2,4-Dihalogenoquinolines. Synthesis, Orientation Effects and ^1H and ^{13}C NMR Spectral Studies

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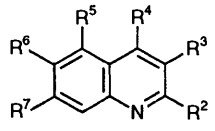
Isomer ratios for the syntheses of 2,4-dichloroquinolines from *meta*-substituted and 3,4-disubstituted anilines are reported, a synthesis of 2,4-dibromoquinoline **1b** is also described. The structures of certain bromination products **17** and **1f** obtained from 4-hydroxy-2-quinolone have been revised. A thorough study of the ^1H and ^{13}C NMR spectra of a series of 2,4-dihalogenoquinolines is presented and the effects of the halogen substituents on J_{CH} couplings are highlighted.

We have recently reported[1] a study of the regioselective alkoxydehalogenation of 2,4-dihalogenoquinolines **1a** and **1b** to the appropriate 2-alkoxy-4-halogenoquinolines. This paper is concerned with the synthesis and spectral characteristics of the starting materials **1a–12a**, **1b** and **2b**.



	R^5	R^6	R^7		R^2	R^3	R^4
1	H	H	H	a	Cl	H	Cl
2	H	Me	H	b	Br	H	Br
3	Me	H	H	c	Cl	Cl	Cl
4	H	H	Me	d	H	Cl	Cl
5	Cl	H	H	e	Cl	Br	Cl
6	H	H	Cl	f	Br	Br	Br
7	MeO	H	H	g	Cl	H	H
8	H	H	MeO	h	H	H	Cl
9	Me	Me	H	j	H	H	H
10	H	Me	Me	k	H	H	Me
11	Cl	Cl	H				
12	H	Cl	Cl				

It has long been known[2] that condensation of an aromatic primary amine with malonic acid in the presence of phosphorus oxychloride affords the 4-hydroxy-2-quinolone **15**, which with an excess of the reagent[3] then gives the required 2,4-dichloroquinoline **1a**. Ziegler and Gelfert[4] have subsequently reported a facile 'one-pot' synthesis and the procedure has been extended to the preparation of further derivatives by Shah *et al.*[5] However, as far as the present authors are aware the synthesis of 2,4-dibromoquinoline **1b** by this route has not been reported.

A feature of particular interest[6–8] in the synthesis of quinoline derivatives is the possibility of the formation of isomeric products from reactions commencing with *meta*-substituted or 3,4-disubstituted anilines. However, only a few isolated studies of orientation effects in syntheses leading to 2,4-dichloroquinolines are available.[5,9–11] Moreover, in most instances no spectroscopic evidence was given to support any of the reported structures. Thus Shah *et al.*[5] suggested that the reaction of *meta*-toluidine gave only 2,4-dichloro-7-methylquinoline **4a**, however, the m.p. of their product was very close to that of 2,4-dichloro-5-methylquinoline **3a**, previously obtained[12] by an unambiguous nine-stage synthesis from 2-methyl-6-nitroaniline. Although reaction with *meta*-chloroaniline has been reported[5,10] to furnish 2,4,7-trichloroquinoline **6a** only (product identification by comparison with an authentic sample),[13] in contrast, that with 3,4-dichloroaniline[10] gave a mixture. Narasimhan and Mali[11] have studied the reaction with *meta*-anisidine and obtained a mixture of products in which 2,4-dichloro-7-methoxyquinoline **8a** predominated over 2,4-dichloro-5-methoxyquinoline **7a**, from the respective ratios of the corresponding trimethoxyquinolines isolated after methoxydechlorination. A thorough re-examination of these orientation effects studies, with product identification by spectroscopic techniques, is therefore clearly warranted.

Apart from our very recent work,[1,14] reports of NMR spectral data for 2,4-dihalogenoquinolines are particularly scarce. Beak *et al.*[15] measured the ^1H NMR spectra of **1a** and also reported a 220 MHz analysis of 2,3,4-trichloroquinoline **1c**, in which 8-H was assigned as the most downfield signal. Tong[16] studied the chlorination of quinoline and identified the products, which were mainly 3,4-dichloroquinolines, including **6d** and **12d**, by ^1H NMR spectroscopy. In all cases 5-H was located downfield of 8-H in contradistinction to the earlier work.[15]

Smith and co-workers[17] have reported ^{13}C chemical shifts for **1g** and **1h**; whilst studies of J_{CH} couplings constants are available for quinoline **1j**,[18] and also for the halogenopyridines.[19,20] In this paper we present a detailed discussion of the assignments of the ^1H and ^{13}C NMR spectra of the 2,4-dihalogenoquinolines, some of the results have been previously reported.[1,14]

For the previous study[8] on orientation effects, three independent techniques were utilised for isomer identification and distribution, *viz:* GC, ^1H NMR spectroscopy and fractional crystallisation of the picrate derivative. In view of the lower volatility of the 2,4-dihalogenoquinolines, GC techniques have not been employed in the present study. The old established technique[21] of fractional crystallisation has been employed to isolate pure samples of individual isomers for direct comparison with the products reported by the earlier workers.[5,9–13] Structural identification of isomers was initially by ^1H NMR spectroscopy from their characteristic carbocyclic ring-splitting patterns as discussed previously.[8] Isomer ratios were assessed by comparison of peak areas of the appropriate well separated, sharp 3-H singlet signals, and also from the alkyl or alkoxy signals where applicable. Product identifications were further supported by ^{13}C NMR spectral studies. The results of the orientation effects studies are collected in Table 1, the properties of all of the synthesized/isolated compounds are shown in Tables 2 and 3.

From *meta*-toluidine, in contradistinction to the earlier work,[5] a mixture of 2,4-dichloro-5-methylquinoline **3a** (58%) and 2,4-dichloro-7-methylquinoline **4a** (42%) was obtained as

assessed by NMR spectroscopy. Fractional crystallisation of the initial product from aqueous ethanol resulted in a partial separation providing two samples each enriched in a particular isomer. Subsequent careful fractional crystallisation of the first sample then provided the pure 5-isomer (m.p. 133–4 °C), consistent with compound **3a** previously synthesised by Gabriel and Thieme.[12] Shah *et al.*[5] previously isolated a similar product but erroneously presumed their single isomer to be the 7-methyl compound. Subsequent careful fractional crystallisation of the second sample then provided the pure 7-isomer (m.p. 106–7 °C), the m.p. of which was surprisingly consistent with the sample of compound **4a** obtained in the earlier study of Hardman and Partridge.[9] These workers investigated the interaction of ethyl cyanoacetate with some *meta*-substituted arylammonium arenesulfonates to provide the isomeric 5- and 7-methyl-2-amino-4-quinolones. For product identification the separated 7-isomer was then converted through five steps into compound **4a**. Subsequent reduction then gave 1,2,3,4-tetrahydro-7-methylquinoline authenticated by comparison with a sample obtained by reduction of 7-methylquinoline **4j**.[6] However, since it has subsequently been shown[7,8] that the allegedly authentic sample of **4j**[6] used for the degradation would still have been contaminated with the 5-methyl isomer, a doubt is therefore cast over the precise composition of the actual isolated products. It would thus appear that through the many stages that the preparations required, and the numerous purifications involved, the respective pure 7-methyl isomers were unwittingly separated.

