A STUDY ON THE ELECTROPHILIC IODINATION OF CHLOROQUINE

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SUMMARY

Chloroquine can be iodinated with radioactive iodine in radiochemical yields 60-75% with chloramine-T or H_2O_2/lactoperoxidase. With both methods a rather complex mixture of labelled products is formed. The yield and ratios of the labelled products depend upon the chloroquine-concentration, the amount of carrier iodide present and in the case of the chloramine-T method, the chloramine-T concentration. With the chloramine-T method the main product is 3-iodochloroquine, with H_2O_2/lactoperoxidase an unidentified iodinated chloroquine-derivative, probably a dimer, is the main labelled product. With chloramine-T products such as 3-chlorochloroquine and deethylchloroquine are formed in mass amounts.

Key words: Melanoma, chloroquine-analogs, electrophilic iodination, radioactive iodine-compounds

INTRODUCTION

Chloroquine (1) has a marked affinity for melanine-containing tissues and several groups of investigators[1-6] tested chloroquine-analogs labelled with radioactive iodide for the detection of melanoma. Several synthetic routes to labelled quinolines have been described. Our results on exchange-reactions were described earlier [7,8,9]. In earlier investigations on the labelling of chloroquine with the chloramine-T method [8] it was found that this is a very complicated reaction: several labelled quinolines were formed with 3-iodochloroquine (2) being one of the main labelled products. The ratio of the products depended upon the amount of carrier iodide present during the labelling. Therefore it was decided to study in more

0362-4803/80/0517-0667$01.00

Received April 10, 1979
Revised June 19, 1979

detail the electrophilic iodination with $Na^{131}I$ of 4-alkylamino-quinolines, in particular chloroquine (1), to get some insight in the mechanism.

