SYNTHESIS OF ^{123}I-4-(3-DIMETHYLAMINOPROPYLAMINO)-7-IODOQUINOLINE

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SUMMARY

^{123}I-4-(3-dimethylaminopropylamino)-7-iodoquinoline (IAQ), a potential localizing agent for melanoma, was prepared by isotopic exchange between ^{123}I-iodide and the phosphate or sulphate of IAQ. Yields up to 96% were obtained. The total time for preparation is restricted to 30 minutes.

KEY WORDS

Radiopharmaceutical, ^{123}I-4-(3-dimethylaminopropylamino)-7-iodoquinoline, melanoma, ^{123}I, isotopic exchange.

INTRODUCTION

In 1969 Counsell *et al.* [1] reported that 4-(3-dimethylaminopropylamino)-7-iodoquine (1) (IAQ) has a marked affinity for melanine-containing tissues and therefore could be used as a localizing agent for melanoma. Because of this property we were interested in this compound labeled with the radionuclide ^{123}I, the near ideal iodine-isotope for diagnostic purposes.

Packer *et al.* [2] already described the synthesis of ^{123}I-IAQ. They prepared this compound by melting IAQ with ^{123}I as an undefined chemical "species". However, this method suffered from low radiochemical yields (20 - 30%), low specific activities (10 - 20 μCi/mg) and the need for purification of the resulting ^{123}I-IAQ. We tried to circumvent these disadvantages by modifying this method in the following way:

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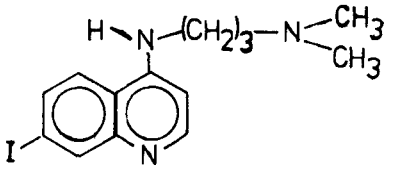
1) by performing the isotopic exchange with pure ^{123}I-iodide
2) by reaction with a suitable salt of IAQ (in minimal amounts) rather than with IAQ itself.



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EXPERIMENTAL

IAQ was synthesized starting from 3-iodoaniline and diethyl ethoxy methylenemalonate as described by Counsell [1]. Colourless crystals, m.p. 95° - 98° (lit. 101° - 102°).

IAQ-phosphate was prepared by adding 0.1 ml 85% H_3PO_4 to a solution of IAQ in ether (100 mg in 5 ml). The resulting precipitate was collected, dried and recrystalized twice from water /ethanol. Colourless crystals, m.p. 238° - 240°, IR (KBr): 1630, 1250, 1120, 960, 520 cm^{-1}.

IAQ sulphate was prepared by adding 0.1 ml sulphuric acid (96%) to a solution of IAQ in freshly purified and distilled ether (100 mg in 5 ml). The resulting precipitate was collected after 20 hours by filtration and was recrystalized from ethanol/ether. Slightly yellow, hygroscopic crystals, m.p. 170° - 180°. IR (KBr): 1630, 1200, 1010, 590 cm^{-1}.

^{123}Xe was produced with the IKO-cyclotron by the reaction ^{127}I(p,5n)^{123}Xe as described earlier [3]. During decay of ^{123}Xe H_2S was present to convert the daughter ^{123}I into the iodide-form with a radiochemical purity > 99.5% [4].

For the labeling of IAQ two methods were employed:

A. This method was based on a technique for the labeling with ^{123}I of Hippuran (o-iodohippuric acid) described previously by us [5]; it could only be applied for the phosphate. The inner-wall of a glass ampoule (10 x 0.8 cm Ø) provided with a teflon stop-cock was covered with finely ground IAQ-phosphate (about 3 mg).

After the irradiation the ampoule was filled by standard vacuum-line techniques with ^{123}Xe (and carrier) and H_2S-gas (both in the order of 5 mg). The ^{123}Xe was allowed to decay at room-temperature, usually for a period of 6 hours. The remainder of the (radio)xenon and the H_2S were removed by means of a vacuum-pump; the ^{123}I formed sticks to the ground IAQ-phosphate. Labeling was achieved in vacuo by immersing the ampoule up to the stop-cock in an oil-bath of 250° C.