From 3,4-dimethylaniline a 50:50 mixture of 2,4-dichloro-5,6-dimethylquinoline **9a** and 2,4-dichloro-6,7-dimethylquinoline **10a** was produced, fractional crystallisation from aqueous ethanol afforded a pure sample of the 5,6-dimethyl isomer. This result contrasts with our earlier work[8] on the analogous Skraup reaction in which the separation procedure ultimately gave 6,7-dimethylquinoline. These differing solubility characteristics thus hinder interpretation of the outcome of the reaction.

Lutz *et al.*[13] presumed that use of *meta*-chloroaniline in a quinoline ring closure with malonic acid and phosphorus oxychloride seemed certain to lead to a mixture of the 5- and 7-isomers, as found in a related synthesis with acetylmalonic ester then recently reported.[23] Hence, for their detailed methanolysis studies, the required sample of 2,4,7-trichloroquinoline **6a** was instead obtained by an unambiguous six-stage route from 2-acetamido-4-chlorobenzoic acid. However, despite this earlier reservation and presumption,[13] in both later studies[5,10] only the 7-chloro isomer was claimed to have been formed in the cyclisation reaction. In both cases, however, this conclusion was only reached since the m.p. of the isolated product appeared to be completely consistent with that of the authentic **6a** obtained unambigously by Lutz *et al.*,[13] no spectral evidence was offered in support. In the present work, ^{1}H NMR analysis indicated that a mixture of 2,4,5-trichloroquinoline **5a** (63%) and the 2,4,7-isomer **6a** (37%) was indeed obtained, in accordance with the original presumption of Lutz *et al.*[13] Numerous attempts were then made to effect a separation of the isomers by fractional crystallisation from acetone, methanol, ethanol and aqueous ethanol, but these were generally unsuccessful. However, in one particular attempt in which the *exact* ethanol:water solvent ratio had fortuitously been employed, a small sample of pure **5a** was isolated as the first separated fraction. Hence it would appear that the product actually obtained by the previous workers[5,10] was likely to have been a mixture (see Table 2) and not pure **6a**, the accidental correspondence of m.p. being most unfortunate. Hardman and Partridge[9] also obtained a mixture of products from *meta*-chloroanilinium benzenesulfonate, which were instead identified as chloroisatins rather than as the corresponding tetrahydroquinolines described earlier.

The reaction with 3,4-dichloroaniline gave a 60:40 mixture of 2,4,5,6-tetrachloroquinoline **11a** and 2,4,6,7-tetrachloroquinoline **12a**, however, all attempts to separate the isomers failed. Previously Ziegler *et al.*[10] had reported that a mixture of

Table 1 2,4-Dichloroquinoline product isomer ratios

Substituted aniline	Yield (%)[b]	M.p. (°C)	Composition of mixture (%)[a] Isomer 1	Isomer 2
m-Me	66	84–86	**3a** (58)	**4a** (42)
m-Cl	76	80–83	**5a** (63)	**6a** (37)
m-OMe	78	92–96	**7a** (28)	**8a** (82)
3,4-Me_2	62	74–76	**9a** (50)	**10a** (50)
3,4-Cl_2	62	112–116	**11a** (60)	**12a** (40)

[a] By ^{1}H NMR, 3-H peak integrations. [b] Initial yield of mixed isomers.

Table 2 Synthesis of 2,4-dihalogenoquinolines

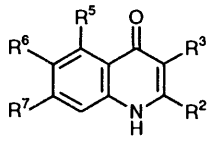
Compound	Yield (%)[a]	M.p. (°C)[a]	Lit. m.p. (°C) (ref.)
1a	63	65–66	66–67 (5)
2a	84	93–94	94–95 (5)
3a	7[b]	133–134	132 (12)[c]
4a	1[b]	106–107	107–108 (9)[c]
5a	3[b]	122–124	*c*
6a	15[d]	95–100	106–107 (13)
8a	4[b]	131–132	132 (9)[c]
9a	5[b]	112–113	*c*
12a	12[e]	135–139	*c*
1b	76	92–93	93–93 (22)[c]
2b	73	101–102	*c*

[a] For yields and m.p.s of combined mixed isomers see Table 1. [b] Yield of pure compound obtained after fractional crystallisation. [c] For elemental analysis, see Table 3. [d] Fractional crystallisation was unsuccessful, fraction quoted was mixture of **6a** (55%) and **5a** (45%). [e] Fractional crystallisation was unsuccessful, fraction quoted was mixture of **11a** (70%) and **12a** (30%).

Table 3 Elemental analyses of quinoline products

Compound	Molecular formula	Calc. (%) C	H	N	Found (%) C	H	N
3a	$C_{10}H_7Cl_2N$	56.63	3.32	6.60	56.9	3.25	6.5
4a	$C_{10}H_7Cl_2N$	56.63	3.32	6.60	56.7	3.05	6.45
5a	$C_9H_4Cl_3N$	46.49	1.73	6.02	46.75	1.6	6.15
8a	$C_{10}H_7Cl_2NO$	52.66	3.09	6.14	52.6	3.2	6.2
9a	$C_{11}H_9Cl_2N$	58.43	4.01	6.19	58.4	3.9	6.1
11a/12a	$C_9H_3Cl_4N$	40.49	1.13	5.24	40.6	1.3	5.1
1b	$C_9H_5Br_2N$	37.67	1.75	4.88	37.7	1.65	4.75
2b	$C_{10}H_7Br_2N$	39.90	2.34	4.65	39.7	2.25	4.4

