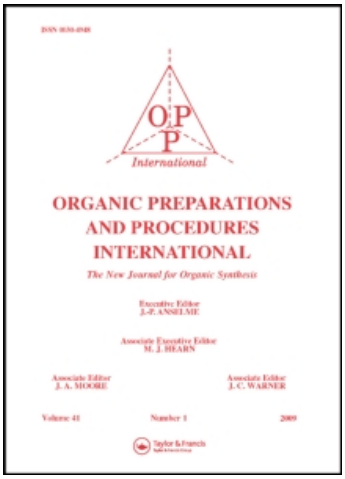

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ANALOGS OF TRYPTOPHAN

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3. *via* the 2-Trimethylammonium chloride salt: F. H. Case and E. Koft, *J. Am. Chem. Soc.*, **81**, 905 (1959). The reported yields in this two step procedure were 97 % and 54 % respectively.

4. Other routes to (**1**) involve dehydrations of 2-carbon-substituted derivatives normally prepared from (**1**) e.g. via the 2-carboxamidopyrimidine with phosphoryl chloride, M. Robba, *Ann. Chim. (France)*, **5**, 351 (1960).

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7. It is likely that under these reaction conditions a competing pyrimidine ring-opening occurred affording water-soluble organic by-products.

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ANALOGS OF TRYPTOPHAN

Submitted by (05/09/94) Emil Pop*, Katalin Prókai-Tátrai, Marcus E. Brewster and Nicholas Bodor

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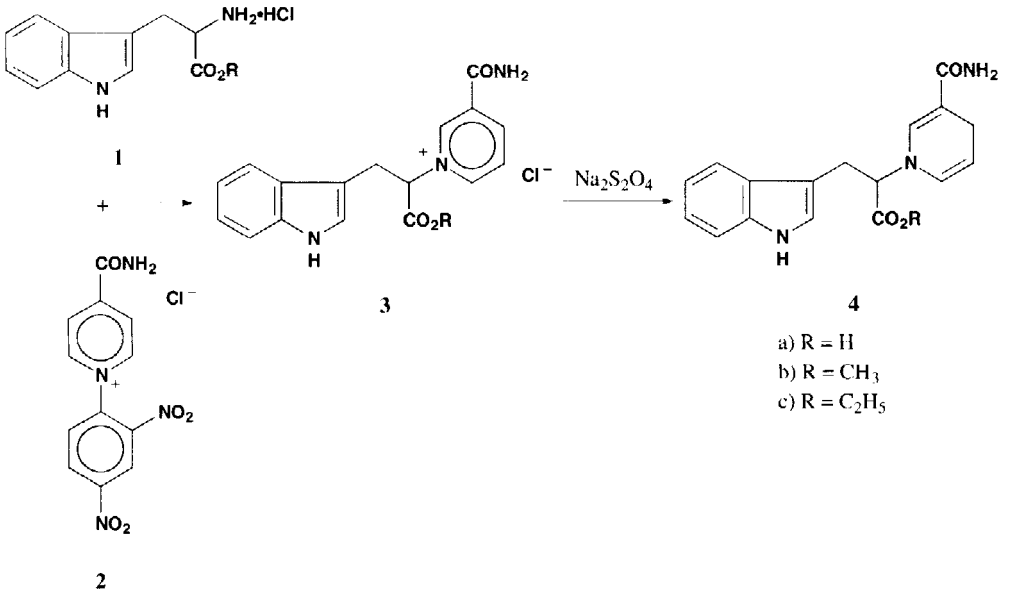
L-Tryptophan (L-Trp), an essential amino acid commonly used as nutrient has recently been tested as a potential antihypertensive agent.[1-3] Unfavorable properties (high polarity, low lipophilicity) and competition with other amino acids however limit the large neutral amino acid mediated transport of Trp to the central nervous system (CNS), the site of its primary action.[2-4] Since administration of high doses of Trp may have unwanted side-effects,[5] methods of enhancing CNS concentrations of Trp were investigated.[6] The synthesis of novel, analogues of Trp is described herein. Replacement of the amino group of Trp with a dihydropyridine ↔ pyridinium salt moiety (Scheme 1) confers a dual lipophilic ↔ hydrophilic character on the analogues, which could result in brain selective delivery and activity properties.[7]

