# NOTE

## HIGH YIELD PREPARATION OF $^{123}$I-N-ISOPROPYL-p-IODOAMPHETAMINE (IAMP) IN PRESENCE OF Cu(I)

John MERTENS*, Wim VANRYCKEGHEM*, Axel BOSSUYT**

*Cyclotron Unit, **Nuclear Medicine-A.Z.,
Vrije Universiteit Brussel, Laarbeeklaan 103,
B-1090 Brussels, Belgium

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## INTRODUCTION

Cu(II) salts have often been used for the nucleophilic isotopic exchange of aryl bound iodine, such as the radioiodination of N-isopropyl-p-iodoamphetamine (IAMP). (1,2,3). The role of Cu(II) in this type of reaction has never been clearly explained and its use is rather unexpected from a theoretical point of view.

Cupric salts are generally assumed to be effective agents for electrophilic (4), but not for nucleophilic substitution reactions. Some authors claim that inorganic Cu(II)-iodide complexes rule this type of reaction (5). This is doubtful as Cu(II) and $I^-$ react to yield CuI and $I_2$, which are reagents propagating electrophilic reactions.

This paper deals with the role of Cu(I) in the labeling reaction of IAMP. Cu(I) is generated in situ by addition of Sn(II) to a Cu(II) containing reaction mixture, allowing a high labeling yield (> 95%) to be obtained within a reaction time of 30 minutes.

## EXPERIMENTAL

### Labeling procedure

50 µl of a $Cu(NO_3)_2$ in acetic acid (96%) solution (0.135 µmol Cu(II)) are mixed with 1 mg of $SnCl_2.2H_2O$ (4.43 µmol Sn(II)) until decoloration in a mini-vial with connical cavity. Respectively 1 mg IAMP (supplied by Dr L.Carlsen,

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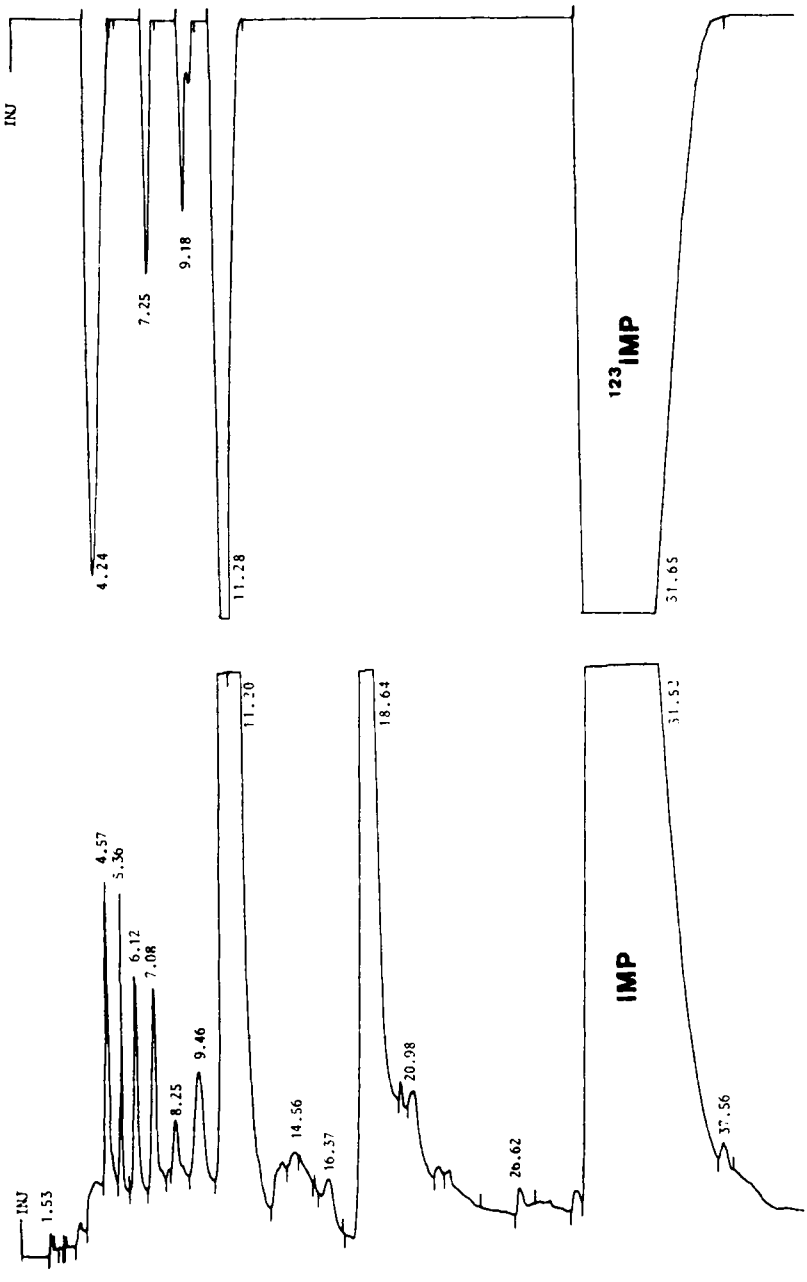


