THE LABELING OF 4-ALKYLAMINO-IODOQUINOLINES WITH RADIOACTIVE IODINE BY ISOTOPIC EXCHANGE.

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SUMMARY:

4-alkylamino-iodoquinolines can be labeled as their phosphate salts in high yields and in a short period of time by nucleophilic exchange in a melt with radioactive iodide. The iodide must be free of NaCl and reducing agents.

Key words: Radiopharmaceuticals, radioactive chloroquine-analogs, melanoma, isotopic exchange, radioactive iodine-compounds.

INTRODUCTION

Labeled analogs of chloroquine (1) are of interest for the detection of melanoma and several publications [1-6] dealt with the synthesis and biological studies of these compounds. For the preparation of these compounds labeled with radioactive iodine the following methods have been published:

1) Isotopic exchange with 7-iodoquinolines [7-9]
2) A Sandmeyer-reaction [10] with quinoline-diazonium salts
3) Electrophilic iodination of 7-chloroquinolines [11].

The most straightforward method for the labeling of 4-alkylamino-iodoquinolines is by isotopic exchange with radioactive iodide. In this article some results for the labeling of 4-alkylamino-iodoquinolines by the isotopic exchange method are described.

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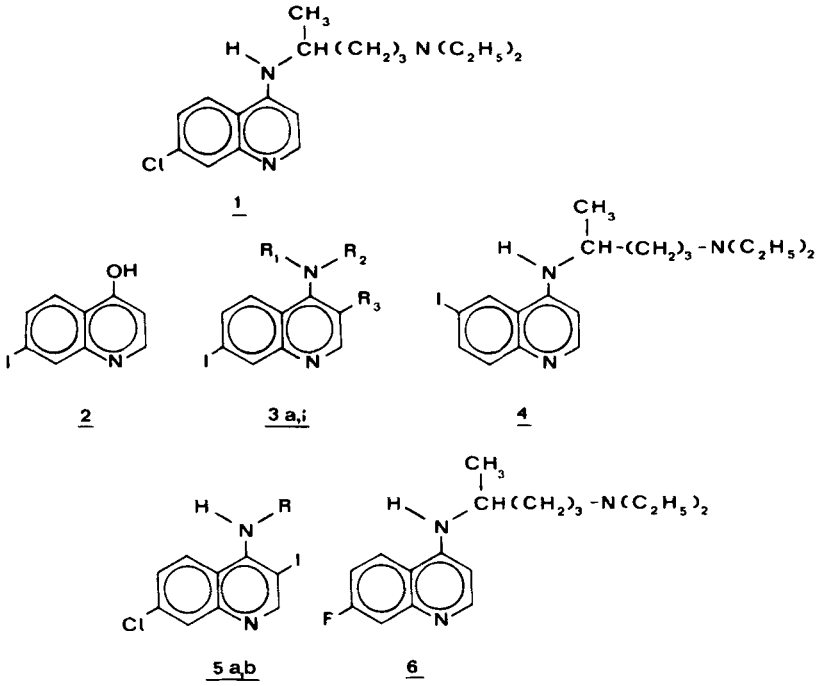

3 : a : $R_1 = R_2 = R_3 = H$

b : $R_1 = R_3 = H$ $R_2 = -(CH_2)_3-N-(CH_3)_2$

c : $R_1 = R_3 = H$ $R_2 = -(CH_2)_2-N(CH_3)_2$

d : $R_1 = R_3 = H$ $R_2 = -(CH_2)_3-NH-CH_3$

e : $R_1 = R_3 = H$ $R_2 = -(CH_2)_3-OH$

f : $R_1 = R_3 = H$ $R_2 = -(CH_2)_3-O-\overset{O}{\overset{\|}{P}}(OH)-OH$

g : $R_1 = CH_3$ $R_2 = -(CH_2)_3-\overset{H}{N}CH_3$ $R_3 = H$

h : $R_1 = R_3 = H$ $R_2 = -\overset{CH_3}{CH} - (CH_2)_3 - N(C_2H_5)_2$

i : $R_1 = H$ $R_2 = -\overset{CH_3}{CH} - (CH_2)_3 - N-(C_2H_5)_2$ $R_3 = CH_3$

5a: $R = -\overset{CH_3}{CH} - (CH_2)_3 - N - (C_2H_5)_2$

b: $R = -(CH_2)_3 - CH_3$

Figure 1

Results and Discussion:

The synthesis of several 4-alkylamino-7-iodoquinolines labeled with radioactive iodine by exchange using ethanediol as solvent have been described [7,10]. However, rather low yields (30-50%) were obtained and long reaction times were necessary (about 24 hours at 170° - 200°C). The rate of exchange can be enhanced considerably by performing the exchange reactions with the quinolines in protonated form. This was demonstrated by a serie of experiments with 4-(3-dimethylaminopropylamino)-7-iodoquinoline (3b) and $Na^{131}I$ in ethanediol in the presence of a number of acids. (HOAc, CF_3COOH, citric acid, H_3PO_4, H_2SO_4)
The results for the exchange-reaction in the presence of H_3PO_4 and acetic acid are given in table I.

Table I: Yields of ^{131}I-4-(3-dimethylaminopropylamino)-7-iodoquinoline (3b) with $Na^{131}I$ in 0,1 ml ethanediol at 120°C after 3 hours reaction. Quinoline-concentration: 150 mM ; $Na^{131}I$: 10 µCi (carrierfree).

equivalents acid present		approximate pH of reaction mixture	yield 3 hours
	-	> 8	< 0,5%
H_3PO_4:	0,4	> 8	< 0,5%
	1	7,5	2,5%
	2	4,8	17 %
	6	2,8	10 %
	10	2,2	4 %
HOAc	10	6,5	26 %
	12,5	5,1	23 %
	20	4,9	39 %
	25	4,7	43 %
	40	4,3	74 %

The exchange-rate increases as protonation of the quinoline-nucleus (pKa $\approx$ 8) occurs. For H_3PO_4 the yield shows a maximum at pH-values between 4 and 6. Acetic acid was a more convenient additive so the pH of the reaction-mixture is not the only important factor. HOAc could even be used as solvent for the exchange reaction with good results: 95% exchange after 3 hours reaction at 100°C. The fact that the rate of exchange increases on protonation of the quinoline nucleus is an indication for the nucleophilic character of this substitution. Protonation stabilizes the intermediate adduct and enhances the exchange-rate [9] (see fig. 2).

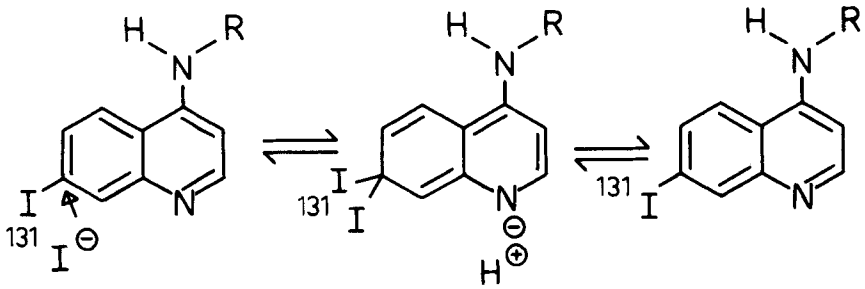

Figure 2

Much shorter reaction-times could be achieved by performing the reaction in a melt similar to the method developed by Elias for hippuran [12]. This is described for 4-(3-dimethylaminopropylamino)-7-iodoquinoline (3b) by Packer et al [8]. We did find an enhanced rate of exchange for this substrate [13] when instead of the free base, the phosphate-salt of this quinoline was used in the (near)-melt [14] reaction. This method could also be applied for other 4-alkylamino-iodoquinolines. The phosphate-salts of the quinolines are stable products and can be prepared quite easily. The exchange-reactions gave good results.