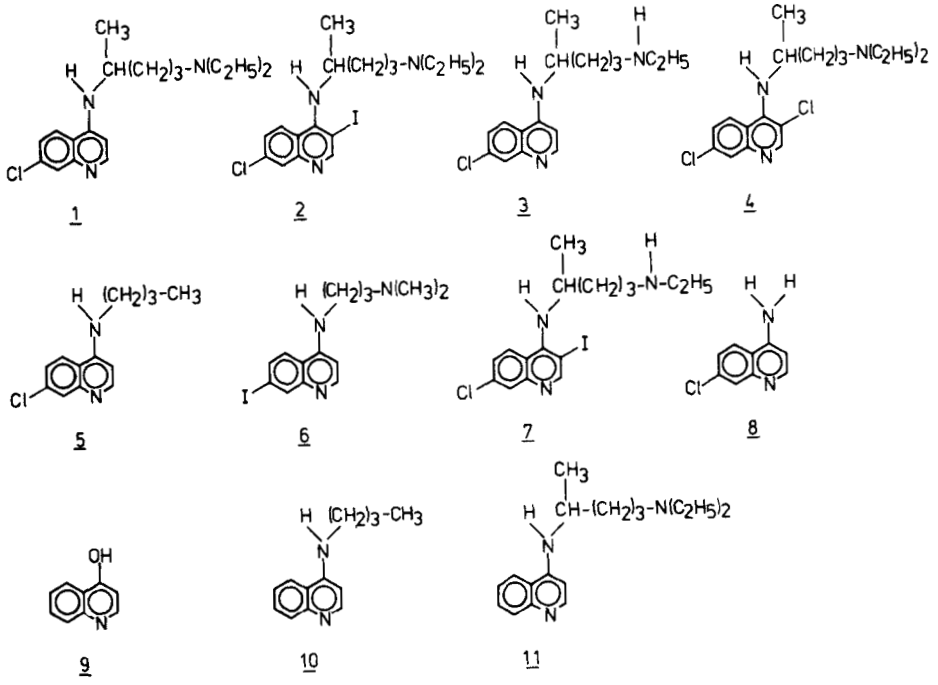

Figure 1

RESULTS AND DISCUSSION

We investigated a number of methods for the electrophilic labelling of chloroquine with $Na^{131}I$. The reactions with ^{131}I-iodide with H_2O_2, HNO_2 [10], HNO_3 [11] and I_2 gave very low yields (< 5%) of labelled quinolines. Reaction with ^{131}I-ICl gave 3-iodochloroquine (2) as product, however, the yield is low (≈ 20%). Iodination with H_2O_2/lactoperoxidase and with chloramine-T were more successful and labelled quinolines in yields up to 75% were obtained. It was surprising that I_2, contrary to ICl, was not able to iodinate chloroquine. Experiments on gram-scale revealed that I_2 reacts with the alkyl-side chain of chloroquine with formation of deethyl-chloroquine (3); no iodinated quinolines could be isolated. The electrophilic iodination with chloramine-T and with H_2O_2/lactoperoxidase were studied in detail.

The chloramine-T method gave the following results:

1) A complex mixture of labelled products with a maximum total yield of about 75% is formed. The yields and ratios between the different products not only depend on the amount of carrier KI, but also on the pH of the reaction mixture and the chloroquine and chloramine-T concentrations. An example is given in figure 2 and some results are summarized in table I. The main products are a still unidentified quinoline "X" and 3-iodochloroquine (2), when carrier or low chloroquine concentrations were used.
2) Besides iodinated quinolines also other compounds are formed in mass amounts. These are 3-chlorochloroquine (4) as a result of chlorination by chloramine-T and degradation products of chloroquine such as deethylchloroquine (3) in the presence of large amounts of carrier.

   The results for the lactoperoxidase/H_2O_2 method are summarized in table II. Again "X" and 3-iodochloroquine (2) are the main products (see figure 2).

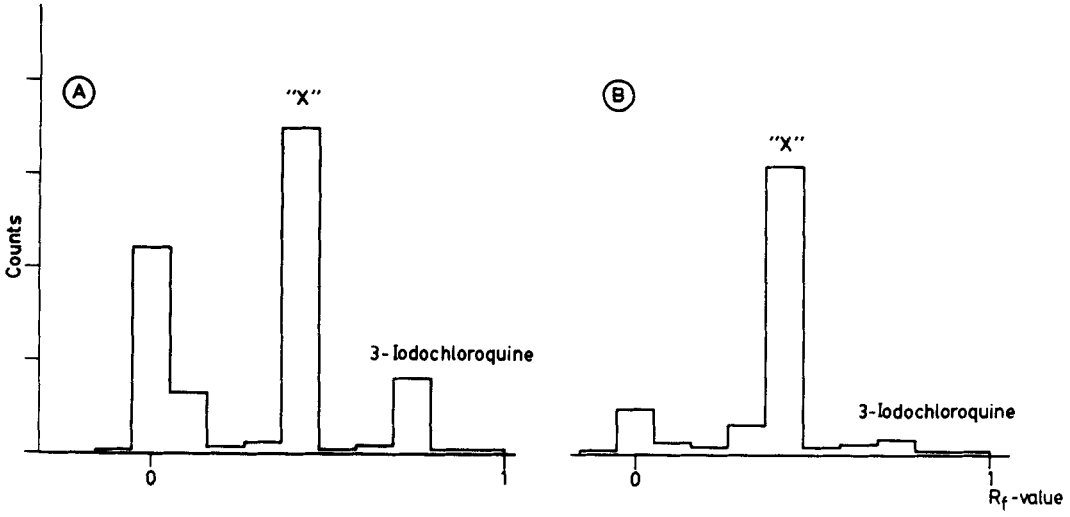

Figure 2 Thin layer analysis (SiO_2, benzene/triethylamine/H_2O = 5:5:1.5) of reaction mixtures of reactions of $Na^{131}I$ with chloroquine after removal of inorganic iodine species by chromatography over DEAE-sephadex.