B. This method was applied for both the phosphate and the sulphate. ^{123}I-iodide was prepared as described [4]. To a solution of this iodide in water 2 mg IAQ-phosphate or sulphate was added and the resulting solution was evaporated to dryness. In case of the sulphate a colourless oil was obtained after evaporation. Exchange was carried out in vacuo at 180° for the sulphate and at 250° for the phosphate.
Analysis of the products was performed on thin-layer plates of silicagel on plastic-foil. Routinely the organic phase of a mixture of benzene, triethylamine, butanol-1 and water (5:5:2:1½) was used as eluent. When other solvent systems [2c] (n-butanol, acetic acid, H_2O/6:15:2½ or methanol, triethylamine/40:1) were used, the same results were obtained. In all these cases the main ^{123}I-activity peak coincided with the mass peak of IAQ. About 1 µg NaI was added to the samples to prevent losses of ^{123}I-iodide. After development of the chromatogram, it was wrapped in adhesive-tape and cut in segments of 0.5 cm. Counting was performed in a NaI(Tl) well-type crystal at the 159 keV gamma-ray of ^{123}I.

RESULTS AND DISCUSSION

One of the conditions for labeling organic molecules with ^{123}I by isotopic exchange is the fixation of the iodine in a chemical form suitable for exchange-reactions such as the iodide-form. A method generally used to obtain this form is the reduction with thiosulphate [6]. As described earlier [4] we have circumvented the use of such troublesome chemicals by using gaseous H_2S as hydrogen-donor during decay of the parent ^{123}Xe. This results in a preparation of pure (> 99.5%) ^{123}I-iodide free of any additives. This preparation was used in exchange reactions with IAQ.

IAQ itself appeared to be not very reactive towards ex-

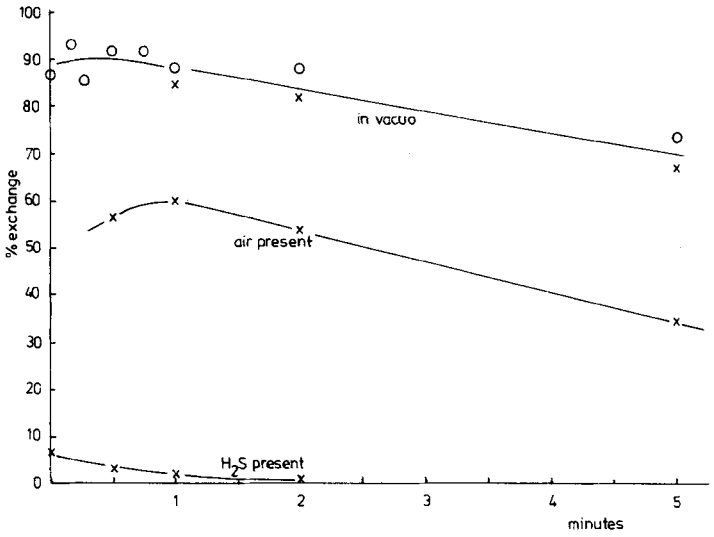

Fig. 1 Exchange reactions with IAQ-phosphate as a function of time in a melt at 250° C.
x: method A; o: method B.

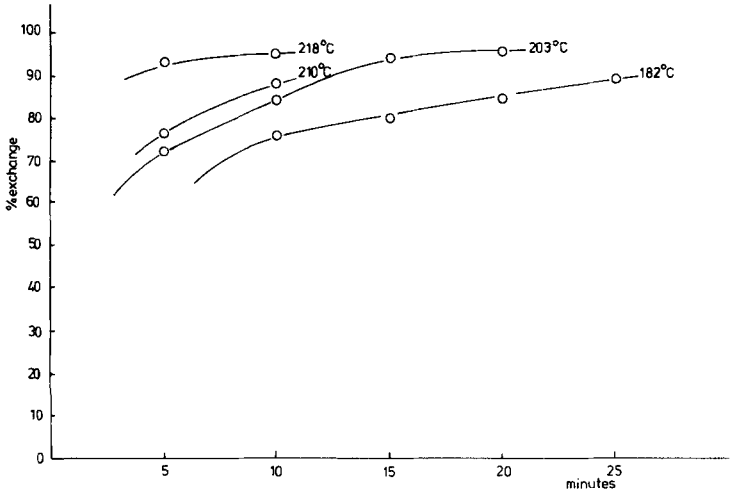

Fig. 2 Exchange reactions with IAQ-phosphate according to method B at different temperatures below the melting-point.

