

<sup>75,77</sup>Br-Nor-zimelidine: Radiohalogenation of a Complex Molecule via a Trimethylstannyl Precursor

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SUMMARY

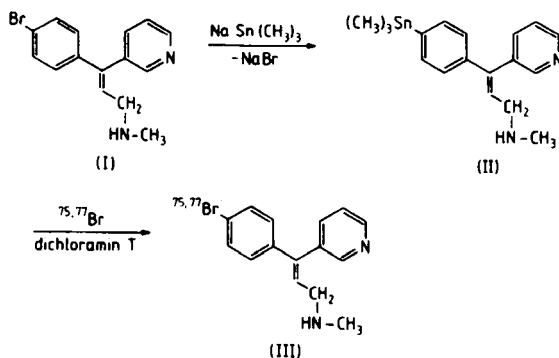
This communication describes the preparation of radiobrominated nor-zimelidine (III), a potential tracer for the serotonin reuptake system of the brain, by a bromodemetalation reaction using a suitable trimethylstannyl precursor (II). (II) was prepared from  $\text{NaSn}(\text{CH}_3)_3$  and nor-zimelidine in low yield and thoroughly purified by preparative hplc. Bromodemetalation reaction using an equimolar amount of  $\text{Br}_2$  showed quantitative formation of nor-zimelidine without any detectable side-products. Radiobromination yields using n.c.a. <sup>75,77</sup>Br at the 100  $\mu\text{Ci}$  level were 60 % with one hour preparation time including purification. Conditions were not optimized for large scale production of high specific activity (III) since the compound was withdrawn from the market by the producer during the course of this study.

INTRODUCTION

Zimelidine (2-3-(4-bromophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine) was a new antidepressant drug with promising properties. (for a review see [1]). Its mode of action was shown to be related to the inhibition of presynaptic reuptake of serotonin [2-5], thus prolonging the action of serotonin released from its neurons.

Thus, we felt that a labelled version of zimelidine in conjunction with positron emission tomography (PET) was a good choice for a radiopharmaceutical aimed at the presynaptic serotonin transport site. The most obvious choice for labelling zimelidine would be to introduce  $^{11}\text{C}$  into the dimethylamine group, and indeed this has been published [6]. On closer inspection, however, this approach seems ill suited because a) zimelidine is extensively metabolised by N-demethylation [1,7] and b) the resulting nor-zimelidine has higher affinity to the serotonin transport system than zimelidine [3] itself. Indeed, nor-zimelidine was claimed to be the actual drug inducing the desired action, with zimelidine acting as a prodrug [8]. Thus, we decided to label nor-zimelidine in the phenyl ring with  $^{75}\text{Br}$ , a radionuclide well-suited for in-vivo studies in conjunction with PET [9].

Since the number of serotonin transport sites is limited in the human brain [2-5], a labelling method capable of yielding high specific activity products has to be employed. We selected to use the halodemetalation reaction that has recently been systematically studied in our laboratory [10] (see Scheme 1). This method allows for the rapid introduction of radiohalogen at the n.c.a. level, provided that the corresponding trimethyl-aryltin precursor can be synthesized.



SCHEME 1

## EXPERIMENTAL

Nor-zimelidine was a generous gift of Astra Chemicals GmbH, Wedel, FRG. Trimethylstannyl sodium was prepared according to published procedures [11,12]. <sup>75</sup>Br and <sup>77</sup>Br were produced by the <sup>75</sup>As(<sup>3</sup>He,3n)<sup>75</sup>Br- and <sup>75</sup>As(α,2n)<sup>77</sup>Br-reactions, respectively, at the Jülich CV-28 compact cyclotron [9]. All solvents were analytical grade and used without further purifications unless stated otherwise.

2-3-(4-trimethylstannylphenyl)-N-methyl-3-(3-pyridyl)-allylamine(II)

A 10 ml ampoule was heated using a bunsen burner to remove all traces of water. 303 mg nor-zimelidine (1 mmole) was added to this ampoule under Ar and the vial was then closed with a teflon septum. After cooling to 0°C, 4 ml of dimethoxyethane (DME/absolute, distilled from sodium) was added to dissolve (I). 1.05 mmole of NaSn(CH<sub>3</sub>)<sub>3</sub> in DME were added at 0°C. The solution turned brown immediately, and a precipitate (probably NaBr) was formed. The solution was allowed to warm to room temperature and stirred for 180 min. The reaction mixture was purified by multiple injections onto a preparative hplc column (Lichrosorb RP 18, 25x1.0 cm, 10 μ) with methanol: 13 % aqueous triethylamine 85:15 as eluent at a flow rate of 2.1 ml/min. Three products were collected and characterized by their nmr spectra:

a) 130 mg of 2-3-phenyl-N-methyl-3-(3-pyridyl)-allylamine at k' = 1.27, b) some unreacted (I) at k' = 2.54 and c) 187 mg of II at k' = 7.05. (II) had characteristic nmr resonances for the trimethylstannyl protons at δ = 0.28 with <sup>119</sup>Sn-satellite bands 27.5 Hz apart.

Nor-zimelidine (I) / inactive from (II)

2 mg of (II) were dissolved in 2 ml of chloroform/dichloromethane 1:1. At room temperature, one equivalent of a solution of  $\text{Br}_2$  in chloroform were added dropwise until the bromine colour persisted. The solvent was immediately evaporated, the residue taken up in methanol and analysed on an analytical hplc column (Lichrosorb RP 18, 10  $\mu$ , 25x0.4 cm) with methanol: 0.1 % aqueous triethylamine 70:30 as eluent (see figure 1) at a flow rate of 2.0 ml/min. The analysis showed nor-zimelidine (I) as the sole detectable product.