Racemic D,L-tryptophan (**1a**) was used in these experiments. The carboxylic group of Trp was esterified to provide lipophilic character. Both methyl (**1b**) and ethyl (**1c**) esters were used. The synthesis of redox analogues utilized the Zincke procedure for forming pyridinium salts.[8-10] The amino group of **1b** and **1c** were reacted in dry methanol with 3-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride (**2**), obtained from nicotinamide and 1-chloro-2,4-dinitrobenzene,[9] in the presence of sodium bicarbonate and catalytic amounts of pyridine. The pyridinium salts (**3b** and **3c**) were formed *via* a ANRORC mechanism[11] and were purified through several recrystallizations. The 1,4-dihydropy-

ridines (**4b** and **4c**) were obtained by regioiselective reduction of the pyridinium salts with sodium dithionite in a biphasic system (ethyl acetate, aqueous sodium bicarbonate) at pH ~ 7. Preferential formation of 1,4-isomers of the dihydropyridines arises from thermodynamic control.[12]



Some physicochemical properties of **4b** and **4c** were examined; their oxidation to the corresponding quaternary salts occurred easily by means of methanolic silver nitrate solution or H_2O_2 in the presence of catalytic amounts of cupric ions. Chromatographic R_m values, used as lipophilicity indexes,[13] indicated that both **4b** (R_m = 2.00) and **4c** (R_m = 2.24) are more lipophilic than **1a** (R_m = 0.08). These data suggest that **4b** and **4c** could be delivered specifically to the CNS. They might also have biological activity as it was proven for analogues prepared in the same way for other amino group containing drugs[14,15] as well as for structurally related combinations of **1**.[6]

EXPERIMENTAL SECTION

Uncorrected melting points (mp) were determined on an Electrothermal® melting-point apparatus (Fischer Scientific). Elemental microcombustion analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. Ultraviolet spectra (UV) were obtained on a Hewlett-Packard 8451A diode array spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian XL 200 (200-MHz; FT mode) spectrometer. Samples were dissolved in an appropriate deuterated solvent and chemical shifts were reported as parts per million (δ) relative to the tetramethylsilane internal standard. Coupling constants (J) are reported in Hertz (Hz). Mass spectra (ms) were recorded on a Kratos, MS 80-RFA double focusing instrument. Fast atom bombardment (FAB) ionization was performed using a xenon beam (6 KeV) and dissolving the samples in a glycerol matrix.[16] Thin layer chromatography (TLC) was performed on EM Reagents DC-aluminum foil plates coated to a thickness of 0.2 mm with silica gel 60. A mixture of isopropanol:chloroform, 1:8 was used as solvent for development to determine R_f. All chemicals were reagent grade. Tryptophan esters were obtained from Sigma.

3-Carbamoyl-1[(*RS*)-1-carboxy-2-indol-3-ylethyl]pyridiniumchloride, Methyl Ester (3b).- A solution of 2.55 g (10 mmol) of **1a** in 20 mL dry methanol was added to a suspension of 3.25 g (10 mmol) of 1-(2,4-dinitrophenyl)-3-carbamoyl pyridinium chloride (**2**) prepared by the method of Lettré (9) in 20 mL dry methanol. Sodium bicarbonate (0.8 g) and five drops of dry pyridine (catalyst) were then added and the reaction mixture was stirred overnight at room temperature and the precipitate (2,4-dinitroaniline and sodium chloride) was filtered off. Ether was added to the filtrate and the resulting precipitate was filtered off and recrystallized twice from methanol:ether, yielding 2.70 g (75%) of **3b** as a yellow solid, mp. 181-184° (dec). UV (MeOH): λ_{max} 213, 271 nm; MS (FAB), C^+: m/z: 324; ^{1}H NMR (DMSO-d_6): δ 3.16-3.21 (m, 2H), 3.36 (s, 3H), 4.16-4.22 (m, 1H), 6.49-6.53 (m, 1H), 6.94-7.56 (m, 5H), 8.20-8.23 (m, 2H), 9.34-9.36 (m, 2H), 9.86 (d, 1H, J = 6.12), 10.21 (s, 1H).