Table 4 Orientation effect studies leading to 4-quinolones



Substituted aniline	R^2	R^3	Isomer ratios[a] Isomer 1[c]	Isomer 2[d]	Identif. techn.[b]	Ref.
m-Me	Me	H	Mx	Mx	M	26
m-Me	Me	H	56	44	F	27
m-Me	Me	H	Mx	Mx	F	28
m-Me	Me	H	57	43	N	29
m-Cl	Me	H	Mx	Mx	F	27, 28
m-Cl	Me	H	10[e]	40[e]	F	30
m-Cl	CO_2Et	Me	Mx	Mx	F	31
m-Cl	OH	COMe	16	84	F	23
3,4-Me_2	Me	Me	24[f]	76[f]	F/N	29
3,4-Cl_2	CO_2Et	H	Mx	Mx	M	32
3-F-4-MeO	CO_2Me	H	23	77	N	33

[a] Mx = mixture, proportions not specified. [b] M = wide range m.p. suggesting mixture. F = fractional crystallisation to give one or both isomers. N = NMR spectral analysis by integration. [c] R^5 = subst., R^6 = R^7 = H or R^5 = R^6 = subst., R^7 = H. [d] R^7 = subst., R^5 = R^6 = H or R^6 = R^7 = subst., R^5 = H. [e] Isolated yields of products. [f] Partial separation may have occurred, isomer values could be unreliable.

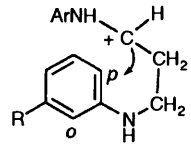
5,6- and 6,7-dichloro-4-hydroxy-2-quinolones was obtained by a similar process but without the chlorination stage. No product ratio was reported, the individual isomers were identified by conversion into the appropriate dichloroisatins. That these workers[10] should report a mixture of products from 3,4-dichloroaniline but only a single isomer from *meta*-chloroaniline does appear somewhat inconsistent.

A mixture of 2,4-dichloro-5-methoxy- **7a** (28%) and 2,4-dichloro-7-methoxy-quinoline **8a** (82%) was obtained from the reaction with *meta*-anisidine. Previously Narasimhan and Mali[11] had reported that the 7-isomer predominated. However, in contrast to this earlier work it did prove possible to separate a pure sample of **8a** by careful fractional crystallisation from aqueous ethanol. The m.p. of the product was again consistent with that reported by Hardman and Partridge[9] through their multi-stage authentication sequence from *meta*-methoxyanilinium benzenesulfonate and ethyl cyanoacetate.

Since 4-methyl- and 4-chloro-groups have been reported[29] to have similar spatial requirements, the results of the orientation effects studies leading to the 2,4-dichloroquinolines **4a** and **10a** might appear, at first sight, to be in conflict with the earlier study[8] of 4-alkylquinoline syntheses which gave the appropriate 7- or 6,7-isomers **4k** and **10k**, exclusively. However, since the halogenation step actually occurs after ring closure,[4] then such a direct comparison is obviously inappropriate, since the intermediate 4-hydroxy group would be able to rotate out of the aromatic ring plane to an approximately orthogonal position and thereby relieve the effect of steric hindrance. A more appropriate correlation may therefore be attempted with the Conrad–Limpach synthesis[25] of 4-quinolones. However, unlike the detailed orientation effect studies available for the Skraup synthesis,[6–8] no such investigation has been performed for those syntheses leading to 4-quinolones, a collection of some of the available work is given in Table 4.

It is evident from Table 4 that few reliable isomer ratios[27,29,33] are available, and that many of the older reports[26,28] lack rigorous structural proof. However, it is clear that most authors have concluded that mixtures of isomers are produced, which, at least, is in accordance with the present study. The following rules may therefore now be proposed concerning orientation effects leading to 2,4-dichloroquinoline derivatives *via* the intermediate 4-hydroxy-2-quinolones: (a) Weakly activating (*e.g.* methyl) and deactivating (*e.g.* chloro) *ortho*/*para* directing groups lead to mixtures of products of approximate equal proportions, or with a slight preponderance of the 5- or 5,6-isomer [in the (unhindered) Skraup reaction enhanced formation of the 7- or 6,7-isomer results[7] in these cases]. (b) Strongly activating (*e.g.* methoxy) *ortho*/*para*-directing groups lead to mixtures of products in which the 7- or 6,7-isomer predominates [as found previously[7] in the (unhindered) Skraup reaction].

The Skraup reaction has been considered[7] to be compatible with attack by a fully charged carbonium ion (*e.g.* **13**) on the position of maximum electron density.



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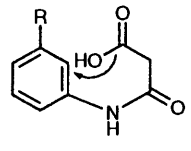
With *meta*-substituted and 3,4-disubstituted anilines containing *ortho*/*para* directing groups such as methyl or chloro, *ortho* or *para*-cyclisation is equally probable on statistical grounds, moreover, their respective weak-inductive and resonance effects would not be expected to particularly favour either route. Thus the enhanced proportion of the 7- or 6,7-isomers has been considered[7,8] to result mainly through steric effects since *para*-cyclisation (see **13**) is clearly the least hindered pathway. The bulky ArNH group would therefore be expected to contribute to the overall steric effect.

Ring closure of the malonanilide **14** may therefore be regarded as being subject to a less severe steric effect (in the absence of a bulky ArNH group) resulting in the enhanced



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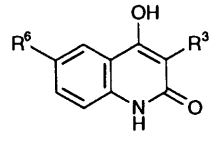
formation of the 5- and 5,6-substituted methyl and chloro quinolines. Other factors may also be of significance, such as the lower temperature of reaction, and lesser acid strength, each of which could affect the degree of randomisation. However, should any cyclisation occur *via* the alternative bis-anilide pathway,[10] then the additional steric effect of the second anilino group would then still apply. When the strongly electron-donating methoxy group is present the 7-isomer **8a** was found to predominate, as previously observed[7] in the (unhindered) Skraup reaction. In this case, the extent of *para*-activation is presumably sufficiently enhanced so as to partially overcome the steric effect.

Considerable controversy is evident from the literature concerning the identity of the brominated quinolines **1b** and **1f** obtained by Meyer and Heimann[34] from the bromination of 4-hydroxy-2-quinolone **15**. Reaction with phosphorus pentabromide (no experimental details provided) was claimed[34] to give **1b** (m.p. 265 °C), however, this m.p. is considerably higher than all of the other known dibromoquinolines,[35,36] and also with that of subsequently synthesised **1b** (m.p. 92–93 °C). Likewise, their isolated sample[34] of **1f** (m.p. 288 °C) obtained from another brominated intermediate of uncertain structure (see later) was also considerably higher than expected. Accordingly the bromination of **15** has been re-examined.