A: reaction with chloramine-T; 1 M chloroquine-phosphate, pH = 3

B: reaction with lactoperoxidase/H_2O_2 at pH = 5; 0.1 M chloroquine-phosphate; 50 µM KI.

Table I Yields of labelled quinolines as a result of the reaction of chloroquine and chloramine-T with $Na^{131}I$ i) at pH = 6

Chloroquine concentration mM	Chloramine-T concentration mM	KI-conc. mM	Yield of labelled chloroquines in % total	3-iodo-chloroquine	"X"
1000	0	0	1.0	0.3	0.3
1000	2	0	45.0	15.0	20.0
		0.03	58.0	32.5	19.0
		0.3	57.0	39.0	14.5
		0.75	55.5	38.0	14.5
		1.5	33.0	15.0	14.0
		3.0	15.0	7.0	6.0
		3.75	2.5	1.5	2.0
		4.5	< 0.2	< 0.1	< 0.1
1000	4	0	47.5	17.0	17.5
		0.03	46.0	29.0	11.0
		0.3	58.5	45.0	8.0
		0.75	52.0	40.1	7.5
		1.5	54.0	45.0	6.5
		2.4	60.5	43.5	6.5
		3.0	25.0	12.0	10.0
		4.5	5.5	1.9	3.0
		6.0	1.0	0.6	0.1
250	2	0	31.0	16.0	12.0
		0.15	65.5	53.5	10.0
		0.3	69.0	60.5	6.5
		0.6	68.5	61.5	4.0
		1.5	9.0	2.5	4.0
100	2	0	39.5	18.0	13.0
		0.03	67.0	49.5	12.0
		0.15	77.0	67.0	6.0
		0.3	68.5	69.0	4.5
		0.75	63.5	56.0	4.0
		1.5	6.5	2.5	2.5

Table I - continued -

100	4	0	24.0	16.0	3.5
		0.3	44.5	37.5	4.5
		0.6	51.5	43.5	1.5
		0.75	54.0	49.5	1.4
		1.5	21.0	15.5	1.5
		3.0	5.0	4.0	0.5
25	2	0	33.0	26.0	4.0
		0.3	24.0	23.0	0.5
		0.6	11.0	11.0	0.2
		0.75	10.0	6.5	0.1
		1.5	0.5	0.2	0.1

i) Some experiments were performed with $Na^{123}I$; they gave the same results as the $Na^{131}I$ experiments.

Table II Formation of labelled quinolines by reaction of chloroquine and $Na^{131}I$ with H_2O_2/lactoperoxidase at pH = 6. Total H_2O_2-concentration 50 µM

Chloroquine concentration in mM	KI-concentration in µM	Yield in % 3-iodochloroquine	"X"
1000	5	1.0	18.0
250	5	2.0	26.5
100	0	0.7	6.9
	2.5	2.0	25.0
	5	3.0	37.5
	25	6.0	50.0
	50	3.5	38.0
	250	0.4	1.4
	500	0.1	0.3
25	5	2.5	22
10	5	2.0	16

Both labelling methods show a dependence on the iodide concentration. The carrier dependence with the case of lactoperoxidase is not surprising. From studies with other substrates it is known[12] that iodide has to be present in low concentrations to improve the labelling yields. The decrease of the yield at higher iodide concentrations is caused by the limited amount of oxidant present.

