Regioselective Alkoxydehalogenation of 2,4-Dihalogenoquinolines and a Reinvestigation of the Bromination of 2-Methoxyquinoline

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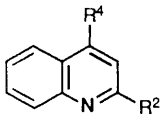
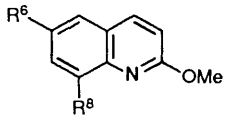
Regioselective alkoxydehalogenation of 2,4-dichloro- and 2,4-dibromo-quinoline with solid sodium alkoxide in toluene gives the 2-alkoxy-4-halogenoquinolines **7–10**, identified by ^{1}H and ^{13}C NMR spectroscopy. Bromination of 2-methoxyquinoline occurs at the 6- and 8-positions and does not give the 4-bromo derivative as originally reported.

The alkoxydehalogenation[1] of 2,4-dihalogenoquinolines **1**, **2** with alcoholic sodium alkoxide solution provides a convenient route to 2,4-dialkoxyquinolines **3**, **4**.[2–4] However, the complete two stage process is rather slow, and normally requires a 25 hour reaction period,[2,3] and in some cases as long as 200 hours.[5]

With shorter reaction times (*e.g.* 0.5 h) mixtures of products result, in which only a single halogen has been replaced,[6] kinetic studies have indicated that introduction of the first alkoxy group considerably inhibits the reactivity of the remaining halogen.[7,8] However, despite this considerable difference in reactivity, attempts to secure the individual monoalkoxy compounds have so far failed. Although an early attempt, using alcoholic potassium hydroxide as the reagent, was originally thought[9] to give **8** as the sole product, subsequent studies[4] have shown that this reaction medium also produced the other isomer **6**, with the 4-chloro substituent being only slightly the more reactive.[6,8] Consequently the monoalkoxyhalogenoquinolines **5–8** must either be obtained *via* the potassium hydroxide route, which then requires very laborious separations[4,8] or instead be prepared by chlorination of the appropriate quinoline[10] or quinoline *N*-oxide.[11,12]



	R^2	R^4
1	Cl	Cl
2	Br	Br
3	OMe	OMe
4	OEt	OEt
5	Cl	OMe
6	Cl	OEt
7	OMe	Cl
8	OEt	Cl
9	OMe	Br
10	OEt	Br



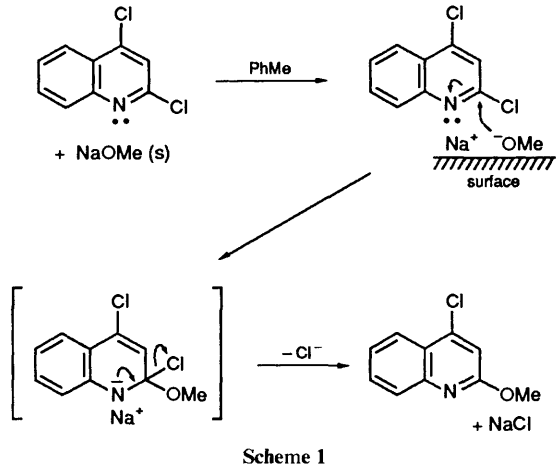
	R^6	R^8
11	H	H
12	Br	H
13	H	Br
14	Br	Br

We now wish to report a technique for the regioselective monoalkoxydehalogenation of 2,4-dihalogenoquinolines leading exclusively to the 2-alkoxy-4-halogenoquinolines **7–10** using solid sodium alkoxide suspended in toluene. The results are shown in Table 1. Such a selective reaction at the 2-position appears to be in contradistinction to the earlier kinetic studies[7,8] which indicated that the 4-chloro group in **1** was about 1.9 times the more reactive site towards methoxide ion in solution in the first stage. However, with our revised experimental conditions a high concentration of methoxide ion in solution is unlikely and therefore it is proposed that the observed selectivity arises from a surface reaction. It is probable that there is an initial mutual attraction between the sodium ion and the quinoline lone pair; once established the associated close methoxide ion can then only react at the 2-position, the 4-position being too distant (see Scheme 1). Moreover, the unsolvated methoxide ion would then exhibit increased nucleophilicity. A similar result was also obtained using anisole as solvent, however, since its subsequent removal proved more tedious, toluene is therefore preferred as the reaction medium.