	R^3	R^6
15	H	H
16	Br	H
17	Br	Br
18	Cl	H

However, our study has been conducted in solution rather than with solid phosphorus pentabromide as used previously.[34] Since both phosphorus tribromide[38] and phosphorus oxybromide[39,40] have been used successfully for the bromination of other quinolone derivatives, these were the preferred reagents. In each case **1b** (m.p. 92–93 °C) was the only isolated product. Although liquid phosphorus tribromide was more convenient to use, freshly re-distilled phosphorus oxybromide gave a cleaner reaction and higher yield, however, it did require more careful handling particularly when quenched in water whilst still molten. Although phosphorus tribromide was a suitable reagent for the bromination of **15**, it proved completely ineffective for the 'one-pot' synthesis of **1b** by cyclisation of malonanilide. The reaction was successful with phosphorus oxybromide, however, it needed to be conducted in an open vessel to facilitate dispersal of the reaction crust. The general applicability of the method was demonstrated by a synthesis of **2b** from *para*-toluidine, the results are shown in Tables 2 and 3. It is therefore clear that the product (m.p. 265 °C) isolated by Meyer and Heimann[34] was not **1b**. We wish to suggest that this was most probably 4-bromo-2-quinolone (m.p. 265 °C), as subsequently isolated, along with **1b**, from the reaction of 4-bromoquinoline 1-oxide with phosphorus oxybromide by Hamana *et al.*[22] These workers, incidentally, made no reference to the earlier, potentially doubtful study.

Meyer and Heimann[34] also investigated the reaction of **15** with bromine in various media. From reactions conducted in cold formic acid and in boiling benzene two supposed carbocyclic ring-brominated products (referred to as the a-bromo and c-bromo compounds) were obtained. Bromination in hot formic acid, or in the cold with an excess of bromine gave the b-bromo compound (m.p. 281 °C) which was claimed to be the 3-substituted isomer **16**. Hardman and Partridge[41] have re-investigated the reaction in formic acid with 1 mol equiv. of bromine. Fractional crystallisation of the crude product from ethanol afforded a substance (m.p. 232–233 °C) which was considered to be 3-bromo-4-hydroxy-2-quinolone **16**, the m.p. discrepancy with the earlier work[34] was noted. Also isolated[41] was a dibromo 4-hydroxy-2-quinolone (m.p. 276–278 °C) of uncertain structure. More recently, Gaston *et al.*[42] have repeated this reaction, but isolated only **16**, the structure of which was firmly established by conversion into the known 3-bromo-2,4-dimethoxyquinoline which was identified by ^{1}H NMR spectroscopy.

We have also re-investigated this reaction; when **15** was treated with the calculated amount of bromine in formic acid solution, in the cold, **16** was the only product, the structure being supported by ^{1}H and ^{13}C NMR spectroscopy (see Table 5), such that the 3-H signal had disappeared, whilst C-3 had become quaternary. Using the conditions previously specified,[41] the crude product obtained with an excess of bromine was examined by ^{1}H and ^{13}C NMR spectroscopy which indicated that a mixture of **16** (91%) and 3,6-dibromo-4-hydroxy-2-quinolone **17** (9%) had been produced. The dibromo compound was identified as **17** by the characteristic AMX ^{1}H NMR splitting pattern and by the excellent ^{13}C NMR chemical shift correlation obtained by addition of 6-Br Substituent Chemical Shifts (S.C.S.) values[43] to **16**. Previously Ziegler and co-workers[44] have shown that bromination of **15** in dioxane–HBr gave some **17** (m.p. 264 °C), which readily gave a tribromo derivative on further treatment with bromine. The discrepancy in m.p. of **17** with that of Hardman and Partridge[41] may therefore be caused by such an impurity.

Meyer and Heimann[34] claimed that their b-bromo compound (m.p. 281 °C) on subsequent treatment with phosphorus pentabromide gave 2,3,4-tribromoquinoline **1f** (m.p. 288 °C). However, this m.p. is considerably higher than that of the sample of **1f** (m.p. 129–130 °C) later obtained by den Hertog and Buurman[37] from **16** and phosphorus oxybromide. Whether the samples of the b-bromo compound (m.p. 281 °C) and the supposed **1f** (m.p. 288 °C) obtained previously[34] were actually different species must remain open to question, however, from their high m.p. values we wish to suggest that they were both brominated quinolones. The similarity of m.p. with that of **17** (m.p. 276–278 °C) might indicate a probable identity. Alternatively, the reaction with phosphorus pentabromide could again have resulted in 4-bromination to give 3,4-dibromo-2-quinolone which, as far as the present authors are aware, is still unknown.

The ^{1}H NMR spectral results for the halogenoquinolines studied in this work are collected in Table 6. Although 60 MHz spectra generally sufficed for compound identification, for the **1** series and for certain isomeric mixtures 360 MHz measurements were necessary.

For **1a** the major assignment problem was the initial unequivocal identification of the A component of the ABCD spin system. Haigh *et al.*[45] have previously observed a *peri*-deshielding effect of 0.42 ppm at 4-H in 5-chloro-2-methylquinoline; assuming that a similar reverse effect was operative in **1a**, then the respective shifts of 5- and 8-H would be expected to be almost coincident at *ca.* δ 8.05. Previously Tong[16] reported 5-H as the most downfield signal in the **1d** series, however, Beak *et al.*[15] suggested that 8-H of **1c** (and by implication 8-H of **1a** also) was the lowest field resonance. Den Hertog and Buurman[37] reported only a multiplet at δ 7.4–8.2 for **1f**.

In the present work the readily assigned AMX patterns of 2,4-dichloro-6-methylquinoline **2a** and 2,4-dichloro-7-methylquinoline **4a** were examined to provide the initial A component assignments. Since the appropriate *meta*-methyl substituent

Table 5 NMR spectra of 4-hydroxy-2-quinolone and some brominated drivatives in [$^2H_6$]DMSO

Compound	δ_H 3-H	5-H	6-H	7-H	8-H	NH	OH
(a) 360 MHz ^1H							
15	5.824	7.802	7.166	7.515	7.300	12.0	11.4
16	—	7.919	7.198	7.538	7.309	11.8	11.2
17	—	8.042	—	7.689	7.258	—	—

Coupling constants (J/Hz)

	J_{56}	J_{57}	J_{67}	J_{68}	J_{78}
15	8.0	1.4	7.1	1.3	8.4
16	8.1	1.3	7.1	1.1	8.3
17	—	2.3	—	—	8.7

(b) 15 MHz ^{13}C

	δ_C C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
15	163.90	98.39	162.80	122.88	121.30	131.06	115.35	139.44	115.23
16	159.50	97.33	159.38	123.00	121.86	131.30	115.56	137.65	114.86
17	158.27	98.44	158.27	125.02	115.43	133.79	117.77	136.65	116.47

