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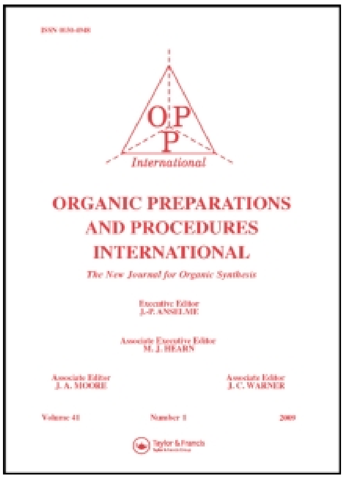

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AN IMPROVED SYNTHESIS OF METHYL- AND BENZYL-ESTERS AS WELL AS HYDRAZIDE OF L-PYROGLUTAMYL-L-HISTIDYL-L-TRYPTOPHAN

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The title compounds, pGlu-His-Trp-OMe, pGlu-His-Trp-OBzl and pGlu-His-Trp-$NHNH_2$ are useful in the synthesis of gonadoliberin and/or its analogs. pGlu-His-Trp-OMe has been synthesized from pGlu-His-$NHNH_2$ and HCl·Trp-OMe by the azide method[1,2] which is known to be difficult.[3] pGlu-His-Trp-OBzl can easily be synthesized from pGl-His-OH and HCl·Trp-OBzl using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt).[4] However, pGlu-His-OH is hygroscopic,[5] and therefore not convenient to handle. The yield of pGlu-His-Trp-OBzl, calculated on pGlu-His-OMe as a starting material for pGlu-His-OH does not exceed 69%.[5] pGlu-His-Trp-$NHNH_2$ was obtained as a hemi-hydrate in 79% yield by hydrazinolysis of pGlu-His-Trp-OMe for 60 hrs in a large volume (1000 ml/15 mmol) of methanol.[1] The hydrazide hemi-hydrate is unstable and a stable, water-free product could not be obtained.

We present simpler and higher yield syntheses of the title compounds. pGlu-His-Trp-OMe or pGlu-His-Trp-OBzl was obtained from pGlu-His-OMe and HCl·Trp-OMe or HCl·Trp-OBzl, respectively, in a "one-pot" reaction with the following simple modification:[6] pGlu-His-ONa resulting from pGlu-His-OMe after alkaline hydrolysis was neutralized, *in situ*, not with an ion exchanger as in the case of pGlu-His-OH preparation[5] but with HCl·Trp-OM or HCl·Trp-OBzl. In that way the preparation of pGlu-His-OH and Trp-OMe or TrP-OBzl was omitted. The mixture of pGlu-His-OH and Trp-ester readily gave the desired tripeptide in the presence of DCC/HOBt. Hydrazinolysis of pGlu-His-Trp-OMe in a small amount of dimethylformamide led to the

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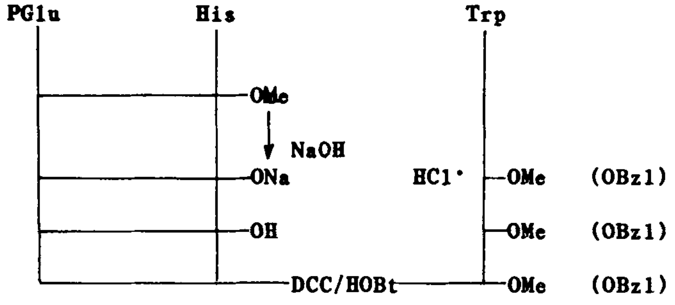
stable, anhydrous hydrazide.



EXPERIMENTAL SECTION

Melting points were determined on a Boetius apparatus and are uncorrected. Optical rotations were measured on a Zeiss polarimeter Model Polamat A. Chromatograms were performed on silica gel plates (Merck 5553) using the following systems: A = 1-butanol-acetic acid-ethyl acetate-water (1:1:1:1), B = 1-butanol-acetic acid-pyridine-water (5:1:4:1), C = ethanol-water (7:3), D = 2-butanone-pyridine-acetic acid-water (70:15:2:15), E = chloroform-methanol-dioxane-concd ammonia (12:7:5:1). Spots were visualized with ninhydrin and chlorine-tolidine reagent.