Table 1 Synthesis of 2-alkoxy-4-halogenoquinolines

Reactants	Product	Yield (%)	m.p. (°C)	Lit. m.p. (°C) and ref.
1, NaOMe	**7**	61	72–73	73 (8)
1, NaOMe	**7**	58[a]	72–73	73 (8)
1, NaOMe	**7**	68[b]	71–72	73 (8)
1, NaOEt	**8**	58	41–42	43 (4)
2, NaOMe	**9**	62	79–80	93 (19)[c,d]
2, NaOEt	**10**	65	43–44	*e*

[a] Reaction time 3 h. [b] Solvent anisole (removed by distillation *in vacuo*). [c] For product *claimed* to be 4-bromo-2-methoxyquinoline (see Scheme 2). [d] Found: C, 50.6; H, 3.35; N, 5.85. C_9H_8BrNO requires C, 50.45; H, 3.39; N, 5.88%. [e] Found: C, 52.7; H, 4.1; N, 5.6. $C_{11}H_{10}BrNO$ requires C, 52.41; H, 4.00; N, 5.56%.



Scheme 1

An alternative explanation for the regioselectivity could envisage kinetic/thermodynamic control, however, this is considered unlikely. If the reaction was under kinetic control then the more favourable 4-alkoxy products **5**, **6** *etc.* would be expected; whilst the exclusive formation of **7–10** even after a

Table 2 270 MHz ^{1}H NMR spectra of some 2-alkoxy-4-halogenoquinolines and related compounds

	δ_H[a]								
						2-OR		4-OR	
Compound	3-H	5-H	6-H	7-H	8-H	CH_2	CH_3	CH_2	CH_3
1	7.480	8.162	7.627	7.769	8.011	—	—	—	—
2	7.838	8.146	7.655	7.770	8.026	—	—	—	—
3[b]	6.218	8.045	7.327	7.592	7.780	—	4.056	—	3.984
4	6.193	8.075	7.317	7.581	7.747	4.512	1.435	4.200	1.545
7	7.031	8.105	7.460	7.671	7.860	—	4.048	—	—
8	7.003	8.080	7.426	7.644	7.837	4.486	1.415	—	—
9	7.233	8.060	7.445	7.648	7.831	—	4.051	—	—
10	7.205	8.032	7.414	7.619	7.790	4.496	1.426	—	—
Coupling constants (J/Hz)									
	J_{56}	J_{57}	J_{58}	J_{67}	J_{68}	J_{78}	J_{alk}		
1	8.4	1.4	0.6	7.0	1.2	8.5	—		
2	8.4	1.5	0.6	7.0	1.3	8.4	—		
3[b]	8.2	1.6	0.6	6.9	1.2	8.4	—		
4	8.3	1.6	0.6	6.8	1.2	8.3	7.1		
7	8.2	1.4	0.6	6.9	1.2	8.3	—		
8	8.4	1.4	0.6	7.1	1.2	8.3	7.1		
9	8.3	1.5	0.6	6.9	1.2	8.4	—		
10	8.3	1.4	0.6	7.0	1.2	8.5	7.1		

[a] In $CDCl_3$ solution. [b] Data from ref. 3.

Table 3 67 MHz ^{13}C NMR chemical shifts of some 2-alkoxy-4-halogenoquinolines and related compounds [a]

	δ_C									
Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	O-Alkyl
1	150.14	122.19	144.65	124.43	128.13	131.79	129.23	148.44	125.40	—
2	140.95	129.07	135.42	127.19	128.50	131.75	129.43	149.04	127.03	—
3	163.77	90.62	163.81	121.80	123.21	129.86	126.86	147.04	119.23	53.31 (2-OMe) 55.56 (4-OMe)
4	163.52	91.27	163.03	121.87	123.02	129.77	126.83	147.19	119.28	14.41 (2-Me) 61.54 (OCH_2-2) 14.68 (4-Me) 64.01 (OCH_2-4)
7	161.83	112.81	143.65	124.04	124.72	130.46	127.55	146.93	123.27	53.67
8	161.52	113.01	143.52	123.97	124.56	130.33	127.55	147.02	123.20	14.50 (Me) 62.05 (OCH_2)
9	161.78	116.71	134.86	126.63	124.99	130.46	127.62	146.66	124.49	53.73
10	161.45	116.91	134.75	126.56	124.85	130.35	127.58	146.74	124.40	14.52 (Me) 62.14 (OCH_2)