Table 6 ^1H NMR spectra of some halogenoquinolines in $CDCl_3$[a]

Compound	δ_H 3-H	5-H	6-H	7-H	8-H	Freq. (MHz)
1a	7.480	8.162	7.627	7.769	8.011	360
1b	7.838	8.146	7.655	7.770	8.026	360
1c	—	8.089	7.633	7.741	7.960	360
1e	—	8.102	7.610	7.746	7.945	360
2a	7.48	7.97	(2.59)	7.61	7.97	60
2b	7.770	7.867	(2.547)	7.569	7.869	360
3a	7.40	(2.98)	7.32	7.55	7.85	60
4a	7.43	8.07	7.47	(2.58)	7.80	60
5a	7.412	—	7.562	7.531	7.848	360
6a[b]	7.388	7.988	7.488	—	7.890	360
7a[b]	7.369	(3.948)	6.916	7.621	7.581	360
8a	7.329	8.027	7.244	(3.923)	7.322	360
9a	7.48	(2.92)	(2.49)	7.60	7.85	60
10a[b]	7.46	7.95	(2.92)	(2.92)	7.84	60
11a[b]	7.59	—	—	7.83	7.91	60
12a[b]	7.52	8.27	—	—	8.15	60

Coupling constants (J/Hz)

	J_{56}	J_{57}	J_{58}	J_{67}	J_{68}	J_{78}
1a	8.4	1.4	0.6	7.0	1.2	8.5
1b	8.4	1.5	0.6	7.0	1.3	8.4
1c	8.4	1.4	0.6	7.0	1.2	8.4
1e	8.5	1.4	0.6	7.0	1.3	8.4
2a	—	1.8	—	—	—	7.8
2b	—	1.8	0.8[c]	—	—	8.6
3a	—	—	—	*m*	*m*	*m*
4a	8.2	—	—	—	2.0	—
5a	—	—	—	7.7	1.8	8.0
6a	8.9	—	—	—	2.1	—
7a	—	—	—	7.3	1.7	8.5
8a	9.2	—	—	—	2.5	—
9a	—	—	—	—	—	8.3

[a] Chemical shifts of alkyl protons shown in parentheses. [b] In admixture with other isomer (see Table 1). [c] $J_{5,Me}$. *m* = Multiplet.

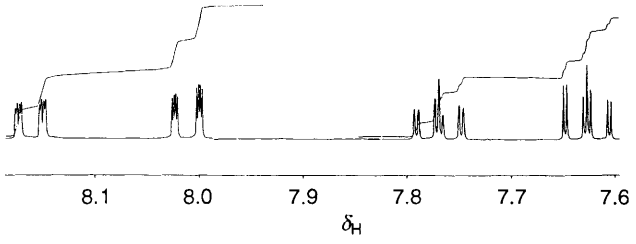


Fig. 1 360 MHz ^1H NMR spectrum of 2,4-dichloroquinoline **1a** showing long range coupling effects

effects are minimal,[8] that 5-H (δ 8.07) in **4a** was downfield of 8-H (δ 7.97) in **2a** suggested that the previous assignments of Beak *et al.*[15] required reversal. These tentative assignments were then verified by the coincident signals of 5-H and 8-H in **2a**, since 5-H was then subject to an upfield *ortho*-methyl substituent effect; and also by the increased separation (0.27 ppm) in **4a** when 8-H then experienced the upfield shift. Had the assignments of 5-H and 8-H in **1a** been reversed, then wider and closer shift separations respectively for these protons in **2a** and **4a** would have been expected. At higher precision (digital resolution 0.04 Hz), the 5- and 8-H signals of **1a** were each ddd with the upfield signal more clearly defined (see Fig. 1). This further supported the assignment as 8-H in accordance with the work of Attimonelli and Sciacovelli[46] which indicated that $^6J_{38}$ (-0.13 Hz) $< {}^5J_{35}$ ($+0.24$ Hz). That the stronger J_{35} coupling was responsible for the broadening of the downfield 5-H signal was confirmed by spin decoupling experiments at 3-H with both **1a** and **1b**, and also by the identical ddd's observed for 5- and 8-H in the spectra of **1c** and **1e**. Thus at high field the effects of these very weak long range inter-ring interactions are discernible and therefore present a valuable additional aid for the assignment of those quinolines with a non-proton containing group substituted at the 4-position such that a NOEDIFF experiment[47] would not be feasible.

The assignments of 5- and 8-H were finally and unequivocally confirmed through their appropriate 2D HETCOR connectivities to C-5 and -8 respectively and also by the unique COLOC[48] connectivity (4 Hz threshold) between 5-H and C-4. A spin decoupling experiment at 5-H then located 6-H (collapse of *ortho*-coupling) and 7-H (collapse of *meta*-coupling).

The assignments for **1b** were made by direct comparison with **1a**, they were again supported by the almost coincident signals for 5- and 8-H in **2b**. The 3-H signal in these compounds was further downfield amid the carbocyclic proton resonances in accordance with the greater deshielding effect of the bromine

Table 7 ^{13}C NMR chemical shifts of some halogenoquinolines in $CDCl_3$[a]

	δ_H									
Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Alkyl
1a[b]	150.14	122.19	144.65	124.43	128.13	131.79	129.23	148.44	125.40	
1a[c]	150.0	122.6	145.6	124.0	128.1	131.6	129.0	148.6	125.4	
1b[b]	140.95	129.07	135.42	127.19	128.50	131.75	129.43	149.04	127.03	
1c[b]	148.64	126.55	142.06	124.74	128.98	131.54	129.23	145.49	126.26	
1e[b]	150.18	118.53	144.73	125.00	128.98	131.67	129.23	146.11	126.38	
2a	149.17	122.11	143.88	123.29	138.51	133.95	128.98	147.05	125.36	21.85
2b	139.89	128.94	134.68	126.05	138.91	133.95	129.15	147.66	126.91	21.89
3a	149.37	123.94	144.73	135.90	131.46	130.90	128.53	150.51	124.79	25.11
4a	150.14	121.33	144.45	124.14	130.37	142.66	128.37	148.76	123.53	21.85
5a	150.55	125.61	143.83	130.65	131.51	130.86	129.43	150.55	122.84	
6a[d]	151.48	122.43	144.61	125.77	129.19	138.14	128.25	148.72	123.94	
7a[d]	150.55	123.61	143.55	156.65	107.66	131.63	121.74	150.14	*e*	56.23
8a[d]	150.39	119.87	144.77	125.65	121.26	162.84	107.10	150.06	120.52	55.99
9a	148.31	124.10	144.00	132.97	137.41	134.44	127.40	149.25	125.00	19.37 (5) 21.73 (6)
10a[d]	149.09	121.17	143.51	123.57	138.42	142.45	128.62	147.50	123.81	20.26 20.34
11a[d]	150.63	126.38	143.55	128.50	135.25	132.65	129.64	148.84	123.94	
12a[d]	151.69	125.33	143.39	123.12	133.30	136.88	130.29	146.81	124.67	