Fig.1 0.135 µmol Cu(II) + 10 mg IAMP + 50 µl Acetic Acid (100%) + 5 µl $^{123}I^-$ solution. 60 min. at 130°C.
Left trace: UV 0.5 AUFS; Right trace: Radiochromatogram

Risø National Laboratory, Roskilde, Denmark), a micropellet of metallic tin and 10-25 µl of $^{123}I^-$ solution (IRE, Fleurus, Belgium - spec. activ. 0.5 mCi/µl) are added. The septum closed vial is heated up to 175°C in a Silli-Therm heating module (Pierce Chemicals) for 30 minutes. All reagents used are Merck p.a. grade.

### HPLC separation

The HPLC system consists of a Waters set-up (U6K injector, M 6000 A pump, Lambda Max 480 UV detector) coupled to a γ-scintillation detector unit (3"NaI(Tl) Ortec, Ortec electronics) and HP 3380 A integrators. Chromatography is carried out on a 16 x 250 mm Chrompack Lichrosorb 10µ-RP 18 column for preparative work and a 4 x 250 mm Merck Lichrosorb 7µ-RP 18 column for reaction control, using a mixture of Acetonitrile/$H_2O$/methanol/trimethylamine/acetic acid : 20/20/60//0.07/0.1.

## RESULTS AND DISCUSSION

When applying labeling methods as described in the literature (1,2,3), using Cu(II) salts ($Cu(NO_3)_2$ and $CuSO_4$) in acetic acid, the labeling yield does not exceed 60% and HPLC analysis shows different cold (Fig. 1, left UV trace) and labeled side products (Fig. 1, right radiochromatogram) to be generated. On the other hand, when adding only radioiodide to the IAMP, as described by Kuhl et al. (6), low and unpredictable labeling yields are obtained. In both cases a loss of $^{123}I_2$ has been observed.

Figure 2 (left UV trace and right radiochromatogram, obtained in the same HPLC conditions as in Fig. 1) shows that the addition of Sn(II) to the initial reaction mixture containing Cu(II) and generating Cu(I) in situ (see experimental), allows a high temperature (175°C) to be used and a high labeling yield (> 95%) to be obtained. Only a negligible amount of cold and radioactive side products is produced.

The addition of the radioiodide to the Cu(I)-Sn(II) mixture prior to the IAMP results in a labeling yield lower than 2% due to the formation of slightly soluble Cu $^{123}I$. The use of only Sn(II) in the reaction mixture does not yield any labeled product.