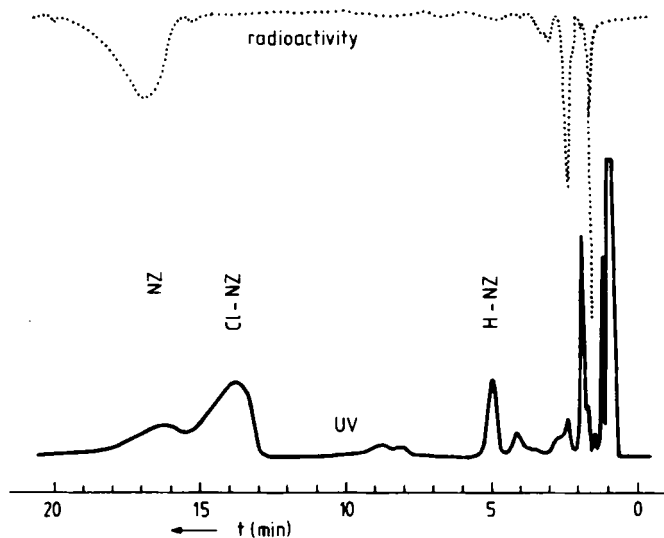


Figure 1: Analytical separation of products formed during radio-halogenation of nor-zimelidine (NZ = nor-zimelidine(III); Cl-NZ = Z-3-(4-chlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine; H-NZ = Z-3-phenyl-N-methyl-3-(3-pyridyl)-allylamine; DCT = dichloramine-T); separation conditions: column: Lichrosorb RP 18, 10  $\mu$ , 25x0.4 cm; solvent: methanol: 0.1 % aqueous triethylamine 70:30; flow: 2.0 ml/min; recorder drive: 1 cm/min)

<sup>75,77</sup>Br-nor-zimelidine (III) from (II)

About 100  $\mu$ Ci of n.c.a. <sup>75,77</sup>Br-bromide (50  $\mu$ l aqueous solution) were evaporated to dryness. 1 mg of (II), dissolved in 1 ml of methanol was added at room temperature. 1 mg of solid dichloramine-T was added as an oxidant [13]. After 10 min of stirring at room temperature, 300  $\mu$ l of 5% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> were added to stop the reaction. The reaction mixture was analyzed on hplc as described for inactive (I). No trace of residual (II) was detected. A typical chromatogram is shown in Figure 1. The radiochemical yield of isolated (III) was  $60.8 \pm 9.5$  % (n=6). Total preparation time, including purification, was an average of one hour.

The product (III) chromatographed as described still contains significant amounts of the corresponding chloro-compound Cl-NZ (see figure 1) which is formed from dichloramine T and (II). By use of standard column switching techniques (see for example [14]), this separation can be improved significantly. Another possibility is to use oxidizing agents like H<sub>2</sub>O<sub>2</sub> [16] which do not contain chlorine and thus avoid formation of Cl-NZ. Thus, high specific activity products can be obtained.

## DISCUSSION

At the onset of this work, nor-zimelidine seemed to be a rather promising tracer for the brain serotonin reuptake system. In the meantime, however, the supplier has withdrawn the parent drug zimelidine from the market owing to a small number of

serious side-reactions and cancelled all in-vivo studies using zimelidine or its metabolites. Consequently, we report here only a non-optimized synthesis of  $^{75,77}\text{Br}$ -nor-zimelidine which, we feel, has merits in itself due to the regiospecific labelling of a complex molecule using electrophilic bromination. Halodemetallation reactions are favourable for the regiospecific radiohalogenation of molecules like nor-zimelidine which contain functional groups that will easily react with electrophilic bromine species [15]. In nor-zimelidine, these positions are the allylic methylene group and the secondary amine. The trimethylstannyl residue, however, is more vulnerable to electrophilic attack than most other functional groups.

The trimethylstannyl-compound (II) was prepared from nor-zimelidine by reaction with  $\text{NaSn}(\text{CH}_3)_3$ . Although at low yields, (II) can easily be prepared by this route. The inverse procedure using  $(\text{CH}_3)_3\text{SnCl}$  and an organometallic precursor compound prepared from nor-zimelidine failed, since it was impossible to prepare the organometallic precursor from nor-zimelidine.

Using compound (II) in the bromination reaction shows that the Sn-aryl bond is the bond most vulnerable to electrophilic attack. No trace of other products could be detected (addition to the double bond, allylic oxidation, N-oxidation, positional isomers). In radiohalogenation reactions, high yields ( $60.8 \pm 9.5\%$ ) were consistently obtained in reaction times acceptable for labelling with  $^{75}\text{Br}$  ( $T_{1/2} = 96$  min). However, we have not performed labelling experiments at the 100 mCi level, where slightly lower yields have to be expected.

Furthermore, we have not optimized separation conditions in order to obtain a high specific-activity product. The chloro-compound formed as the major product from (II) and dichloramine-T was not separated completely from (III) (see figure 1). However, methods to achieve this separation, like column switching, are standard in radiopharmaceutical laboratories. Furthermore, use of H<sub>2</sub>O<sub>2</sub> [16] as oxidizing agent would eliminate this by-product. Thus, we are confident, that a high specific activity product can be prepared in slightly lower yields and slightly prolonged retention times. Should it be possible in the future to again use nor-zimelidine for in-vivo studies, these optimization studies will be carried out.

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