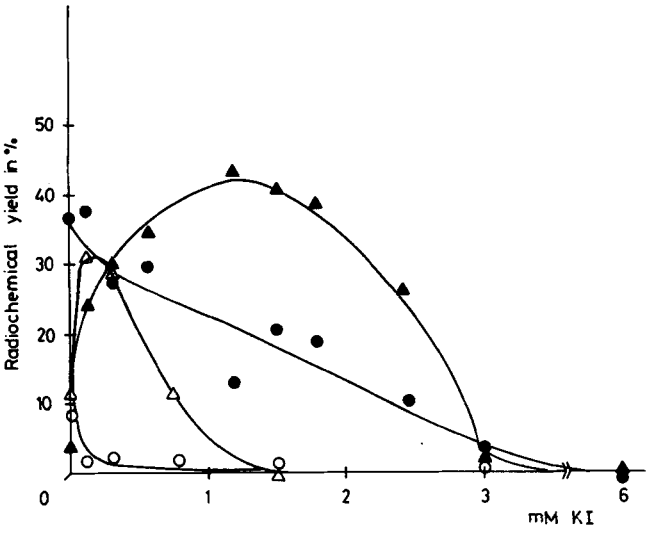

Figure 3 Radiochemical yields of 3-iodochloroquine (Δ) and other labelled chinolines (o) at pH = 4 with 2 mM chloramine-T.
▲ and ● yields at 1 M chloroquine
Δ and o yields at 0.1 M chloroquine

The carrier-effect with the chloramine-T method is striking. As can be seen in Table I and Figure 3 (where an example is given for labelling at pH = 4) two effects can be distinguished:

1) Without iodide-carrier the yield of 3-iodochloroquine (2) is rather low. This latter product becomes important with carrier-concentrations in the order of 0.15 - 1.0 mM.This appeared to be a common effect for all 7-halo-4-alkylaminoquinolines since both 7-chloro-4-butylaminoquinoline (5) and 4-(3-dimethylaminopropyl-amino)-7-iodoquinoline (6) showed similar carrier-dependences of the yield of labelled quinolines. With substrates like phenol and aniline, these effects were absent[13].
2) With large amounts of carrier - in the order of 1-2 equivalents with regard to chloramine-T - the yield of all labelled quinolines decreases to zero. Under these circumstances $^{131}I\text{-}I_2$ is formed[14] (brown colour of the reaction mixture). This species leads to deethylchloroquine (3) instead of to labelled quinolines as mentioned earlier. When no tertiary amino-group is present in the quinoline-side chain (such as in 7-chloro-4-butylamino-quinoline (5)) $^{131}I\text{-}I_2$ reacts as iodinating agent.
An interesting feature of the electrophilic iodination is the formation of "X" in the lactoperoxidase reaction or in the

chloramine-T reaction at high chloroquine concentrations and low iodide concentrations (Table I and Table II). We have not been able to isolate this product in amounts sufficient for identification. Synthesis by reaction of chloroquine with iodide and chloramine-T was not feasible due to the special reaction conditions. Also reactions with iodinating-agents like N-iodosuccinimide, $CF_3COOAg-I_2$, ICl and I_2 under different circumstances only yielded 3-iodochloroquine (2), deethylchloroquine (3) and 3-iododeethylchloroquine (7), but never product "X". Analysis of the labelled quinolines on sephadex LH20 in $CHCl_3$ indicated that product "X" is probably some iodinated dimer of chloroquine. Such a structure is in agreement with the dependence of this product on the chloroquine concentration in both the chloramine-T reaction and the H_2O_2/lactoperoxidase method (Fig. 4a).