An example of an exchange reaction is given in fig. 3 for 4-(2-dimethylaminoethylamino)-7-iodoquinoline (3c). There is not only a considerable increase in the exchange-rate with the phosphate-salt, but the formation of side-products is also inhibited (in the case of the free base the sum of the labeled quinoline and free iodide is less than 100%). This is due to the fact that the nucleophilic amino-group in the alkyl-chain is deactivated by protonation.

In table II the results for the exchange-reactions with a number of iodoquinoline-phosphates are given. In general high yields are obtained in short reaction times. A special compound is 4-(3-hydroxypropylamino)-7-iodoquinoline (3e); this was partly converted to its phosphate ester (3f) during the exchange reaction.

It was investigated whether the formation of labeled quinolines was also feasible starting from other 7-haloquinolines; exchange reactions were carried out with ^{131}I-iodide and the phosphates of chloroquine (1) and fluoroquine (6).

As can be seen in table 2 poor yields were obtained with the fluoro- and the chloro-derivatives, analogous to the exchange reactions of radioactive iodide and m-halobenzoic acids [15]. This indicates that the rate limiting step for the reaction is probably the loss of the original halogen-substituent and not the attack of the nucleophile to the aromatic ring as has been found for other nucleophilic aromatic substitutions [16]. The unreactivity of the chlorine was further demonstrated in the exchange-reactions of the 7-chloro-3-iodoquinolines (5a,b) : only replacement of the 3-iodo-substituent was observed [17].

Attention should be given to the radioactive iodine used because the iodide-form is essential. Usually the iodine is obtained in alkaline solutions (diluted NaOH). Because the exchange-reactions are carried out under mild acidic conditions neutralization is necessary. It was found that in the presence of NaCl in amounts of more than 50 µg/mg quinoline-phosphate two phases formed after removal of the water. With 4-(3-dimethylaminopropylamino)-7-iodoquinoline (3b) the yield decreased to 20%. The Na^{131}I dissolves in the NaCl-phase and is not available for exchange, so

