Pergamon

*Tetrahedron Letters*, Vol. 38, No. 46, pp. 8033-8036, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10214-3

# Synthesis of 3-Phenylindoline-2-carboxamides as Semi-Rigid Phenylalanine Mimetics

**Valérie Collot, Martine Schmitt, Ashok K. Marwah, Bernadette Norberg[1] and Jean-Jacques Bourguignon***

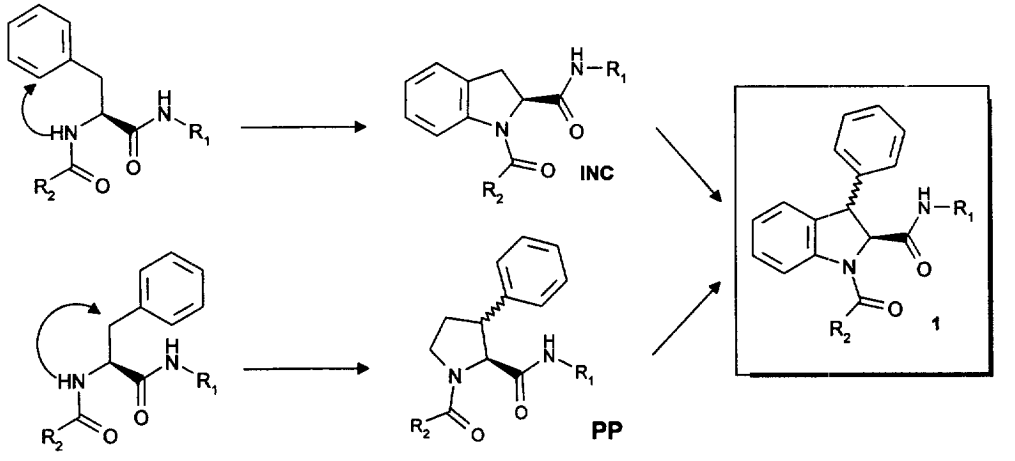
Laboratoire de Pharmacochimie Moléculaire du CNRS, Faculté de Pharmacie, 74 route du Rhin BP24 67401 Illkirch Cedex (France)

[1] Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaires Notre-Dame de la Paix, B-5000 Namur (Belgique)

**Abstract:** Regioselective catalytic hydrogenation of N-acyl 3-phenylindole-2-carboxylates is the key step for the preparation of *cis* and *trans* indoline-2-carboxamides which can be considered as phenylalanine semi-rigid derivatives. © 1997 Published by Elsevier Science Ltd.

Phenylalanine (Phe) plays an important role in binding processes of many endogenous neuropeptides particularly those involved in control of nociception: endorphines[1,2], tachykinins[3,4] and cholecystokinin.[5] In addition, the presence of the C-terminal Phe of the neuropeptide FF (NPFF), a peptide which modulates morphine analgesia, is crucial for binding to its receptors.[6]

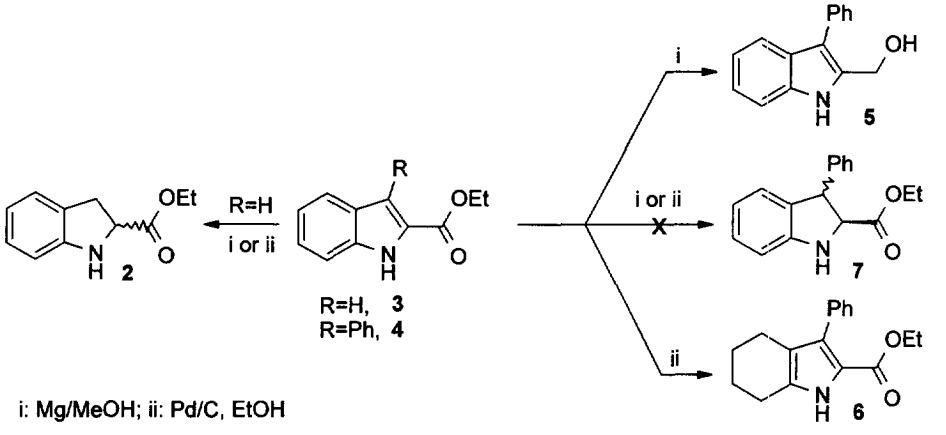
The replacement in peptidic ligands of Phe by semi-rigid derivatives is an efficient approach for better characterize the active conformation of such peptides. Moreover it may help to design new non peptidic ligands with significant increased *in vivo* stability towards proteases and peptidases. Previous works have already described N-acylindoline-2-carboxamides (**INC**) or 3-phenylproline-2-carboxamides (**PP**) as efficient Phe semi-rigid analogues.[7] Both involve linkage of the amide nitrogen of Phe onto its aromatic (**INC**), or β-carbon atom (**PP**). We describe here an efficient method of preparation of compounds **1** which combine both modes of rigidification in a common structure (scheme 1).