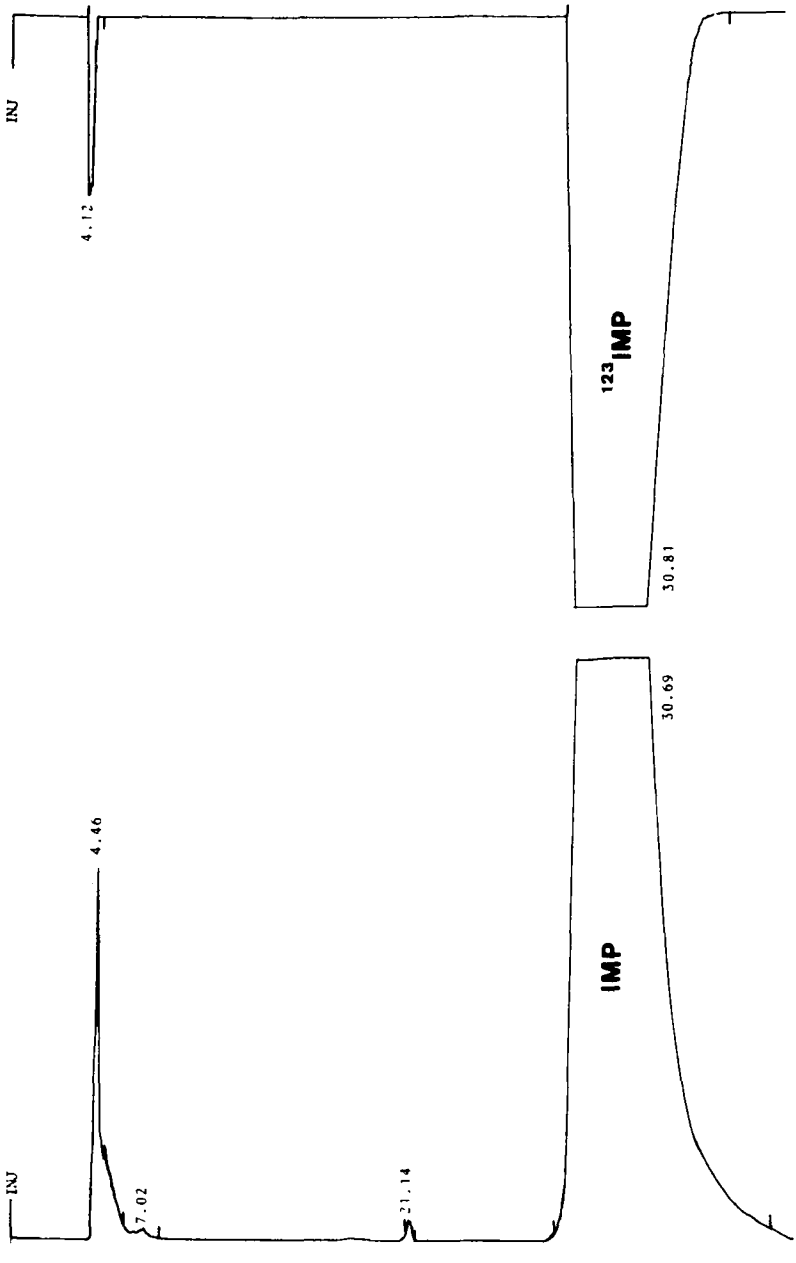


Fig.2 0.135 µmol Cu(II) + 1 mg IAMP + 50 µl Acetic Acid (96%) + 4.43 µmol Sn(II) + micropellet of metallic tin + 10 µl $^{123}I^-$ solution. 30 min. at 175°C.
Left trace: UV 0.1 AUFS; Right trace: Radiochromatogram

The initial use of Cu(I) salt (CuCl) in a $N_2$ atmosphere also results in the formation of side products and a labeling yield that does not exceed 50-60%. This can be explained by the fact that Cu(I) as such is not stable in solution, resulting in the formation of Cu(II). Cu(I) can only exist in a complex state and/or in presence of a reductor. The addition of Sn(II) remains a must to reach optimal labeling reaction conditions. The presence of Sn(II) also avoids the formation of $^{123}I_2$. Combining both the described labeling procedure and HPLC method results in reproducible and high labeling yields. The specific activity of the chromatographically pure $^{123}$IAMP amounts to 12 mCi/mg. The proposed reaction mechanism associated with the use of the Cu(I)-Sn(II) couple is also found to be appropriate for the labeling of other compounds containing a halogenated aryl group. These results will be published in a subsequent paper.

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