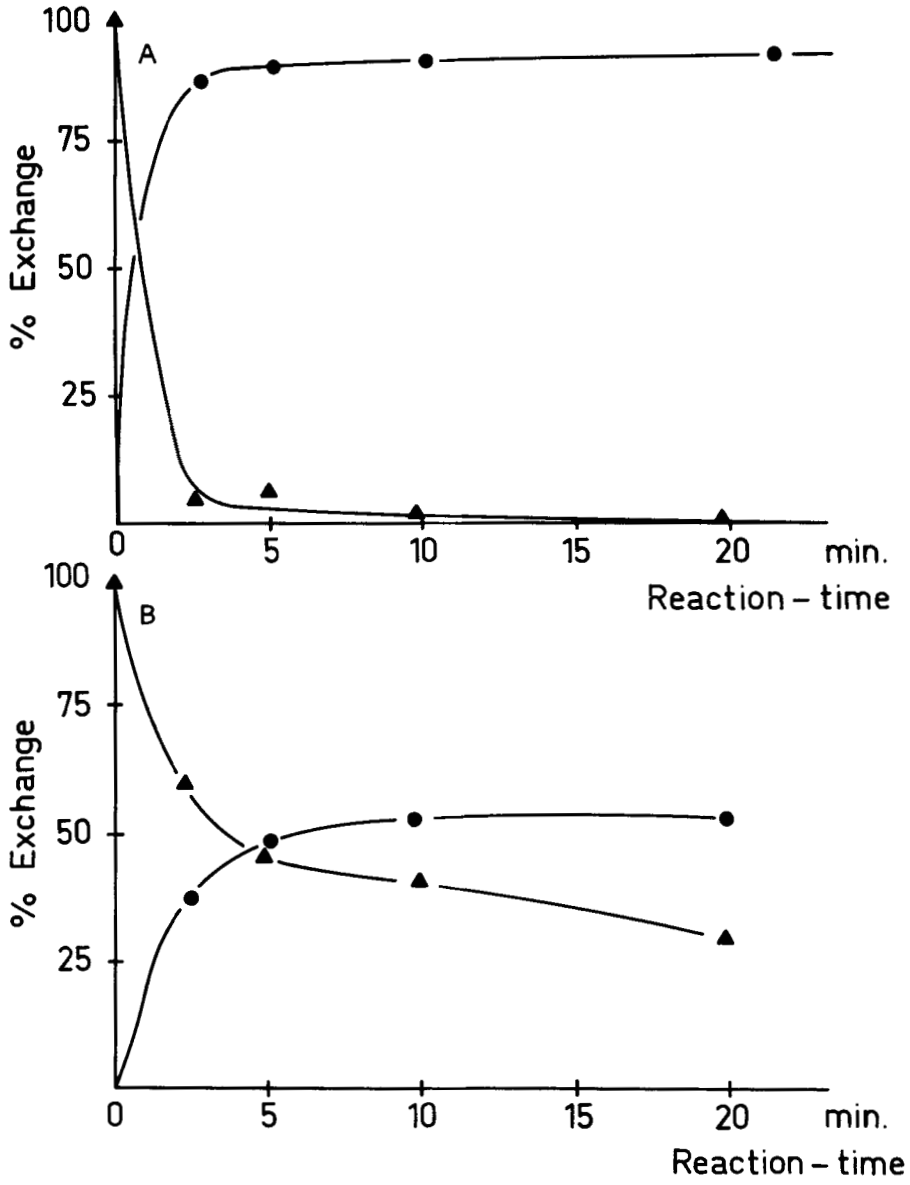

Figure 3 Exchange-reaction at 185°C of 4-(2-dimethylaminoethyl-amino)-7-iodoquinoline (3c). ● - ● ^{131}I-quinoline, ▲ - ▲ ^{131}I-iodide.

A : quinoline-phosphate B : free quinoline

Table II: Yields of labeled (^{123}I, ^{125}I, ^{131}I)[i]-quinolines by exchange-reactions of quinoline-phosphates with radioactive iodide.

Substrate	m.p. phosphate	reaction-temperature	reaction time[ii]	yield[ii]
2 : 4-hydroxy-7-iodo-quinoline	248°-225°C	200°C	5 min	87 %
3a: 4-amino-7-iodo-quinoline	not determined	200°C	30 min	84 %
3b: 4-(3-dimethyl-aminopropylamino)-7-iodoquinoline	238°-242°C	200°C	15 min	92 %[13]
3c: 4-(2-dimethyl-aminoethylamino)-7-iodoquinoline	215°C	180°C	15 min	92 %
3d: 4-(3-methylamino-propylamino)-7-iodoquinoline	210°C (decomp.)	180°C	15 min	87 %
3e: 4-(3-hydroxy-propylamino)-7-iodoquinoline	202°-206°C	200°C	15 min	≈40 % and ≈40 % 3f
3g: 4-N-(2-methyl-aminoethyl)-N-methylamino-7-iodoquinoline	198°C	180°C	15 min	85 %
3h: iodoquine	225°-235°C	190°C	15 min	94 %
3i: 3-methyl-iodoquine	210°C	200°C	20 min	93 %
4 : 6-iodoquine	oil	200°C	15 min	90 %
5a: 3-iodo-chloroquine	140°-150°C (decomp.)	105°C	15 min	65 %[16]
5b: 4-butylamino-7-chloro-3-iodoquinoline	132°C (decomp.)	105°C	15 min	83 %
1 : chloroquine	214°-216°C	190°C	30 min	1,6%
6 : fluoroquine	199°-203°C	190°C	30 min	0,5%

i) In general the yields obtained for ^{123}I were 2-5% higher than those found for ^{125}I and ^{131}I. The presence of peroxides in the last two isotope-preparations resulted in the formation of labeled by-products.

ii) For each quinoline exchange-curves (similar to the one given in figure 3a) were measured.

HCl cannot be used for neutralization. Neutralization with H_3PO_4 gives better results: exchange-reactions with up to 200 µg NaH_2PO_4/mg quinoline-phosphate did not show a decrease of the yields.