change with iodide. Melting of IAQ with ^{123}I-iodide (method B) only gave little exchange at rather high temperatures (> 200° C) and it was accompanied by substantial decomposition. This is not surprising since the nitrogen-atoms in IAQ, because of their nucleophilic properties, can compete with the iodide in the reaction. We therefore investigated the exchange reactions of salts of IAQ. Then not only the quinoline-system would be activated towards nucleophilic substitution by introducing a positive charge, but also side-reactions of the nitrogen-atoms would be suppressed because of this protonation. However, as counterions only those anions could be applied that are not nucleophilic themselves and because of biological aspects, only phosphate and sulphate were considered. These salts could be prepared easily by the addition of phosphoric or sulphuric acid to a solution of IAQ in ether. IAQ-phosphate appeared to be a stable compound, m.p. 240° - 242°. The sulphate was hygroscopic and could only be obtained in crystaline-form by working under anhydrous conditions.

Exchange with IAQ-phosphate

Both method A as well as method B were applied to the phosphate. As can be seen in Fig. 1, it proved to be essential that no additives like H_2S, air (or thiosulphate) were present during the melting; the results in vacuo appeared to be markedly better than in the presence of additives.

Because of the high reaction-temperature (250° C) very short reaction-times were sufficient. Exchange of about 92% was achieved within 0 - ½ min [7]. Prolonged heating only resulted in losses of label. It is also evident from Fig. 1 that at the actual time of melting already 90% has exchanged. This exchange has occurred during the heating of the salt to the melting-temperature. We therefore tried to reduce the reaction-temperature and bring about exchange below the melting point of IAQ-phosphate. Fig. 2 shows that this leads to fairly good results for method B: depending on temperature and reaction-time up to 96% exchange could be obtained.

Method A completely failed at these temperatures since irreproducible results were obtained (10 - 50% exchange).

Exchange with IAQ-sulphate

As mentioned earlier IAQ-sulphate was slightly hygroscopic, thus only method B could be applied to this salt. In Table I some results are reported.

Table I Exchange of IAQ-sulphate with ^{123}I-iodide by method B

Reaction-temp.	time	% exchange	% free iodide
140°	15 min	90	8.5
160°	15 min	94	5
160°	30 min	96.3 ± 1.2	2.9 ± 1.3
180°	15 min	96.4 ± 1.5	2.8 ± 0.9
180°	30 min	96.7 ± 1.4	2.5 ± 1.8

CONCLUSION

As is shown IAQ can be labeled with ^{123}I by exchange near the melting point between ^{123}I-iodide and appropriate salts of IAQ. Both the phosphate and the sulphate give high radiochemical yields (96%), while decomposition is limited. The labeling of IAQ-phosphate at elevated temperatures below the melting point (240° C) was prefered to labeling in a melt as the process is easier to control and more reproducible because of the longer reaction-time; also less decomposition is found under these circumstances.

Purification of the final labeled product prior to use is considered unnecessary. As a consequence the total time for labeling IAQ was restricted to 30 minutes. Also minimal amounts of IAQ can be used; specific activities up to 4×10^7 Bq/mg IAQ ($\approx$ 1 mCi/mg) are possible.

As control a preparation of ^{123}I-IAQ-sulphate (labeled at 180°) was given to guinea-pigs; indeed the expected affinity to melanine-containing tissues (the eyes) was found.

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7. In the conditions used it took about 2 - 3 minutes before the IAQ started to melt. The times used in Fig. 1 are the actual melting times.