[a] Measured at 15 MHz unless otherwise stated. [b] Recorded at 75 MHz, some data from ref. 1. [c] Calculated chemical shifts from δ_C (**1g**)[17] + 4-Cl S.C.S.[17] [d] In admixture with other isomer (see Table 1). [e] Peak obscured.

Table 8 ^{13}C–^{1}H Coupling constants (J/Hz) of some halogenoquinolines[a]

	J/Hz				
	1a	**1b**	**1c**	**1e**	**1j**[b]
J_{23}	0	0	—	—	3.7
J_{33}	176.1	177.8	—	—	165
J_{43}	−4.4[c]	−4.2[c]	—	—	—[d]
J_{45}	5.4	5.9	5.5	5.4	5.4
J_{48}	−1.6[c]	−1.8[c]	−1.6[c]	−1.5[c]	—[d]
J_{55}	165.0	164.2	164.8	165.1	160
J_{57}	7.0	7.5	7.4	7.6	7.3
J_{66}	162.7	162.7	162.9	163.0	161
J_{68}	8.6	8.6	8.7	8.6	8.6
J_{77}	163.8	162.9	163.4	163.6	162
J_{75}	9.0	9.2	8.9	9.0	8.5
J_{88}	166.1	166.0	166.5	166.5	161
J_{86}	6.5	6.8	7.1	7.1	6.3
J_{95}	6.4	6.4	6.6	6.6	—[d]
J_{97}	9.7[e]	9.9	9.7	9.8	—[d]
$J_{10.3}$	5.1	5.3	—	—	—[d]
$J_{10.6}$	8.9	8.8	9.0	9.2	—[d]
$J_{10.8}$	5.1	5.3	5.3	5.4	—[d]

[a] Measured at 75.47 MHz in $CDCl_3$. [b] Data from ref. 18. [c] See also ref. 14. [d] Not reported. [e] Previously given (from low field 15 MHz study) as 6.7 Hz.[1]

substituents. Compounds **1c** and **1e** were also initially assigned by the appropriate 2D HETCOR connectivities. The chemical shifts of **1c** were in accordance with the work of Beak *et al.*[15] with the assignments of 5-H/8-H and 6-H/7-H now interchanged.

In **3a** CH_3-5 was subject to a downfield *peri*-proximity effect[49] which facilitated the assignment. Further discussion of these effects will be the subject of a future paper. Following the re-assignment of **1c**, the coupling constants (see Table 6) now follow the previously established pattern[46] such that $J_{56} \sim J_{78} > J_{67}$ (due to partial bond fixation) and $J_{57} > J_{68}$.

Smith and co-workers[17] have previously reported ^{13}C chemical shifts and Cl S.C.S. values for **1g** and **1h**, calculated shifts for **1a** were thus obtained, a very good correlation resulted with no assignment ambiguity. The ^{13}C NMR chemical shifts are reported in Table 7.

A detailed examination of J_{CH} coupling constants for selected examples from the **1** series of compounds has also been undertaken, determined at 75 MHz, these results are shown in Table 8. As far as the present authors are aware, no comprehensive examination of the J_{CH} interactions in chloroquinolines has yet been reported. Coupling constants[8] for **1j** have also been included in Table 8 for comparison.

The carbocyclic ring couplings were, as expected, in complete accordance with the general trends previously established[18] for **1j** such that the short range ^{1}J couplings were close to 160 Hz, whilst those ^{3}J *meta*-interactions at the β-carbons (*viz*: J_{68}, J_{75}) were greater than those at the α-carbons (*viz*: J_{57}, J_{86}). The couplings at the bridgehead carbons have been reported previously,[50] measured at 15 MHz, when they were classified as 'cross' and 'through' ring interactions, it was generally found that the latter were the stronger. However, at low field poorly resolved triplets were only observed[50] for C-9 of **1a** and **1b** such that $J_{95} \sim J_{97}$. Upon re-examination at 75 MHz the signals then appeared as well-resolved doublets of doublets with $J_{97} > J_{95}$ in accordance with expectation: similar results were also obtained for **1c** and **1e** (see Table 8).

Halogen substituents are known to influence both the size and sign of J_{CH} interactions as previously studied by Tarpley and Goldstein[51] for the isomeric dihalogenobenzenes and by Denisov *et al.*[19,20] for some monohalogenopyridines. Thus both *ipso*-chloro and *ipso*-bromo substituents have been observed to promote negative ^{2}J couplings, which in the 2,4-dihalogenoquinolines **1a** and **1b** would be expected to suppress J_{23} but to increase J_{43}. A correlation of heterocyclic ring coupling constants has been presented in Table 9. The reduction of $^{2}J_{23}$ from 3.7 Hz in **1j**, to *ca.* 0 Hz in both **1a** and **1b** is thus in accordance with the influence of the halogens, the second substituent having a smaller influence than the first resulting in an overall substituent factor (S) of about 0.73 compared with the respective single substituent effects. A similar degree of increase (S = 0.74 − 0.79) was observed for $^{1}J_{33}$.