The use of reducing agents like sulphite or thiosulphate should be avoided. It was found by TLC-analysis that 4-alkylamino-quinolines decompose under the exchange conditions by reaction with these reducing agents and very low yields of labeled products were obtained.

In conclusion it can be said that the exchange-reaction of iodoquinoline-phosphates in a near-melt with radioactive iodide is a rapid and easy method for the labeling of quinolines with radioactive iodine.

Materials and Methods:

$Na^{131}I$ (Philips Duphar) carrierfree (spec. act. > 5 Ci/mg) in NaOH without reducing agents.

$Na^{123}I$ (Würenlingen/Philips Duphar) carrierfree in NaOH without reducing agents.

$Na^{125}I$ (Amersham) carrierfree in NaOH, free from reducing agents.

Chloroquine-phosphate (1) was a gift from Specia, France.

4-hydroxy-7-iodoquinoline (2) was prepared as described by Counsell et al. [7]; colourless crystalls, m.p. 260°C.

4-amino-7-iodoquinoline (3a): This compound was prepared from iodoquine (3h) by reaction with concentrated H_2SO_4 analogous to the synthesis of 4-amino-7-chloroquinoline from chloroquine [21]. yellow crystals. m.p. 210°C (decomposition)

PMR (CF_3COOH) : 5,95 (d,J = 7 Hz H_3) ; 6,9-8,5 (m,H_2,H_5,H_6 and H_8)

Mass-spectrum (field-desorption): 270 and 271 (M^+ and MH^+)

4-alkylamino-iodoquinolines: these compounds were prepared by reaction of 4-chloro-7-iodoquinoline, 4-chloro-7-iodo-3-methylquinoline, 4-chloro-6-iodoquinoline, 4,7-dichloroquinoline and 4-chloro-7-fluoroquinoline with the alkylamines (10 equivalents) at 100°C during 16 hours. The quinolines were purified by repeated chromatography over SiO_2. The preparations were converted to their phosphate-salts by adding some drops of 85% H_3PO_4 to a solution of the quinoline in ethanol and by collecting the resulting precipitate.

The preparation of the 3-iodoquinolines (5a and 5b), 4-(3-dimethylaminopropylamino)-7-iodoquinoline (3b) and iodoquine (3h) was described before [13,17].

4-(2-dimethylaminoethylamino)-7-iodoquinoline (3c):
slightly yellow crystals: m.p. 120° - 123°C
IR(KBr) : 1585,1608 cm^{-1}
PMR($CDCl_3$): 2.3 (s,N-Me); 2.55 and 3.30 (m,H_1, and H_2,); 6.0 (m,NH); 6.35 (d,J = 6, H_3); 7.60 (m,H_5 and H_6); 8.40 (d,J = 2 Hz, H_8) ; 8.60 (d,J = 6Hz, H_2)
Mass-spectrum (F.D.): 341 and 342 (M^+ and MH^+).

4-(3-methylaminopropylamino)-7-iodoquinoline (3d):
colourless crystals : m.p. 110° - 118°C
IR(KBr): 1585 and 1610 cm^{-1}
PMR($CDCl_3$) : 2,40 (s,Me); 1,82 (m, CH_2) 2,72 and 3,23 (broad. t N-CH_2); 6,12 (d,J = 5 Hz, H_3) ; 7,25 (d,J = 9 Hz,H_5) ; 7,45 (double d, J = 9 and 1 Hz,H_6) ; 8,20 (d,J = 1 Hz,H_8) ; 8,25 (d,J = 5 Hz,H_2)
Mass-spectrum (F.D.): 341 and 342 (M^+ and MH^+)

4-(3-hydroxypropylamino)-7-iodoquinoline (3e):
colourless crystals : m.p. 153° - 158°C
IR(KBr): 1585, 1608 cm^{-1}
PMR (d_6-DMSO): 1.85 (m,H_2); 3,2-3,8 (m, H_1, and H_3,); 6.54 (d, J = 6 Hz,H_3); 7.65 (broadened d, J = 9 Hz,H_6) ; 8.18 (d,J = 9 Hz,H_5); 8.21 (br. s,H_8) 8.35 (d, J = 6Hz,H_2)
Mass-spectrum (F.D.): 328 and 329 (M^+ and MH^+).
During the exchange-reaction of the phosphate-salt at 200°C a compound was formed which was retarded on DEAE-sephadex with respect to the parent-compound.
Mass-spectrum (F.D.): 409 (MH^+ for the phosphate-ester 3f).