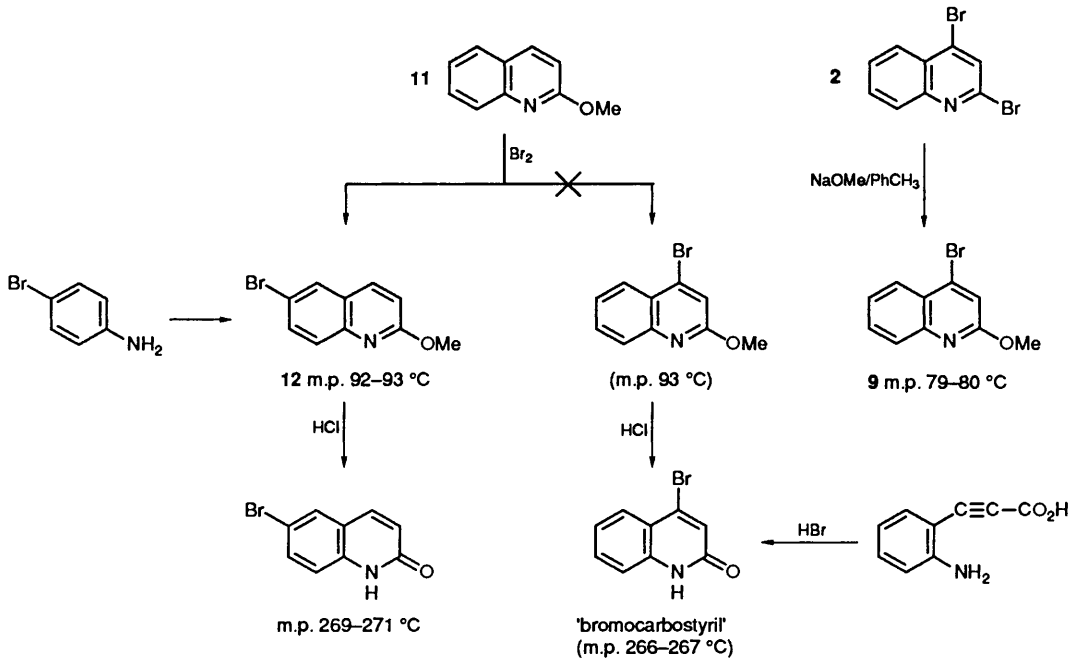
[a] In $CDCl_3$

very short reaction period (10 min) is inconsistent with thermodynamic control.

Since the melting points of **5** and **7** are very similar,[8] product identification was by NMR spectroscopy. The results are shown in Tables 2–4. In the 270 MHz ^{1}H NMR spectrum of **7**, it was immediately evident that a monoalkoxy compound had been obtained since the 3-H absorption was intermediate between those of **1** and **3** and only a single OMe peak was present, the shift of which was more consistent with the 2-OMe of **3**. However, since the respective *peri*-deshielding effects of the 4-Cl and 4-OMe substituents upon the chemical shift of 5-H were very similar, *viz*: **1** (δ 8.162) and **3** (δ 8.045) the intermediate observed shift (δ 8.105) did not permit a firm identification.

The final definitive structural differentiation followed from a ^{13}C NMR spectral study. That the regioselective products were the 2-alkoxy-4-halogenoquinolines was initially suggested by the methoxy resonance of **7** at *ca.* δ 53, clearly more in accordance with a 2-OMe group. Likewise the shifts of C-4 and C-5 were each consistent with these carbons being *ipso* and γ respectively to the 4-chloro substituent. Further support came from the proton coupled spectrum, and in particular from the heterocyclic ring splittings, J_{33} being intermediate between the couplings in **1** and **3**. The most informative signal was that for C-4 which appeared as a triplet of fine doublets. The lack of any quartet splitting thus indicated that the methoxy group was at the 2-position. Additional confirmation of the retention of the 4-chloro substituent came from the weak $^4J_{48}$ coupling which has recently been shown[14] to occur with 4-halogenoquinolines. The J_{43} coupling, which does not occur in quinoline[15] is enhanced by both chloro and methoxy substituents.[3,16] A quartet was observed for C-2 of **7**, confirming 2-alkoxy substitution, there was no coupling to 3-H, this splitting being characteristically reduced by both chloro and methoxy substituents.[3,17] All proton and carbon assignments were confirmed by the appropriate connectivities in the 2D HETCOR spectrum.[18]

The sample of **9** (m.p. 79–80 °C) obtained in the present work



Scheme 2

Table 4 ^{13}C–^{1}H Coupling constants (Hz) of some 2-alkoxy-4-halogenoquinolines and related compounds [a]