Anal. Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.08; H, 5.04; Cl, 9.85, N, 11.16
Found: C, 60.36; H, 4.87; Cl, 10.11; N, 11.32

3-Carbamoyl-1-[(*RS*)-1-carboxy-2-indol-3-ylethyl]pyridiniumchloride, Ethyl Ether (3c).- Reaction of 2.6 g (10 mmol) of **1b** with 3.25 g (10 mmol) of **2** following the procedure described above gave 2.62 g (70% yield) of **3b** as a yellow solid, mp. 172-175° (dec). UV (MeOH): λ_{max} 213, 272 nm; MS (FAB), C^+: m/z: 338; ^{1}H NMR (DMSO-d_6): δ 1.8 (tr, 3H, J = 5.97), 3.07-3.19 (m, 2H), 3.97-4.11 (m, 3H), 6.45-6.47 (m, 1H), 6.97-7.29 (m, 5H), 8.24-8.27 (m, 2H), 9.34-9.36 (m, 2H), 9.85 (d, 1H, J = 6.14), 10.3 (s, 1H).

Anal. Calcd for $C_{19}H_{20}ClN_3O_3$: C, 61.04; H, 5.39; Cl, 9.48; N, 11.24
Found: C, 61.30; H, 5.02; Cl, 9.81; N, 11.45

Methyl(*RS*)-α-(3-carbamoyl-1(4H)-pyridyl)indole-3-propionate (4b).- To a solution of 1.80 g (5 mmol) of **3b** in 350 mL deaerated water and 350 mL ethyl acetate, a mixture of 2.52 g (30 mmol) $NaHCO_3$ and 3,48 g (30 mmol) $Na_2S_2O_4$ was added. The system was maintained under an argon stream and was stirred for 2 hrs. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with cold, degassed water (2 x 50 mL) dried and evaporated under reduced pressure to give 1.14 g (70% yield) of **4b** as an oil UV (MeOH): λ_{max} 214, 346 nm; ^{1}H NMR (DMSO-d_6): δ 290-2.91 (m, 2H), 3.22-3.27 (m, 2H), 3.37 (s, 3H), 4.30-4.33 (m, 1H), 4.55-4.58 (m, 1H), 5.96 (d, 1H, J = 8.21), 6.59 (bs, 1H), 6.94-7.56 (m, 8H).

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.82; H, 6.95; N, 4.23

Ethyl (*RS*)-α-(3-carbamoyl-1(4H)-pyridyl)indole-3-propionate (4c).- Reduction of 1.87 g (5 mmol) of **3c** as described above gave 1.10 g (65%) of **4c** as an oil UV (MeOH): λ_{max} 213, 280, 350 nm; ^{1}H NMR (DMSO-d_6): δ 2.25 (tr, 3H, J = 4.12), 2.86-2.94 (m, 2H), 3.12-3.27 (m, 2H), 4.20-4.29 (m, 3H), 4.623-4.66 (m, 1H), 5.98 (d, 1H, J = 6.12), 6.49 (bs, 1H), 6.96-7.32 (m, 8H).

Anal. Calcd. for $C_{19}H_{21}N_3O_3$: C, 71.23; H, 6.92; N, 4.37. Found: C, 70.95; H, 7.08; N, 4.15

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