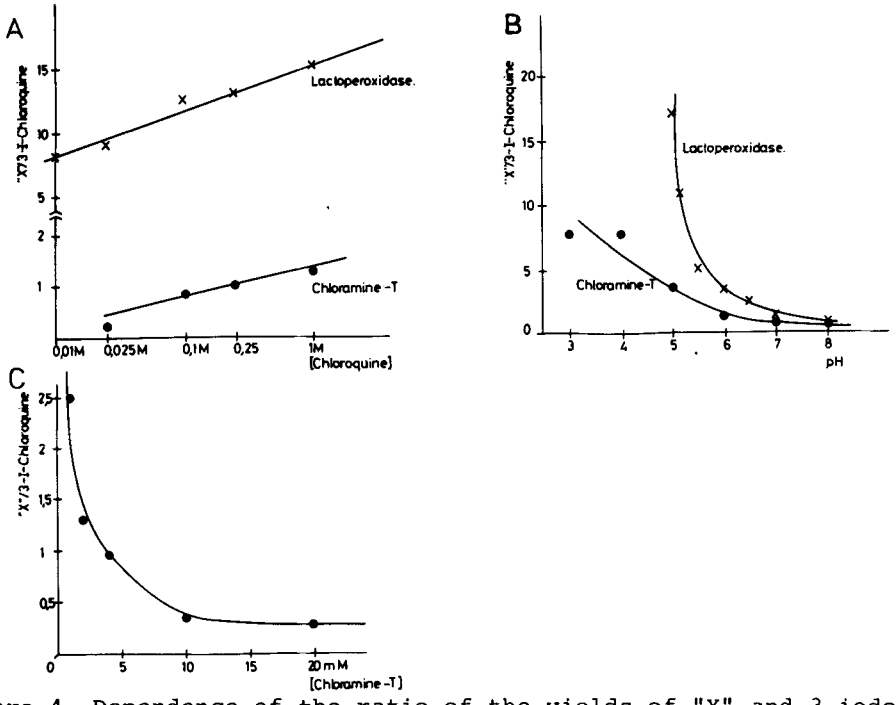

Figure 4 Dependence of the ratio of the yields of "X" and 3-iodochloroquine (3) as a function of several parameters in the reaction circumstances
chloramine-T method: 0 mM KI; lactoperoxidase: 5 µM KI
A) chloroquine concentration; pH = 6; chloramine-T concentration = 2 mM
B) pH; chloroquine concentration = 1 M; chloramine-T concconcentration = 2 mM
C) chloramine-T concentration; pH = 6; chloroquine concentration = 1M

Some variations in reaction conditions were made to study the effect on the formation of "X" and 3-iodochloroquine (2). The results are given in figure 4. As can be seen the ratio "X"/3-iodochloroquine is dependent on the chloroquine concentration (figure 4A), the pH (figure 4B) and for the chloramine-T method on the chloramine-T concentration (figure 4C). All these results can be understood if it is assumed that the electrophilic iodination is not a simple one-step reaction but proceeds via some sort of longer-lived addition complex [15] as is depicted in figure 5. This addition product is converted to 3-iodochloroquine (2) by reaction with OH^-. As can be seen in figure 4C the reaction with chloramine-T must also lead to 3-iodochloroquine, however, this is not a very efficient process. The effect of iodide is more complicated. With the H_2O_2/lactoperoxidase reaction there is no effect of the carrier-iodide up to 50 µM on the product ratios; the effect of the iodide-carrier on the chloramine-T method is evident. (See Table I and Table II). This indicates that in the latter case the carrier-effect is caused by a reaction- or oxidation product of iodide with chloramine-T.

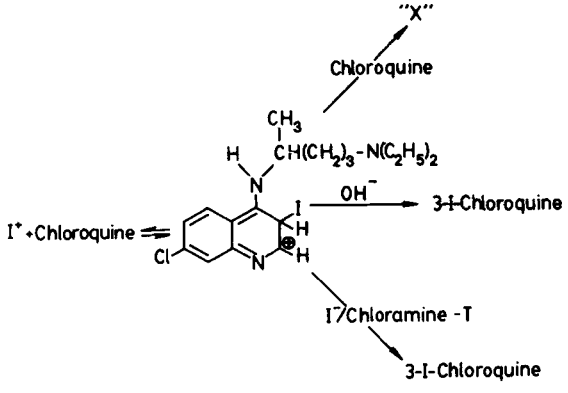

Figure 5 Tentative mechanism for the iodination of chloroquine

From these studies it is clear that small changes in reaction conditions can result in a large variation in the products. For application as radiopharmaceuticals for the detection of melanoma in the eye [4] this is very important because "X" and 3-iodochloroquine have different biological distributions. This can be concluded from Table III, where the results of some animal experiments are given.

3-iodochloroquine has a higher uptake in the tumor but the tumor/non-tumor ratio is better for "X".