	Compound				
Coupling	1 [b]	3 [c]	7	8 [f]	9
J_{23}	0	3.7	0	0	0
$J_{2.OMe}$	—	3.7	2.9	*d*	2.9
J_{33}	176.1	163.6	171.2	170.9	171.2
J_{43}	4.4	3.7	4.9	4.9	4.9
J_{45}	5.4	3.7	4.9	4.9	4.9
J_{48}	1.6	—	2.0	*e*	2.0
$J_{4.OMe}$	—	3.7	—	—	—
J_{55}	165.0	162.4	162.5	162.4	162.4
J_{57}	7.0	7.3	7.9	8.5	7.8
J_{66}	162.7	161.2	162.4	162.4	162.4
J_{68}	8.6	8.6	8.8	8.6	8.8
J_{77}	163.8	162.4	161.4	161.1	161.4
J_{75}	9.0	8.5	8.8	8.5	9.8
J_{88}	166.1	162.3	163.4	163.4	163.4
J_{86}	6.5	7.3	6.3	6.9	6.9
J_{95}	6.7	7.3	6.3	6.4	6.4
J_{97}	6.7	7.3	9.3	9.2	9.2
$J_{10.3}$	5.1	4.9	4.9	4.9	4.9
$J_{10.6}$	8.9	8.5	8.8	8.8	8.8
$J_{10.8}$	5.1	4.9	4.9	4.9	4.9
J_{OCH_3}	—	145.3	145.9	—	145.7
J_{CH_3}	—	—	—	127.0	—
J_{OCH_2}	—	—	—	146.5	—

[a] Coupled spectrum of **10** not included, since of poorer quality. [b] Some data from refs. 13 and 14. [c] Some data from refs. 3 and 13. [d] $J_{2.OCH_2}$ coupling near zero, no indication of splitting. [e] Splitting not resolved. [f] $J_{CH_3CH_2O}$ = 2.4 Hz, $J_{OCH_2CH_3}$ = 4.9 Hz.

Table 5 270 MHz ^{1}H NMR spectra of bromination products (in $CDCl_3$)

Com-	δ_H						
pound	3-H	4-H	5-H	6-H	7-H	8-H	OMe
11	6.877	7.929	7.679	7.348	7.600	7.854	4.064
12	6.830	7.744	7.742	—	7.610	7.663	4.022
13	6.862	7.849	7.570	7.143	7.887	—	4.109
14	6.892	7.794	7.740	—	7.982	—	4.101
Coupling constants (*J*/Hz)							
	J_{34}	J_{56}	J_{57}	J_{68}	J_{67}	J_{78}	
11	8.8	7.9	1.6	1.2	6.9	8.3	
12	8.7	—	2.0	—	—	8.3	
13	8.3	m	m	—	m	—	
14	8.7	—	2.0	—	—	—	

m = multiplet

appears to be inconsistent with the product (m.p. 93 °C) isolated by Friedländer and Weinberg[19] from the bromination of **11**. These workers concluded that 4-substitution had occurred since hydrolysis of the product afforded a 'bromocarbostyril' (m.p. 266–267 °C) which appeared to be identical[9] with 4-bromo-2-quinolone (m.p. 266 °C) then recently obtained from *o*-aminophenylpropiolic acid by Baeyer and Bloom.[20] (See Scheme 2.)

Accordingly we have re-investigated the bromination of 2-methoxyquinoline. Treatment of **11** with bromine vapour, as originally suggested,[19] initially gave an insoluble bromo-addition compound which on treatment with base afforded a 35:65 mixture of **12** and **13** as shown by 270 MHz ^{1}H NMR spectroscopy. Since this reaction was difficult to control quantitatively in the vapour phase, bromination was also conducted in acetic acid solution. With two equivalents of bromine a 40:60 mixture of **12** and **13** was again produced, with one equivalent of bromine a similar mixture was also obtained, with some unchanged **11**. Repeated recrystallisation of the crude **12**/**13** mixture from an ethanol–water solvent pair, as originally detailed by Friedländer and Weinberg,[19] eventually afforded, as the least soluble product, pure **12** (m.p. 92–93 °C). The m.p. was consistent with an authentic sample of **12** recently obtained[21] by an unambiguous synthesis. Subsequent reaction of **12** with hydrochloric acid would then give 6-bromo-2-quinolone (m.p. 269–271 °C)[22] the melting point of which is extremely similar to the reported 4-bromo isomer previously used for characterisation (see Scheme 2). With a large excess of bromine in acetic acid, the dibromo compound **14** was readily isolated in good yield.

Thus the presence of the electron donating methoxy group is still not sufficient to promote substitution in the heteroring.

