified on addition of water (60 ml) while cooling. The solid product was filtered, washed with 5% $NaHCO_3$ (50 ml), water and a mixture of EtOAc–ether. Trituration with EtOAc–EtOH (2:1) under reflux and addition of ether gave 3.3 g (75%) of product; m.p. 169–172°; $[\alpha]_D^{22}$ −52.02° (c, 1, DMF).

Amino acid analysis gave the following molar ratios: Asp, 1.00; Glu, 1.03; Pro, 1.02; Gly, 1.00; Leu, 1.02; Cys (Bzl), 0.90; NH_3, 1.97. (Found: C, 56.86; H, 6.72; N, 14.19. Calc. for $C_{42}H_{59}N_9O_{10}S$: C, 57.21; H, 6.7; N, 14.3%).

(B) The same hexapeptide derivative was obtained by condensation of *p*-nitrophenyl N^2 - carbobenzoxy - (N^5 - dimethyl) - L - glutaminate (2.37 g, 5 mmol, 10% excess) with H - Asn - (S - bzl)Cys - Pro - Leu - Gly - NH_2 (3.53 g, 5 mmol) in DMF for 40 hr. The desired product (2.73 g, 62%) had m.p. 169–171°; $[\alpha]_D^{24}$ −52.3° (*c*, 1, DMF).

N^2 - *Carbobenzoxy* - (N^4 - *dimethyl*) - L - *asparaginyl* - (*S* - *benzyl*) - L - *cysteinyl* - L - *prolyl* - L - *leucylglycine amide* (**5**)

(A) A portion of N - t - Boc - (S - bzl)Cys - Pro - Leu - Gly - NH_2 (3 g, 5.2 mmol), m.p. 172–173°, $[\alpha]_D^{20}$ −52.3° (*c*, 1, DMF), was treated with F_3CCOOH (4 ml) and anisole (1 ml) for 1 hr. The volatile components were removed *in vacuo* and the remaining oil was solidified from ether. The solid was filtered off, washed with ether, dried over P_2O_5 and was allowed to react with *p* - nitrophenyl - N^2 - carbobenzoxy - N^4 - dimethyl - L - asparaginate (2.3 g, 10% excess) in 10 ml DMF, containing 0.5 g of N-methylmorpholine. After 35 hr the solvent was evaporated *in vacuo* and the remaining oily residue solidified by addition of water (60 ml) while cooling. The solid product was filtered off, washed with 5% $NaHCO_3$ (50 ml) and water. Trituration with ether and EtOAc–ether gave 2.26 g (60%) of product, m.p. 161–163°; $[\alpha]_D^{20}$ −65° (*c*, 1, DMF).

Amino acid analysis gave the following molar ratios: Asp, 1.00; Pro, 0.99; Gly, 1.01; Leu, 1.00; Cys(bzl), 0.91; NH_3, 0.95. (Found: C, 58.49; H, 6.70; N, 12.78. Calc. for $C_{37}H_{52}N_7O_8S$: C, 58.88; H, 6.9; N, 13.0%).

(B). Coupling of N^2 - carbobenzoxy - (N^4 - dimethyl) - L - asparaginate (1.3 g, 4.4 mmol) with N - t - Boc - (S - bzl)Cys - Pro - Leu - Gly - NH_2 (2 g, 3.2 mmol) by the N-hydroxybenzotriazole method, as previously described provided 2 g (82%) of product, m.p. 163–165°; $[\alpha]_D^{20}$ −64.3° (*c*, 1, DMF).

N^5 - *Dimethyl* - L - *glutamine* (**6**)

A soln of 1.1 g of **1** in 90% isopropanol was hydrogenated over PdO (150 mg). After 2 hr the catalyst was filtered off, the soln evaporated *in vacuo* and the remaining residue was solidified by addition of 50 ml acetone-ether (1:10); yield 0.4 g (80%); m.p. 167–169°. Besides the main product a faint spot, moving at the position of pyroglutamic acid† was revealed by TLC. Purification from water-acetone-ether (1:20:20) gave a single spot; m.p. 173–174°; $[\alpha]_D^{24}$ −11.3° (c, 2, water). (Found: C, 48.13; H, 8.12; N, 16.20. Calc. for $C_7H_{14}N_2O_3$: C, 48.29; H, 8.04; N, 16.09%).

