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RADIOPHARMACEUTICAL PREPARATION OF 3-^{123}I-α-METHYLTYROSINE FOR NUCLEARMEDICAL APPLICATIONS

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α-Methyltyrosine was iodinated in position 3 of the aromatic ring by means of an electrophilic iodination method using chloramine-T in a phosphate buffer solution. In a mixture containing α-methyltyrosine, chloramine-T and a small amount of NaI as a carrier the reaction was complete within 15 min at room temperature. After purification by radio high pressure liquid chromatography /HPLC/ radiochemical yields of 77.6±3.2% were obtained. Radiochromatograms also revealed a small amount of an impurity, probably chlorinated 3-^{123}I-α-methyltyrosine. After dissolving in isotonic phosphate buffer and sterile filtration the solution was ready for nuclearmedical applications.

INTRODUCTION

For the radio-iodination of compounds such as tyrosine the mechanism of choice is that of an electrophilic aromatic substitution which is well-known and described in literature[1-3]. The iodination method should lead to reasonable radiochemical yields of the product and, if

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desired, to high specific activities. Effective species for the iodination of aromatic substrates are chloramine-T and KIO_3 /Refs 3-6/. However, as could be shown by numerous experiments in our laboratory with different ^{123}I-solutions /commercially available and prepared with our cyclotron/ for the synthesis of 3-^{123}I-α-methyltyrosine, use of KIO_3 leads to a drastic reduction of radiochemical yields when the radio-iodine solution presumably contains unknown chemical impurities. For this reason a labelling method was to be found resulting in radiochemical product yields which are independent on the purity grade of the starting ^{123}I-iodine solution. With respect to an effective and reproducible radiosynthesis of 3-^{123}I-α-methyltyrosine with high radiochemical yield and purity of the product, a method is described using an electrophilic reaction mechanism by means of chloramine-T.

MATERIALS AND METHODS

α-Methyltyrosine and chloramine-T and KIO_3 were obtained from MERCK /Darmstadt, FRG/ with a purity of $\geq$98%. The solvents /BAKER, Gross-Gerau, FRG/ has HPLC purity /$\geq$99%/.

Irradiations

^{123}I was produced at the Essen compact cyclotron CV 28 by means of the ^{124}Te/p,2n/^{123}I nuclear reaction. ^{124}Te /96% enriched/ in the chemical form of $^{124}TeO_2$ on a platinum target holder was bombarded with a 24-MeV proton beam. After irradiation ^{123}I was evaporated in a quartz vessel at an oven temperature of 740 ^{o}C and transported by a stream of air either into a trap containing

0.01N aqueous NaOH or into a stainless steel capillary /volume 60 µl/ previously rinsed with the alkaline solution.

Labelling

Preparation of the reaction mixture for iodination was performed by two different methods:

1. To a mixture of 50-100 µl of 0.01N NaOH containing the desired ^{123}I-radioactivity and 200 µg α-methyltyrosine in 100 µl phosphate buffer /pH = 7/ in a small glass tube 1-2 µg NaI and 50 µl of a chloramine-T containing phosphate buffer solution /0.2-0.4 mg ml^{-1}/ were added.
2. The ^{123}I-radioactivity trapped in the stainless stell capillary was eluted into the reaction tube with a solution of 200 µg α-methyltyrosine and 1-2 µg NaI in 100 µl of 0.01 NaOH followed by the addition of the chloramine-T solution /concentration see above/.

Chromatography and quality control

After a reaction time of 15 min at room temperature the mixture was directly injected onto an HPLC column /chromatograph: WATERS, pump 6000A, UV-detector M440, 254 nm; column: MERCK-LiChrospher 100 RP-18, 10 µm; 250 mm long, 4 mm i.d.; eluent: MeOH/H_2O/AcOH = 40/60/1 at a flow rate of 2 ml min^{-1}. Detection of mass and radioactivity was performed using the standard method measuring UV-absorption /254 nm/ and radioactivity. According to the signals of the detectors the fractions were collected separately. 3-^{123}I-α-methyltyrosine was eluted with a k'-value of 3.7. A minor radioactive impurity appeared after the product peak with a k'-value