No $^{2}J_{43}$ coupling was previously observed in **1j**, the splitting of 4.2–4.4 Hz in **1a** and **1b** appears to be more significantly influenced by the 4-halogeno substituent (S = 0.93 − 0.94)

Table 9 J_{CH} Coupling constant correlations for some heterocyclic compounds

Compound[a]	J/Hz J_{23}	J_{33}	J_{43}	Ref.
Py	3.19	163.79	0.74	18
2-ClPy	−1.0	172.19	0.20	18
2-BrPy	−0.8	172.91	0.38	18
4-ClPy	2.28	170.47	−3.51	19
4-BrPy	2.14	170.96	−3.40	19
Pyridine ring substituent effects (Hz)[b]				
2-Cl	−4.19	+8.40	−0.45	
2-Br	−3.99	+9.12	−0.36	
4-Cl	−0.91	+6.68	−4.25	
4-Br	−1.05	+7.17	−4.14	
2,4-Cl_2 Calc.	−5.10	+15.08	−4.70	
2,4-Br_2 Calc.	−5.04	+16.29	−4.50	
Quinoline ring substituent effects (Hz)[c] [substituent factors (*S*)[d]]				
2,4-Cl_2 Obsd. (**1a**)	−3.7 (0.73)	+11.1 (0.74)	−4.4 (0.94)	
2,4-Br_2 Obsd. (**1b**)	−3.7 (0.73)	+12.8 (0.79)	−4.2 (0.93)	

[a] Py = pyridine. [b] 2-Cl = *J*(2-ClPy) − *J*(Py) *etc.*, 2,4-Cl_2 = 2-Cl + 4-Cl *etc.* [c] **1a** = *J*(**1a**) − *J*(**1j**), **1b** = *J*(**1b**) − *J*(**1j**).

[d] $S = \frac{\text{2,4-Cl}_2\text{ Obsd. (quinoline)}}{\text{2,4-Cl}_2\text{ Calc. (pyridine)}}$ *etc.*

and in accordance with the work of Denisov *et al.*[19,20] must be allocated a negative sign. We have previously reported[14] the first example of a ^4J ring carbon–ring proton interaction in the quinoline series, $^4J_{48}$ again resulted mainly from the influence of the 4-halogeno substituent. It is therefore essential to consider the influence of any halogen substituent(s) for the correct interpretation of carbon signal multiplicities.

The ^{13}C NMR spectra of the other substituted 2,4-dihalogenoquinoline derivatives were examined at 15 MHz, and assigned by direct comparison with the calculated spectra obtained by addition of the appropriate S.C.S. effects.[17,18] Excellent correlations were always obtained for the 2,4,6- and 2,4,7-trisubstituted compounds, however, the correlations were poorer for 2,4-dichloro-6,7-dimethylquinoline **10a** and 2,4,6,7-tetrachloroquinoline **12a** due to the operation of *ortho*-proximity effects.[24,52] Poor correlations were also obtained for the 2,4,5-trisubstituted compounds **3a**, **5a** and **7a** due to the operation of *peri*-proximity effects,[24,49] thus 5-CH_3 in **3a** exhibited a considerable downfield shift which facilitated assignments. A discussion of these proximity effects for the Cl/Me, Cl/Cl and Cl/OMe *peri*-couples[49] will be presented later. All assignments were finally supported by the proton-coupled spectra, measured at 15 MHz which, satisfactorily confirmed the assignments and structures (*e.g.* for **5a**, 5-substitution was readily apparent from the lack of the appropriate J_{75} and J_{95} splittings), coupling constants for these derivatives have not been reported here.

Experimental

General Experimental Details.—M.p.s were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by the City University Microanalysis Service and subsequently by MEDAC Ltd., Chemistry Department, Brunel University. NMR studies were performed with *ca.* 5% solutions in $CDCl_3$ or [$^2H_6$]DMSO solvent as indicated with $(CH_3)_4Si$ as internal reference. 60 MHz ^1H NMR spectra were recorded on a JEOL PMX60Si instrument, whilst 360 MHz spectra were determined using a Bruker WH-360 at the University of Edinburgh. 15 MHz NMR spectra were measured on a JEOL FX60 instrument, proton-coupled spectra were determined using the 'Gated-1' pulse sequence. 75.47 MHz Proton-coupled ^{13}C spectra were taken on a Bruker AC300 spectrometer as described previously,[14] 2D COSY and COLOC spectra were obtained on a Bruker WH-400 spectrometer at the University of Warwick, courtesy of the SERC supported service.

Preparation of 2,4-*Dichloroquinolines: General Procedure, Synthesis of* **1a**.—Malonic acid (8.3 g, 0.08 mol) dissolved in phosphorus oxychloride (60 cm^3) and aniline (9.3 g, 0.10 mol) was slowly added. The mixture was boiled under gentle reflux for 3 h, allowed to cool and then poured into iced water (500 cm^3). After neutralisation with dilute aqueous NaOH, the initial product (12.6 g, 63%) was filtered off. Recrystallisation from an ethanol–water solvent pair with the aid of charcoal afforded pure **1a**, m.p. 65–66 °C (lit.,[5] m.p. 66–67 °C). By a similar procedure pure **2a** and the initial isomeric mixtures **3a**–**12a** were prepared, the results are shown in Tables 1–3, spectral results are given in Tables 6–8.

Examination of Isomeric Mixtures.—Product isomer ratios were assessed by ^1H NMR spectroscopic examination of the initial products [from the respective 3-H integrals referred to by (*) in subsequent experimental sections]. Recrystallisation from an ethanol–water solvent pair with the aid of charcoal then gave the purified mixed samples, free from the unchanged aniline, but generally with altered isomer ratios, which facilitated NMR assignment of individual isomers in certain instances. The purified mixed samples were then treated as described below.

(i) 5-/7-*Methyl isomers* **3a**/**4a**. The purified mixed sample (10.0 g) was dissolved in aqueous ethanol (10% v/v H_2O, 1000 cm^3) and filtered into an especially cleaned beaker, free from dust. A fractional crystallisation sequence was then carried out *via* the following experimental cycle. The solution was allowed to stand for 2 days, any precipitated solid was filtered off, 10% of solvent volume was evaporated off and the cycle was repeated, *et seq.* After two days, the first precipitated fraction 'A' (1.23 g) was collected, composition **3a** (77%):**4a** (23%)(*). From the seventh cycle a suitable second fraction 'B' (0.38 g) was obtained, composition **3a** (13%):**4a** (87%)(*).

The first fraction 'A' was then subjected to another fractional crystallisation from aqueous ethanol, which eventually afforded after standing for several days a sample of composition **3a** (96%):**4a** (4%)(*). Recrystallisation from chloroform then gave pure **3a** (0.7 g, 7%) as colourless stout needles, m.p. 133–134 °C (lit.,[12] m.p. 132 °C), see also Tables 2, 3, 6 and 7.

The second fraction 'B' was also subjected to another fractional crystallisation from aqueous ethanol, which eventually afforded after several days pure **4a** (0.1 g, 1%); recrystallisation from chloroform gave cream needles, m.p. 106–107 °C (lit.,[9] m.p. 107–109 °C), see also Tables 2, 3, 6 and 7.