Table III Distribution of ^{131}I-quinolines in Syrian Golden Hamsters with Greene melanoma; 6 hours after intravenous injection [i)]

Organ	Uptake as % of dose per gram of tissue for 3-iodochloroquine[ii)]	for "X"[iii)]
muscle	0.14	0.9
blood	0.40	0.1
liver	6.9	7.6
skin	0.9	0.55
eye	4.8	0.8
tumor	1.8	0.9

i) mean values of two hamsters

ii) prepared by reaction of chloroquine (0.1 M) with 2 mM chloramine-T and 0.6 mM KI at pH = 6

iii) prepared by reaction of chloroquine (0.1 M) with lactoperoxidase and 5 µM KI at pH = 5.

Chlorination reactions of chloramine-T:

The chlorinating properties of chloramine-T, probably mediated by dichloramine-T [16] are well known [17,18]. Chlorination when used for the labelling of organic compounds was not described before. Therefore we studied the chlorination reaction in comparison with the iodination reaction (in separate experiments) with ^{36}Cl-chloramine-T and Na^{131}I. The results are given in Table IV. The yields of the chlorinated products were determined by extraction with CH_2Cl_2. With three of the quinolines (chloroquine (1), 4-amino-7-chloroquinoline (8) and 4-butylamino-7-chloroquinoline (5) the reactions were repeated on gram-scale, the products were isolated and they were identified as the corresponding 3-chloroderivatives. The reaction of aniline with chloramine-T, with as products o- and p-chloroaniline, is described in the literature [18].

As can be seen in Table IV aniline and the 4-aminoquinolines are readily chlorinated. With the proteins and phenols the chlorination is limited. The pyridines are unreactive both for chlorination and for iodination. Probably stable charge-transfer complexes between the halogenating species and the pyridines are formed [19].

Table IV Yield of chlorinated and iodinated products by reaction with ^{36}Cl-chloramine-T or chloramine-T and $Na^{131}I$

Reaction conditions: 10 mM substrate, 10 mM ^{36}Cl-chloramine-T, (1 µCi $Na^{131}I$) in water at room temperature, pH 5-6

Substrate	% iodination		% chlorination	
	1 min	10 min	1 min	10 min
	reaction time			
bovine serum albumine	40-80 (30 sec)	not determ.	0.8-1.5 (30 sec)	not determ.
phenol	98	97	4.5	8.5
aniline	71	72	22	23
4-hydroxypyridine	3	3	0.2	3.5
4-aminopyridine	1.5	3	0.5	2.5
4-hydroxyquinoline (9)	5.5	5.5	1.5	0.5
4-butylaminoquinoline (10)	n.d.	n.d.	26	36
4-(4-diethylamino-1-methyl-butylamino)-quinoline (11)	n.d.	n.d.	20	30
4-amino-7-chloroquine (8)	3	5	26	44
4-butylamino-7-chloroquinoline (5)	4	7	70	75
chloroquine (1)	1.5	2	9	22

EXPERIMENTAL

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

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

The analysis of the ^{131}I and ^{123}I-products has been described earlier [8].

^{36}Cl-chloramine-T: this compound was prepared by recrystalizing chloramine-T from water of 50 °C containing $Na^{36}Cl$ (Amersham).

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

4-alkylaminoquinolines: these compounds were prepared by reaction of 4-chloro-7-iodoquinoline [20], 4,7-dichloroquinoline [21] or 4-chloroquinoline (Aldrich) 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.