L-Pyroglutamyl-L-histidyl-L-tryptophan Methyl Ester.- To a suspension of pGlu-His-OMe (7.00 g, 25 mmol) in methanol (25 ml), 1 N NaOH (25 ml) was added with stirring; after 1 hr, no ester could be detected by TLC. Then the solvents were evaporated under reduced pressure and HCl·Trp-OMe (6.35 g, 25 mmol) in dimethylformamide (25 ml) was introduced. After a further 3 hrs stirring, 1-hydroxybenzotriazole hydrate (4.22 g, 25 mmol) was added and the mixture cooled to -10°; then dicyclohexylcarbodiimide (5.67 g, 27.5 mmol) in dimethylformamide (5 ml) was introduced. After 1 hr. stirring at temperature (-5° to 0°) and after a further 20 hrs. at 20°, dimethylformamide (10 ml) was added; dicyclohexylurea and NaCl were collected and the filtrate was evaporated. The resulting residue was dissolved in methanol (20 ml) and diethyl ether added to give the product (7.10 g, 70%), mp. 235.5-237°, lit.[1,2] mp. 241-243° and 237-240°; $[\alpha]_D^{25} = -30^\circ$ (c 1, 10% acetic acid); lit.[2] $[\alpha]_D^{20} = -52^\circ$ (c 1, 10% acetic acid); R_f:

A - 0.55, B - 0.59, C - 0.71, E - 0.47.

Anal. Calcd for $C_{23}H_{26}N_6O_5$: C, 59.21; H, 5.61; N, 18.02

Found: C, 58.97; H, 5.72; N, 18.05

L-Pyroglutamyl-L-histidyl-L-tryptophan Benzyl Ester.- The reaction was carried out as described above using HCl·Trp-OBzl (8.21 g, 25 mmol) instead of HCl·Trp-OMe. However, in this case after the reaction, the mixture was not diluted with dimethylformamide and the precipitate (NaCl, dicyclohexylurea and pGlu-His-Trp-OBzl) was collected and not washed. The resulting solid was suspended in acetic acid (15 ml) and after 1 hr. stirring, dicyclohxylurea and NaCl were collected. The filtrate was concentrated under reduced pressure to about half its volume and ethyl acetate (20 ml) was added, to give the product (10.33 g, 75%), mp. 246-247°, lit.[4] mp. 235-238° (for hydrate); $[\alpha]_{546}^{22}$ = -9° (c 1.5 acetic acid) $[\alpha]_D^{22}$ = -6.5 (c 1.5, acetic acid), lit.[4] $[\alpha]_D^{22}$ = -6.8° (c 1.54, acetic acid)]; R_f: A - 0.77, B - 0.68, C - 0.72.

Anal. Calcd for $C_{29}H_{30}N_6O_5 \cdot 0.5\ H_2O$: C, 63.17; H, 5.62; N, 15.23

Found: C, 63.52; H, 5.62; N, 15.06

L-Pyroglutamyl-L-histidyl-L-tryptophan Hydrazide.- To a solution of pGlu-His-Trp-OMe (1.86 g, 4 mmol) in dimethylformamide (24 ml) cooled to -6°, 99% hydrazine hydrate (3.6 ml, 72 mmol) was added and after 24 hrs stirring at temperature (-5° to +1°), the solvents were evaporated under reduced pressure and methanol was added to give the product (1.88 g, 99%), mp. 162-164°, lit.[1] mp. 165-169°.

Anal. Calcd for $C_{22}H_{26}N_8O_4 \cdot 0.5\ H_2O$: C, 55.57; H, 5.72; N, 23.57

Found: C, 55.35; H, 5.94; N, 23.64

Dimethylformamide (9.5 ml) and methanol (41 ml) were added to the precipitate obtained above, to give the product (1.49 g, 80%), mp. 243-245° (dec.): $[\alpha]_D^{20}$ = -20° (c 1, acetic acid), $[\alpha]_D^{23}$ = -39° (c 1, 1 N HCl),

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$[\alpha]_D^{20}$ = -26.5° (c 1, dimethylformamide), lit.[1] $[\alpha]_D^{25}$ = -24.6° (c 1, dimethylformamide)]; R_f: A - 0.50, C - 0.54, D - 0.48, E - 0.31.

Anal. Calcd for $C_{22}H_{26}N_8O_4$: C, 56.64; H, 5.62; N, 24.02

Found: C, 56.48; H, 5.57; N, 24.03

After four and a half years of standing without special precautions (access of moisture and oxygen), no change in its mp. and chromatographic behavior has been observed.

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