α-Benzyl N^2 - *trityl* - (N^4 - *dimethyl*) - L - *asparaginate* (**7**).

To a soln of α-benzyl N^2 - trityl - L - aspartate[11] (0.93 g, 2 mmol) in THF (20 ml) cooled to −10°, were added triethylamine (0.2 g, 2 mmol) and ethyl chlorocarbonate (0.22 g, 2 mmol). After 3 min a soln of dimethylamine hydrochloride (0.48 g, 200% excess) in 10 ml of THF–H_2O (6:4) was neutralised with triethylamine (0.6 g, 6 mmol) and added immediately with vigorous shaking. Half an hour later the solvent was evaporated to dryness and the residue was taken up in CH_2Cl_2 (100 ml). This soln was washed with 3 × 50 ml of 5% $NaHCO_3$, then with water and dried (Na_2SO_4). After removal of the solvent the residue (0.96 g, 98%) was purified through a 4 × 70 cm column of silica gel (120 g) using benzene–EtOH (95:5) as the eluant. An oily compound homogeneous to thin layer chromatography (0.61 g, 63%) was obtained; NMR ($CDCl_3$) δ 2.3 (t, 2H, CH_2CO), 2.75 (d, 6H, $N(CH_3)_2$), 4.8 (s, 2H, $ArCH_2$), 7.1–7.6 (poorly resolved signal, 20 H, aromatic protons).

α-Benzyl N^2 - *trityl* - (N^5 - *dimethyl*) - L - *glutaminate* (**8**)

This compound was prepared in a manner similar to that used in the synthesis of α-benzyl N^2 - trityl - (N^4 - dimethyl) - L -

†As the starting material **1** was chromatographically pure, the appearance of pyroglutamic acid may be due to a nucleophilic attack on the carbonyl of the N-dimethylamide by the α-amino group, provided that there is a difference in the hydrogenolysis rate between N-cbzo and O-benzyl group.

asparaginate and purified through a 4 × 70 cm column of silica gel (120 g) using benzene–EtOH (95:5) as the eluant. The obtained oily product was homogeneous according to tlc (0.6 g, 59%); NMR ($CDCl_3$) δ 2.2 (br signal, 4H, CH_2CH_2), 2.8 (d, 6H, $(CH_3)_2$, 7.1–7.6 (poorly resolved signal, 20H, aromatic protons).

α-Benzyl (N^4 - *dimethyl*) - L - *asparaginate* - p - *toluenesulfonate* (**9**)

A mixture of oily α-benzyl N^2 - trityl - (N^4 - dimethyl) - L - asparaginate (0.35 g, 0.71 mmol) and *p*-toluenesulfonic acid *monohydrate* (0.150 g, 0.78 mmol) in EtOH (2 ml) was heated for 5 min under reflux. The solvent was evaporated, ether (100 ml) was added and the resulting product was solidified on scratching and cooling (0.25 g, 83%); m.p. 101–103°. Crystallisation from EtOH afforded 0.21 g (70%) of product; m.p. 110–111°; $[\alpha]_D^{24}$ + 47.2° (*c*, 1, EtOH). (Found: C, 56.99; H, 6.25; N, 6.50. Calc. for $C_{20}H_{26}N_2O_6S$: C, 56.87; H, 6.16; N, 6.63%).

α - Benzyl (N^5 - *dimethyl*) - L - *glutaminate* - p - *toluenesulfonate* (**10**)

The oily α-benzyl N^2 - trityl - (N^5 - dimethyl) - L - glutaminate (0.6 g, 18 mmol) was detritylated as above to give 0.4 g (77%) of product; m.p. 100–101° (after recrystallisation from EtOAc; $[\alpha]_D^{24}$ + 54.2° (*c*, 1, EtOH). (Found: C, 58.1; H, 6.48; N, 6.38. Calc. for $C_{21}H_{28}N_2O_6S$: C, 57.8; H, 6.42; N, 6.42%).

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