Table 6 67 MHz ^{13}C NMR chemical shifts of bromination products (in $CDCl_3$)

	δ_C									
Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	OMe
11	162.37	113.04	138.61	129.45	123.95	127.40	127.22	146.56	125.05	53.33
12	162.48	113.94	137.46	132.54	117.05	129.36	128.88	145.16	126.13	53.46
13	162.73	113.69	138.99	127.02	124.29	132.97	122.48	143.59	126.04	53.66
14	162.93	114.72	138.02	129.07	116.42	135.42	123.39	142.57	126.63	53.85

Substitution at the 6- and 8- positions is entirely in accordance with the conclusions from previous bromination studies.[23]

The ^1H and ^{13}C NMR spectra of the bromination products are shown in Tables 5 and 6. That substitution did not occur at the 4-position was immediately apparent by the presence of a doublet (J_{34} 8.7 Hz) for 3-H. The identity of **12** was readily deduced from the characteristic hetero ring AMX splitting pattern whilst that of the dibromo compound **14** followed from the symmetrical *meta*-coupled (J_{57}) AB system indicating the lack of any J_{48} 'zig-zag' interaction.[24] The ^{13}C NMR spectra were readily assigned by calculation of estimated chemical shifts from suitable[25] S.C.S. data, no discrepancy greater than 1 ppm was found.

Experimental

General Experimental Details.—M.p.s were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by MEDAC Ltd., Chemistry Department, Brunel University. NaOMe and NaOEt were commercially available. Compounds **1** (m.p. 66–67 °C)[3], **2** (m.p. 92–93 °C)[26] and **11** (b.p. 246–247 °C)[27] were synthesised by established procedures. ^1H (270.17 MHz) and ^{13}C (67.94 MHz) NMR spectra were recorded in $CDCl_3$ solution on a JEOL EX270 instrument with $(CH_3)_4Si$ as internal reference.

Preparation of 2-Alkoxy-4-halogenoquinolines: General Alkoxydehalogenation Procedure.—To a solution of **1** (5.0 g) in toluene (40 cm^3) was added a suspension of solid NaOMe (5.0 g) in toluene (40 cm^3). The mixture was boiled under gentle reflux for 24 h and then allowed to cool. The precipitated NaCl and unchanged NaOMe were filtered off; removal of the toluene by rotary evaporation left crude **7** (61%). Recrystallisation from a methanol–water solvent pair afforded pure **7** as colourless needles, m.p. 72–73 °C (lit.,[8] m.p. 73 °C). Results from other alkoxydehalogenation reactions are shown in Table 1.

Bromination of 2-Methoxyquinoline **11**.—(i) *With bromine vapour.* Exposure of **11** (2.0 g) to bromine vapour for 30 min gave an ether insoluble bromoaddition compound as a thick orange oil. Excess dilute NaOH solution was added and the mixture extracted with ether and dried ($MgSO_4$). Removal of the solvent left a 35:65 mixture of **12** and **13** (by 270 MHz ^1H NMR spectroscopy) as a brown oil.

(ii) *With bromine in acetic acid.* (*a*) To a solution of **11** (2.0 g) in glacial acetic acid (10 cm^3), 10% w/v bromine in acetic acid solution (22 cm^3) was added portionwise and the mixture then allowed to stand at room temp. for 1 h. The reaction mixture was made alkaline with dilute NaOH and then treated and analysed as in (i) to furnish a 40:60 mixture of **12** and **13** as a brown oil, which partially crystallised after standing for several days. Repeated recrystallisation of the solid component from an ethanol–water solvent pair eventually afforded pure **12** (0.09 g, 3%) as colourless needles, m.p. 92–93 °C (lit.,[21] m.p. 92 °C).

(*b*) A similar reaction to (*a*), with less bromine solution (11 cm^3) furnished a mixture of **12** (20%), **13** (30%) and unchanged **11** (50%).

(iii) *With excess of bromine in acetic acid.* A similar reaction to (*a*), with excess 20% w/v bromine solution (150 cm^3) after addition of dilute NaOH gave a thick red oil. Two recrystallisations from an ethanol–water solvent pair with the aid of charcoal gave *6,8-dibromo-2-methoxyquinoline* **14** (1.65 g, 41%) as colourless fine needles, m.p. 111–112 °C (Found: C, 37.95; H, 2.3; N, 4.35. $C_{10}H_7Br_2NO$ requires C, 37.89; H, 2.33; N, 4.42%).

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