(ii) 5-/7-*Chloro isomers* **5a**/**6a**. Several purified samples (10.0 g) were each subjected to fractional crystallisations from aqueous ethanol mixtures [2–20% v/v H_2O] as previously described in (i).

(a) Generally these were unsuccessful, since samples of approx. composition **5a** (45%):**6a** (65%)(*) only separated. Although enhanced in **6a** all attempts to isolate a single isomer failed.

(b) In one particular attempt, in which the (unrecorded) exact ethanol:water solvent ratio had fortuitously been employed, after two days only, a preliminary fraction (0.3 g, 3%) was instead obtained which was almost pure **5a**; recrystallisation from chloroform gave colourless fine needles, m.p. 122–124 °C, see also Tables 2, 3, 6 and 7.

(c) Fractional crystallisations from acetone, methanol and ethanol all failed to produce a pure sample of either isomer.

(iii) 5-/7-*Methoxy isomers* **7a**/**8a**. Fractional crystallisation

of the purified sample (10.0 g) as previously described in (i), eventually afforded after standing for one week, a small sample (0.4 g, 4%) which was almost pure **8a**; recrystallisation from light petroleum (b.p. 60–80 °C) gave colourless small needles, m.p. 131–132 °C (lit.,[9] m.p. 132 °C), see also Tables 2, 3, 6 and 7.

(iv) 5,6-/6,7-*Dimethyl isomers* **9a**/**10a**. Fractional crystallisation of the purified sample (10.0 g) as previously described in (i), eventually afforded, after standing for one week, a small sample (0.5 g, 5%) of pure **9a** as pale yellow needles, m.p. 112–113 °C, see also Tables 2, 3, 6 and 7.

(v) 5,6-/6,7-*Dichloro isomers* **11a**/**12a**. Fractional crystallisation of the purified sample (10.0 g) as previously described in (i), failed to effect a separation. A sample (1.2 g, 12%) enhanced in **11a** (70%) was obtained as fawn needles, m.p. 135–139 °C. See also Tables 2, 3, 6 and 7.

Preparation of 2,4-*Dibromoquinolines: General Procedure, Synthesis of* **1b**.—Malonic acid (4.15 g, 0.04 mol) was dissolved in freshly re-distilled molten phosphorus oxybromide (35 cm^3) kept at 60 °C in an open vessel. Aniline (4.65 g, 0.10 mol) was carefully added portionwise and the mixture was then heated at 130–140 °C for 3 h, the tar-like crust that formed on the surface was dispersed at intervals. The mixture was cooled to *ca.* 70 °C and then very carefully poured into iced water (1000 cm^3). (**CARE!** Ignition of vapour sometimes occurs). After neutralisation with dilute sodium hydroxide solution, the initial product (8.7 g, 76%) was filtered off. Recrystallisation from light petroleum (60–80 °C) gave the title compound **1b** as colourless needles, m.p. 92–93 °C (lit.,[22] m.p. 92–93 °C, lit.,[34] for product claimed to be **1b**, m.p. 265 °C). By a similar procedure compound **2b** was also prepared. The results are shown in Tables 2 and 3, spectral results are given in Tables 6–8.

2,3,4-*Trichloroquinoline* **1c**.—A mixture of 3-chloro-4-hydroxy-2-quinolone **18** (2.4 g) (from 3,3-dichloro-1,2,3,4-tetrahydroquinoline-2,4-dione prepared from 4-hydroxy-2-quinolone **15** and thionyl chloride in dioxane)[53] and phosphorus oxychloride (25 cm^3) was boiled under gentle reflux for 3 h, cooled and poured into iced water (500 cm^3). The crude product (2.7 g, 97%) was filtered off and recrystallised from methanol to afford the title compound **1c** as colourless needles, m.p. 106–107 °C (lit.,[15] m.p. 107–108 °C). For spectral results see Tables 6–8.

3-*Bromo*-2,4-*dichloroquinoline* **1e**.—From 3-bromo-4-hydroxy-2-quinolone **16** and phosphorus oxychloride using the procedure of Hardman and Partridge,[9] **1e** was obtained as colourless needles (from ethanol), m.p. 94–95 °C (lit.,[9] m.p. 95 °C). For spectral results see Tables 6–8.

Bromination of 4-*Hydroxy*-2-*quinolone* **15**.—(a) *With phosphorus tribromide.* A mixture of compound **15** and phosphorus tribromide (50 cm^3) was boiled under gentle reflux for 3 h; at intervals the crust that formed during the reaction was broken up. The mixture was cooled, poured into iced water (500 cm^3) and allowed to stand overnight. The crude product (7.3 g, 41%) was collected and recrystallised from an ethanol–water solvent pair to give 2,4-dibromoquinoline **1b** as pale yellow fine needles, m.p. 91–92 °C. Further recrystallisation from light petroleum (60–80 °C) gave colourless slender needles, m.p. 92–93 °C (lit.,[22] m.p. 92–93 °C).

(b) *With phosphorus oxybromide.* To molten phosphorus oxybromide (20 cm^3) was added compound **15** (3 g) and the mixture boiled under gentle reflux for 3 h. A solid crust formed at the start of the reaction which gradually dissolved. The mixture was cooled and then carefully poured into iced water (500 cm^3) to afford crude **1b** (4.7 g, 87%) subsequently purified as described in (a).

(c) *With bromine in cold formic acid.* To a solution of compound **15** (5 g, 0.031 mol) in formic acid (98%, 50 cm^3) was slowly added a solution of bromine (2.5 g, 0.016 mol) in formic acid (98%, 30 cm^3). The reaction mixture was allowed to stand at room temp. for one week during which time no product separated. Water (500 cm^3) was then added and the precipitated product (6.4 g, 86%) filtered off. Recrystallisation from methanol afforded **1b** as colourless plates, m.p. 232–233 °C (decomp.) [lit.,[41] m.p. 232–233 °C (decomp.)]. For spectral results see Table 5.

(d) *With an excess of bromine in formic acid.* The procedure described in (c) was used except that an excess of bromine (5.0 g, 0.031 mol) was used. The precipitated product (6.2 g, 83%) was a mixture of **16** (91%) and **17** (9%) (by 270 MHz NMR spectroscopy). Fractional crystallisation from methanol (as suggested previously)[41] afforded **16**, m.p. 232–233 °C (decomp.) [lit.,[41] m.p. 232–233 °C (decomp.)], and a series of fractions each of which were mixtures of compounds **16** and **17**; pure compound **17** could not be isolated.

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