SYNTHESIS OF 1,3-BENZODIOXOLE DERIVATIVES CONTAINING A AMINO ACID MOIETY IN SIDE CHAIN

Ana Cristina Lima Leite*, Kezia Peixoto da Silva &
Dalci Jose Brondani

LABSINFA - Departamento de Ciencias Farmaceuticas - Universidade Federal de Pernambuco,
Rua Prof. Artur Sa S/N, CDU, 50740-520, Recife, Pernambuco - Brasil
aclb@npd.ufpe.br

Abstract: The synthesis of the new amino-acyl derivatives starting from a 1,3-benzodioxole unit present in safrole is described. All the synthesised compounds, that could be conveniently prepared in a few steps process, have been characterised by the IR and the ^{1}H-NMR Spectroscopy.

Introduction

The 1,3-benzodioxole moiety present in safrole, has shown interesting and diversified properties when used to obtain new biologically active drugs[1-6]. Safrole, an abundant natural product occurring as the principal chemical constituent of sassafraz oil *(ocotea pretiosa, Benth)*. The 1,3-benzodioxole unit, can be identified in some clinical antitumor agents like, etoposide and teniposide[7]. In 1983, the FDA reported that, safrole or sassafras, the extract or the oil, was an ingredient in 113 over-the-counter drug formulations, generally for topical application, but occasionally for oral administration. However the carcinogenic and other toxicological effects of this product have been pointed out[8,9,10]

For some time, the interest for the design of prodrug containing a peptidyl or an amino acid moiety has increased. The use of amino acid has been exploited for the development of new biologically and less toxic active compounds[11-16].

As part of a research program with the objective to synthesis of bioactive compounds, using abundant Brazilian natural products, we have thus developed a synthetic sequence dealing with the synthesis of the safrole derivatives which present an amino-acyl moiety in a side chain[17].

This paper reports the strategy of synthesising compounds **4a-d** applying the coupling reagents used in the peptide synthesis and the verification of their structures through spectroscopic means.

Results

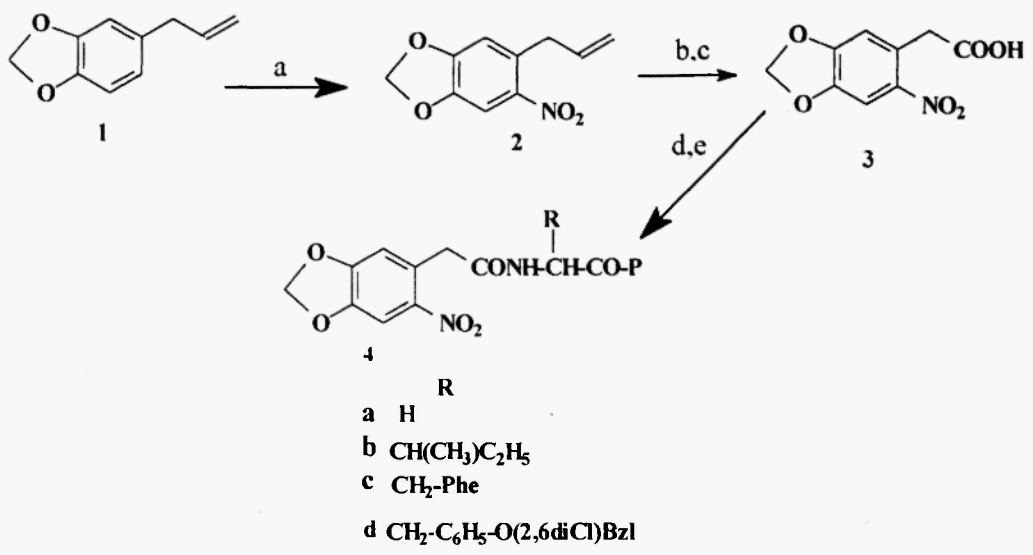
As a first step for the synthesis process, a selective and classical nitration on the 5 position 1,3-benzodioxole moiety was carried out using nitric acid in acetic acid[18]. The oxidation of compound **2** was released in a heterogeneous two-phase water-benzene system by permanganate and a phase transfer catalyst (benzyldimethyltetradecylammonium chloride dihydrate)[19]. The desired carboxilic acid was obtained in 60%.

The synthetic routes were appropriately applied on glycine methyl ester, phenylalaninamide, leucinamide and tyrosinamide. The side chain of tyrosinamide residue was protected by a 2,6-dichloro-benzile group. The expected amino-acyl derivatives **4a-d** were synthesised by condensation with (6-nitro-benzo[1,3]dioxole-5-il) acetic acid **(3)** with α-aminoacids using diciclohecylcarbodiimide and hydroxybenzotriazole to activate the carboxylic acid function from (6-nitro-benzo[1,3]dioxole-5-il) acetic acid to the generation of an active ester *in situ*[19-21] **(Scheme)**. The safrole derivatives were obtained at 18 to 99% yield.

The IR spectra showed a characteristic NH_2 stretching vibration around 3193 and 3387 cm-1, overlap C=O stretching, amide I band around 1627 cm^{-1}. Asymmetrical C-O-C stretching band around 1200-1275 cm^{-1} and symmetrical stretching near 1020-1075 cm^{-1}. The ^{1}H-NMR spectra of compounds showed the same characteristics at (δ) 4.97-4.99 and 5.03-5.05 ppm, corresponding to methilenic protons. Another representative signal occurs at 6.21 ppm and was attributed to the methylenedioxy group. Two signals occurring between 7.53 and 7,72 ppm attributed to aromatic hydrogen pattern near to nitro group. Another aromatic proton occurring between 6.77 and 7.06 ppm. For the NH a characteristic doublet around 7.98-8.60, indicating a coupling constant with CH quiral.. The NH_2 appears as two singlets at about 7.35-7.42 and 7.00-7.09 ppm.

Finally, the amino-acyl 1,3-benzodioxole derivatives from safrole were designed and synthesised. The reactions producing the new compounds are versatile and can be performed to obtain others derivatives. Their biological activity are currently under investigation. These results will be reported in up coming.

Scheme



R

a H

b $CH(CH_3)C_2H_5$

c CH_2-Phe

d CH_2-C_6H_5-O(2,6diCl)Bzl

(a) HNO_3/AcOH; (b)$KMnO_4$(aq)/C_6H_5/AcOH/ Phase Transfer Catalyst; (c) $NaHSO_3/H_2SO_4$;
(d) P-NH-CH(R)-COOH ; (e) DMF, 0°C, Diciclohexilcarbodiimide, Hidroxibenzotriazole;
P= OEt: **4a**; P= NH_2: **4b-d**.

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