4-butylaminoquinoline (10):
colourless crystals: 116° - 122 °C
IR(KBr): 1545, 1585 cm^{-1}
PMR($CDCl_3$): 0.9 (br.t.H_4,); 1.15-1.20 (m,H_2, and H_3,); 3.4 (m,H_1,); 6.52 (d,J = 7 Hz,H_3); 7.0-8.5(m,H_5-H_8); 9.02 (d=7 Hz,H_2)
Mass-spectrum: (Field Desorption) 200 and 201 (M^+ and MH^+)

4-(4-diethylamino-1-methylbutylamino)-quinoline (11):
yellow oil
IR(liq.cap.): 1550, 1585, 1625 cm^{-1}
PMR($CDCl_3$): 1.0 (t,Me); 1.30 (d,1'-Me); 1.65 (m,H_2, and H_3,); 2.52 (q,Me and H_4,); 3.6 (m,H_1,); 5.2 (m,NH); 6.47 (d,J=5 Hz,H_3); 7.2-7.9 (m,H_5-H_8); 8.6 (d,J=5 Hz, H_2)
Mass-spectrum (F.D.): 285 and 286 (M^+ and MH^+)

4-amino-7-chloroquinoline (8):
This compound was prepared as described by Baker *et al.* [22].

Electrophilic iodinations:

1) with chloramine-T: the reaction was carried out in 0.2 ml aqueous solution containing chloroquine-phosphate, $Na^{131}I$ (or $Na^{123}I$) and if necessary carrier KI. The pH of the reaction-mixture was adjusted with either H_3PO_4 or NaOH. The reactions were started by the addition of 0.02 ml chloramine-T (5,10 or 25 mg/ml) and were stopped after 15 minutes by the addition of $Na_2S_2O_5$ (0.05 ml of 10 mg/ml).
2) with lactoperoxidase: these reactions were carried out in 0.2 ml 100 mM phosphate-buffer pH = 6, containing chloroquine-phosphate, $Na^{131}I$, KI and 5 µg lactoperoxidase (Boehringer). The reactions were started by addition of 0.01 ml 1 mM H_2O_2; this addition of H_2O_2 was repeated after 7½ minutes and the reactions were stopped after 15 minutes with $Na_2S_2O_5$.

3-iodochloroquine (2): chloroquine-phosphate was dissolved in 90% H_2SO_4 (250 mg/ml). In portions of 100 mg N-I-succinimide (1.1 eq) was added over a period of 20 min. After stirring at room temperature for another 30 minutes, the reaction mixture was poured on ice and brought to pH = 13 with diluted NaOH. The mixture was extracted with CH_2Cl_2; the extracts were washed with brine and dried on $MgSO_4$. After removal of the solvent the residue was chromatografied on SiO_2 (eluent MeOH/Et_3N = 40:1). Yield 40%.
IR (liq.cap.): 1575, 1610 cm^{-1}.

PMR($CDCl_3$): 0.90 (t,C_2H_5); 1.00 (d,CH_3); 1.52 (m,$(CH_2)_2$); 2.43 (q and m,C_2H_5 and N-CH_2); 3.7-4.5(m, CH and NH); 7.35 (double d.J=9 and 2 Hz,H_6); 7.89 (d,J=9 Hz, H_5); 7.93 (d,J= 2 Hz,H_8); 8.83 (s,H_3).

The chromatographic behaviour, PMR and IR spectra of this compound were identical to those of the product obtained by reaction of 4,7-dichloro-3-iodoquinoline with 4-diethylamino-1-methylbutylamine in ethanol [8].

Deethylchloroquine (3): a solution of chloroquine-phosphate in acetic acid (1 gram/5 ml) was stirred at 70 °C for 3 hours with 1 equivalent I_2. After cooling to room temperature, the mixture was brought to pH = 14 with diluted NaOH. The quinolines were extracted with CH_2Cl_2 and deethylchloroquine was isolated by chromatography of this extract on SiO_2 (eluent methanol/triethylamine = 20:1).
Yield: 45% colourless oil.
m.p. as oxalate: 217° - 218 °C under decomposition (litt. [23]: 217° - 218 °C under decomposition).
IR (liq.cap.): 1550, 1587, 1616 cm^{-1}
PMR($CDCl_3$): 1.06 (t,C_2H_5); 1.25 (d,J=7 Hz,CH_3); 1.68 (m,$(CH_2)_2$); 2.65 (q and m,C_2H_5 and N-CH_2); 3.45-3.90 (m,CH and NH); 5.70 (m,NH); 6.32 (d,J=6 Hz,H_3); 7.25 (double d,J=2 and 9 Hz,H_6); 7.74(d,J=9 Hz,H_5); 7.90 (d,J=2 Hz,H_8); 8.46 (d,J=6 Hz,H_2).