of 7.3. Due to a small UV-detectable impurity being eluted with a similar k'-value as 3-^{123}I-α-methyltyrosine the product fraction was collected, evaporated to dryness, the residue dissolved in eluens and the solution re-injected onto a second column /column: Multospher /CS Chromatographie Service GmbH, Eschweiler, FRG/, 5 µm; 500 mm long, 6 mm i.d., eluens: /see above/ at a flow rate of 1.5 ml min^{-1}. The fraction containing 3-^{123}I-α-methyltyrosine /k' = 7.2/ was again evaporated to complete dryness and the residue dissolved in isotonic phosphate buffer /pH = 7.4/. After sterile filtration /0.22 µm/ into a pre-sterilized ampoule the radiopharmaceutical was ready for nuclearmedical applications.

RESULTS AND DISCUSSION

Labelling results under different experimental conditions are shown in Table 1.

Radiochemical yields of 3-^{123}I-α-methyltyrosine using 10-20 µg of chloramine-T after HPLC purification are 77.6±3.2% /14 individual runs/. Iodination takes place in position 3 of α-metyhltyrosine due to the ortho-directing effect of the hydroxyl group in position 4 of the aromatic ring. The yield of the radioactive impurity which is eluted after the main product with a k'-value of 7.3 is 4.2±0.9%. By increasing the amount of chloramine-T by a factor of 10 to 20, i.e., 50 µl of a solution with a concentration of 2 and 4 mg ml^{-1} the yields of the by-product rise from 4.2% to 26.5% and 40.9%, respectively. Concomitantly, the yields of 3-^{123}I-α-methyltyrosine decrease to 58% and 28%, resp. It is assumed that by-product formation occurs either after oxidation of ^{123}I-iodide to an electrophilic species followed by iodination of the starting compound

TABLE 1

Radiochemical product yields after electrophilic iodination of DL-α-methyltyrosine /MeTy/ /n = 14/

Chloramine-T, µg	Radiochemical yield, % 3-^{123}I-α-MeTy	By-product
10-20	77.6	4.2
100	58	26.5
200	28	40.9

For comparison: KIO_3-method.
Radiochemical yields of 3-^{123}I-α-methyltyrosine: 65% /pure ^{123}I-solutions/, 10-20% /^{123}I-solutions with unknown traces of impurities/.

and chlorination of 3-^{123}I-α-methyltyrosine, thus leading to mono- and/or dichloro-3-^{123}I-α-methyltyrosine or chlorination occurs prior to iodination. In any case and independently from the reaction mechanism this reaction becomes more pronounced with 100 µg of chloramine-T /3-^{123}I-α-methyltyrosine: 58%; by-product: 26.5%/ and is predominant at 200 µg /3-^{123}I-α-methyltyrosine: 28%; by-product: 40.9%/. As no analytical effort has been done to identify the product its exact structure /most probably chlorinated 3-^{123}I-α-methyltyrosine/ is unknown. Comparing the labelling results for the two preparation methods of the ^{123}I reaction solution /see chapter "Mater: and method"/ no difference in radiochemical yields of the product can be observed.

In comparative labelling experiments with oxidation of ^{123}I-iodide by KIO_3 average product yields of 65% are obtained. These findings are in good agreement with data described by Tisljar et al.[7]. However, as could be shown in several experiments, successful labelling by means of

the KIO_3-method is possible only when very pure ^{123}I-solutions are used. Otherwise a drastic decrease of radiochemical yields down to 10-20% takes place. The advantage of the described chloramine-T method over iodide oxidation by KIO_3 is the possibility of using ^{123}I-solutions containing macroscopic amounts of impurities which, for example, can be introduced during processing of the ^{123}I-target.

CONCLUSION

The described labelling procedure represents a fast and effective method for the synthesis of 3-^{123}I-α-methyltyrosine with high and reproducible radiochemical yields. Besides formation of the desired product a minor ^{123}I-labelled impurity is produced which, however, can easily be separated by high pressure liquid chromatography. The advantage of reaction mixtres containing chloramine-T instead of KIO_3 as an oxidizing agent is the possibility of using ^{123}I-solutions which may contain unknown chemical impurities.

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