**Scheme 1:** Semi-rigid derivatives of Phe

fax: (33) 03 88 67 47 94; e-mail: jjb@aspirine.u-strasbg.fr

The ethyl 3-phenylindole-2-carboxylate **4** constitutes a valuable precursor of indolines **1**, through regioselective hydrogenation of its pyrrole ring. However we observed that the structure of the resulting compounds is strongly dependent upon both the nature of the reducing agent and the substituent R. We selected magnesium in methanol and catalytic hydrogenation as two reducing agents known to yield easily the 3-unsubstituted indoline-2-carboxylate **2** starting from indole **3** (scheme 2). Surprisingly same experimental conditions applied to 3 phenyl derivative **4** did not afford the awaited indoline **7**, but led to reduction of the ester into the alcool **5** or hydrogenation of the benzo ring leading the tetrahydro derivative **6** occurred when using magnesium in methanol and catalytic hydrogenation over palladium on charcoal, respectively.



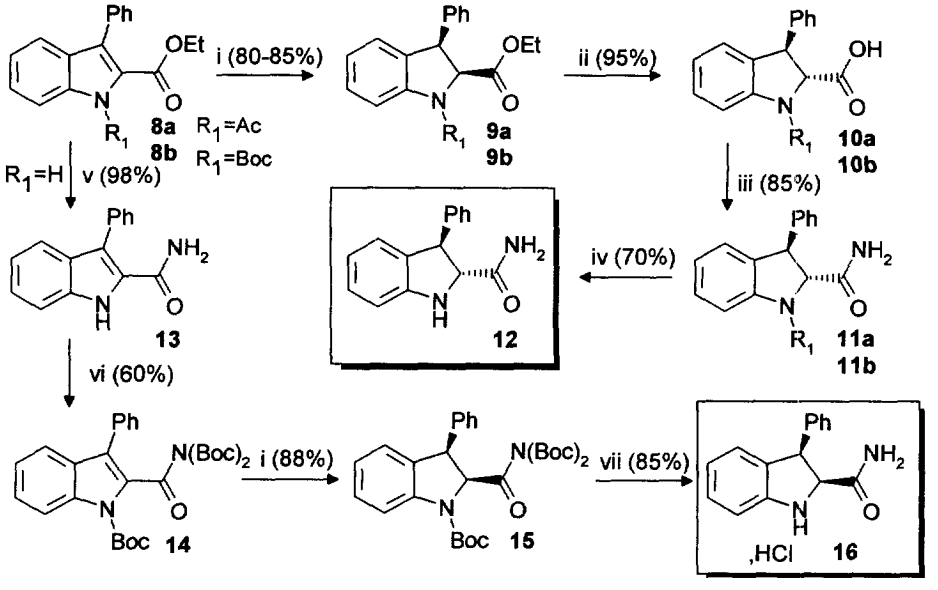

**Scheme 2:** Unexpected reduction pathways of ethyl 3-phenylindole-2-carboxylate **4**

Thus we decided to deplete the electron density of the pyrrole ring of **4** by N-acylation. Catalytic hydrogenation of the corresponding N-acyl indole derivatives **8** should afford the corresponding *cis* indolines **9** as an enantiomeric mixture.