3-iododeethylchloroquine (7): a solution of 3-iodochloroquine in acetic acid (1 gram/5 ml) was stirred at 70 °C with 2 eq. I_2 for 3 hours. The reaction mixture was adjusted to pH = 14 with diluted NaOH under cooling and 3-iododeethylchloroquine was isolated by extraction of the reaction mixture with CH_2Cl_2 and chromatography over SiO_2 with methanol/triethylamine (40:1).
Yield: 30%.
Slightly yellow oil.
IR(liq.cap.): 1570, 1610 cm^{-1}.
PMR($CDCl_3$):1.08 (t,C_2H_5); 1.22 (d,J=7 Hz, CH_3); 1.65 (m,$(CH_2)_2$); 2.65 (m and q, C_2H_5,N-CH_2); 3.8-4.6 (m,CH and NH); 7.42 (double d, J=2 and 9 Hz, H_6); 8.0 (d,J=9 Hz, H_5); 8.08 (d,J=2 Hz, H_8); 8.95 (s,H_2).
Mass-spectrum (F.D.): 417 and 419 (M^+).

Chlorination reactions with ^{36}Cl-chloramine-T: the reactions were carried out in 0.1 ml solutions containing the substrate (0.01 M) and ^{36}Cl-chloramine-T (1 eq.). The pH was adjusted to 5-6 with H_3PO_4. After 1 or 10 minutes the reactions were stopped by addition of sulphite. The reaction mixture was poured into a mixture of 25 ml

CH_2Cl_2/25 ml 0.1 N NaOH (or in the case of phenol CH_2Cl_2/H_2O) and this was thoroughly shaken for 5 minutes. The organic yield was determined by measurement (by liquid scintillation counting) of three aliquots of both the organic and the inorganic layer. For identification of the products the organic layer was chromatografied over SiO_2 with ethanol as eluent.

3-chlorochloroquine (4) has been described before [8].

4-amino-3,7-dichloroquinoline:
colourless crystals: m.p. 235°-237 °C.
IR(KBr): 1580, 1620, 1665 cm^{-1}.
PMR(d_6-DMSO): 7.18 (broad s,NH_2); 7.55 (double d., 2 and 9 Hz,H_6); 7.86 (d,J=2 Hz,H_8); 8.37 (d,J=9 Hz,H_5); 8.46 (s,H_2).
Mass-spectrum (F.D.): 212, 213, 215, 215 (M^+ and MH^+).

4-butylamino-3,7-dichloroquinoline:
slightly yellow crystals, m.p. 67°-71 °C.
IR(KBr): 1560, 1585 cm^{-1}.
PMR($CDCl_3$): 0.95 (m,CH_3); 1.2-2.0 (m,$(CH_2)_2$); 3.7 (m,N-CH_2); 4.82 (m,NH); 7.40 (double d,J=2 and 9 Hz,H_6); 7.98 (d,J=2 Hz,H_5); 8.60 (s,H_2).
Mass-spectrum (F.D.): 268, 269, 270, 271 (M^+ and MH^+).

ACKNOWLEDGEMENT

We thank Drs. J. van der Greef of the University of Amsterdam for recording the mass-spectra and Dr. R. Boer Iwema and Mrs. J.G. Journée-de Korver of the University of Leiden for performing the animal studies.
This work is part of the research program of the Institute of Nuclear Physics Research (IKO) and the Inter University Ophthalmological Institute (IOI), made possible by financial support from the Netherlands Ophthalmic Research Institute (IOI), the Foundation for Fundamental Research on Matter (FOM) and the Netherlands Organization for the Advancement of Pure Research (ZWO).

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