4-N-(2-methylaminoethyl)-N-methylamino-7-iodoquinoline (3g):
colourless crystals : m.p. 80° - 82°C
IR (liq. cap.): 1575, 1598 cm^{-1}
PMR($CDCl_3$) : 2,45 (s,Me), 2,96 (s,Me); 2,7-3,2 and 3,40 (m, CH_2-) 6,83 (d, J = 5Hz, H_3) ; 7,66 (double d. J = 9 and 1½ Hz,H_6) ; 7,87 (d, J = 9 Hz, H_5) ; 8,43 (d, J = 1½ Hz, H_8) ; 8,60 (d, J = 5 Hz,H_2)
Mass-spectrum (F.D.): 341 and 342 (M^+ and MH^+)

3-methyliodoquine (3i):

This compound was synthesized from p-I-aniline as described by Steck et al. [18].

UV (0,1 N HCl): maxima at 232, 268, 341 and 353 nm; litt [19] 232, 268, 342 and 354 nm.

6-iodoquine (4):

colourless oil

IR(liq. cap): 1540 and 1580 cm^{-1}

PMR($CDCl_3$) : 1,02 (t,C_2H_5) ; 1,3 (d, J = 6 Hz, Me) ; 1,65 (m,CH_2) ; 2,60 (q and m, C_2H_5 and CH_2-N) ; 3,65 (m,CH) ; 5,65 (d, J = 6 Hz, NH) ; 6,46 (d, J = 5 Hz, H_3) ; 7,70 (m, H_7 and H_8) ; 8,20 (d, J = 1 Hz, H_5) ; 8,55 (d, J = 5 Hz H_2)

Mass-spectrum (F.D.): 411 and 412 (M^+ and MH^+)

fluoroquine (6):

slightly yellow crystals: m.p.: 77° - 79°C; litt. [20] :85° - 86°C.

IR(KBr): 1555, 1585 and 1630 cm^{-1}

PMR($CDCl_3$) : 0.94 (t,Me), 1.22 (d,1'-Me); 1.60 (m,H_2, and H_3,) ; 2.42 (q,Me); 3.55 (m,H_1,); 5.30 (br.d. J = 6 Hz, NH)); 6.18 (d, J = 6 Hz, H_3); 6.85 (double t, H_5); 7.40 (d.t H_5); 7.41 (t,H_8); 8.20 (d, J = 6 Hz, H_2)

Exchange reactions:

To a solution of $Na^{131}I$ in water, 2 mg quinoline-phosphate was added and the resulting solution was evaporated to dryness under reduced pressure. In most cases a colourless oil was obtained. Exchange was carried out in vacuum at 20° below the melting points of the quinoline-phosphates used.

Analysis:

The analysis of the ^{131}I-products was performed on thin layer plates of SiO_2 on plastic foil. As eluent the following systems were used:

- the organic phase of a mixture of benzene, triethylamine, butanol-1, H_2O (5:5:2:1½)
- the organic phase of a mixture of benzene, triethylamine, H_2O (5:5:1½)

- methanol, triethylamine (40:1).

Before the analysis 1 µg KI was added to the samples to prevent losses of free iodide. After development of the chromatogram over about 15 cm, it was wrapped in adhesive tape and cut into segments of 0.5 cm. These were counted in a NaI(Tl) well-type crystal on the 364 keV photopeak of ^{131}I, the 159 keV photopeak of ^{123}I or in the case of ^{125}I the 30 KeV χ- and γ-rays.

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