We focused our attention on the preparation of the primary indoline-2-carboxamides **12** and **16**, as Phe constitutes the C-terminal part of both CCK and NPFF.[5,8]

Ethyl 3-phenylindole-2-carboxylate **4** was prepared starting from ethyl acetylphenylpropionate by means of a Japp Klingenmann reaction.[9] Acylation of the latter compound with acetic anhydride or in presence of di-*tert*-butyldicarbonate afforded compounds **8a** and **8b** respectively in good yields. Catalytic hydrogenation of N-acyl derivatives **8** afforded the *cis* indolines **9**. Smooth alkaline hydrolysis of **9** in presence of LiOH in aqueous dimethoxyethane yielded nearly quantitatively the acids **10**. However nmr data confirmed by X-ray cristallography[10] showed that epimerization occurred quantitatively during hydrolysis of **9**. Activation of the

acids **10** by means of isobutyl chloroformate and ammonolysis with ammonia followed by easy deprotection of the N-Boc derivative **11b** led to the awaited *trans* indoline-2-carboxamide **12**, m.p.198-200°C.




i: $H_2$, Pd/C, 60 psi, EtOH; ii: LiOH, DME/$H_2O$ 1/1, Δ; iii: 1) $ClCO_2iBu$, TEA, $CH_2Cl_2$, 0°C 2) $NH_{3g}$; iv: TFA, $CH_2Cl_2$, -10°C; v: 1) NaOH, EtOH, RT 2) $(COCl)_2$, DMF; 3) $NH_{3g}$; vi: $(Boc)_2O$ (3 equiv.), TEA, DMAP, $CH_2Cl_2$; vii: $HCl_g$.

**Scheme 3:** Access to *cis* and *trans* 3-Phenylindoline-2-carboxamides **16** and **12**

In order to avoid epimerization, the amide function was introduced before catalytic hydrogenation. The indole-2-carboxamide **13** (scheme 3) was submitted to acylation for that purpose. However attempts to prepare the indoline N-Boc derivative led to a mixture of mono, di and trisubstituted compounds. Thus the tri-Boc derivative **14** was selectively prepared and submitted to catalytic hydrogenation leading to the *cis* indoline **15**. The latter tri Boc indoline **15** afforded easily the awaited *cis* indoline carboxamide **16** in acidic medium.

The indolines **12** and **16** will be coupled with other amino-acids leading to conformationally restricted X-Phe-$NH_2$ mimetics and tested in specific binding experiments. This method is efficient as both couples of *cis* and *trans* diastereomers could be obtained separately through two different pathways. In addition optically pure enantiomers may be obtained from intermediates (starting from the acid **10**[11] or the free base (**12** or **16**). The approach can be generalized to other aminoacids including Tyr and Trp, or other aminoacids bearing functionalized alkyl side chains (Glu, Orn). Works are in continuation for the preparation of similar indoline-2-carboxylic acids bearing an acetic group in position 3 as putative ligands of glutamate receptors.

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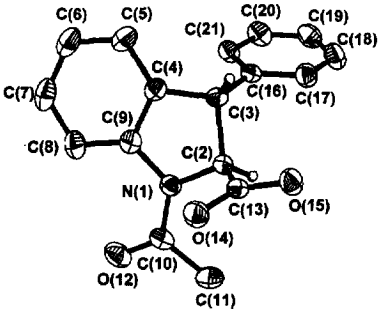
10. Ortep view of *trans* (2*S*, 3*S*) *N*-acetyl-3-phenylindoline-2-carboxylic acid **10a**




11. Resolution of *trans* (2*R*, 2*S*, 3*R*, 3*S*) *N*-acetyl-3-phenylindoline-2-carboxylic **10a** enantiomers :
    -with (+)quinidine, the (2*S*, 3*S*) salt crystallized out from ethanol. This salt was dissolved in water and acidified with 1N HCl, extracted with dichloromethane and washed with water. The organic layer was dried over $Na_2SO_4$, filtred and concentred *in vacuo* to yield white crystals, $[\alpha_D]$ +81 (c, 10 mg/ml, MeOH)
    -with (-)quinine, the (2*R*, 3*R*) salt crystallized out from ethyl acetate. The free base was recovered as described above, $[\alpha_D]$ -80 (c, 10 mg/ml, MeOH).

(*Received in France* 18 *June* 1997; *accepted* 22 *September* 1997)