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Synthetic Approaches to 5,7- and 5,8-Dimethoxyquinoline. Sonochemical Dehalogenation of Substituted 2,4-Dichloroquinolines. Use of the 2D COLOC Spectrum for the NMR Assignment of 5,8-Dimethoxyquinoline

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Summary. Sonochemical dehalogenation of 2,4-dichloroquinoline is very facile. However, with 5,7-dimethoxy-2,4-dichloroquinoline the reaction proceeds stepwise to provide the title dimethoxyquinolines which cannot be prepared via the *Skraup* reaction. The ^{13}C NMR chemical shift assignments for 5,8-dimethoxyquinoline are presented. These were made by utilising the coupling connectivities from the bridgehead carbons in the 2D COLOC spectrum.

Keywords. Sonochemistry; Quinolines; ^{13}C NMR Spectroscopy; 2D COLOC spectrum.

Synthese von 5,7- und 5,8-Dimethoxychinolin. Sonochemische Dehalogenierung von substituierten 2,4-Dichlorochinolinen. NMR-Spektroskopische Zuordnung von 5,8-Dimethoxychinolin mittels eines COLOC-Experiments

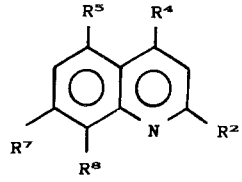
Zusammenfassung. 2,4-Dichlorchinoline können sonochemisch leicht dehalogeniert werden. Mit 5,7-Dimethoxy-2,4-dichlorchinolin verläuft die Reaktion in mehreren Schritten zu den Titelverbindungen, die mittels *Skraup*-Reaktion nicht hergestellt werden können. Das ^{13}C-NMR-Spektrum von 5,8-Dimethoxychinolin wurde, ausgehend von den Brückenkopfkohlenstoffatomen, mit Hilfe eines COLOC-Experiments zugeordnet.

Introduction

In connection with an extension of our studies of *peri*-proximity effects for the Me/MeO couple [1] to the quinoline (**1**) series [2], samples of **2** and **3** were required as reference compounds for ^{13}C NMR spectroscopy. However, earlier synthetic approaches to these compounds have proved difficult. Thus, the traditional *Skruap* synthesis [3] of **3** has been reported [4] to be ineffective, necessitating an alternative multi-stage pathway [5]. Although *Sprio et al.* [6] have examined the mass spectrum of **2** no synthetic details were reported.

We have recently reported [7] the facile sonochemical dehalogenation of some monochloroquinolines in tetrahydrofuran solution with lithium wire. In this connection, since the appropriate dimethoxy substituted 2,4-dichloroquinolines **4** and **5** may readily be obtained by a "one-pot" technique [8, 9], then their subsequent dehalogenation could represent a convenient route to the desired compounds **2** and **3**.

Results and Discussion



	R^2	R^4	R^5	R^7	R^8
1	H	H	H	H	H
2	H	H	OMe	OMe	H
3	H	H	OMe	H	OMe
4	Cl	Cl	OMe	OMe	H
5	Cl	Cl	OMe	H	OMe
6	Cl	Cl	H	H	H
7	Cl	H	OMe	OMe	H
8	Cl	H	OMe	H	OMe

In an initial study, the sonochemical double dehalogenation of **6**, with two "activated" halogeno functions, from which a sample of **1** was readily isolated, was essentially complete in 30 minutes (see Table 1). In contrast, the methoxy derivatives **4** and **5** proved more resistant to dehalogenation; instead, a slow stepwise process took place. After exposure of **4** to ultrasound for 10 hours a sufficiently adequate conversion to **2** had occurred to permit chromatographic isolation of the desired compound. Although a simple rich in the intermediate **7** was obtained, all attempts to isolate the pure monodechlorinated product failed. The conversion of **5** to **3** unfortunately proved too poor to be of synthetic value. It is likely that an interaction between the metal and a methoxy oxygen lone pair is responsible for this variation in reactivity. Moreover, the closer proximity of the 8-OCH_3 and nitrogen lone pairs in **5** could result in the formation of an organometallic species, such as **9**, at the metal surface which could further retard the reaction. Since no such species could result with the 7-OCH_3 compound **4**, in this case some reaction is then able to occur.

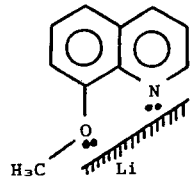


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Table 1. Sonochemical dehalogenation of some 2,4-dihalogenoquinolines

Compound	Reaction time (hr)	Product compositions (%)[a]		
		Unreacted	Less 1 × Cl	Less 2 × Cl
6	0.5	–	–	**1**: 100
4	2	**4**: 70	**7**: 21	**2**: 9
4	10	**4**: 41	**7**: 32	**2**: 27
5	10	**5**: 96	**8**: 4	**3**: ~0.1

[a] By ^{1}H NMR spectroscopy

The *Skraup* reaction was then re-examined. In contrast to earlier workers [4], it did prove possible to obtain a 12% yield of **3** by this process. The yield of **2** was, however, below 1% and hence the alternative sonochemical route to this compound is to be preferred.

The identification of **7** and **8** as the intermediate monodehalogenation products was readily evident from their ^{1}H NMR spectra which featured an AX system ($J_{3,4} = 8.3$ Hz) [10] for the heteroring protons.

The carbocyclic ring protons of **2** were readily identified, since the lower field 8-H was subject to a smaller substituent effect from a single methoxy group and was additionally broadened by a $^4J_{4,8}$ "zig-zag"-coupling [10]. In contrast, the unambiguous assignments of 6-H and 7-H in **3**, essential for the *peri*-proximity effects study, [1], were not trivial. Each proton was subject to a single methoxy substituent effect and neither was involved in any specific long range coupling which could be used for the purposes of differentiation. It was therefore necessary to utilise the 2D COLOC spectrum [11a] to effect the assignments through the specific connectivities of these protons to the bridgehead carbons C-10 and C-9, respectively, *via* the appropriate "cross-ring" couplings [12].

Initial ^{13}C chemical shift assignments followed from the appropriate MeO Substituent Chemical Shift (S.C.S.) values [13, 14] and an examination of the proton coupled spectrum. As indicated previously, for **3** the characteristic bridgehead carbon multiplicities were the starting points for the assignments. Thus C-9 (dt, $J_{9,2} = 12.5$ Hz; $J_{9,4} = 5.5$ Hz; $J_{9,7} = 6.9$ Hz) and C-10 (t, $J_{10,3} \simeq J_{10,6} = 6.9$ Hz) could be readily identified. The appropriate 2D COLOC [11a] connectivities then located 6-H and 7-H, from which C-6 and C-7 could be identified from the 2D HETCOR spectrum [11b]. The characteristic $^3J_{C,H}$ *meta*-couplings [15], $J_{6,8}$ and $J_{7,5}$ then permitted definitive assignments for the closely separated C-5 and C-8. Further $^3J_{CO,CH}$ interactions [8] then specifically located the individual methoxy carbons, an essential prerequisite for the subsequent Me/MeO *peri*-proximity effects study, in which the $J_{C,H}$ coupling interactions for a series of methoxyquinolines will also be reported. The spectral results are shown in Tables 2 and 3.

Sonochemical dehalogenation of substituted 2,4-dichloroquinolines can therefore represent a suitable route to those quinoline derivatives which are not directly accessible through the *Skraup* synthesis [4].

Table 2. 270 MHz ^{1}H NMR spectra[a]

Compound	2-H	3-H	4-H	6-H	7-H	8-H	MeO[b]
Chemical shift (δ)							
2	8.797	7.224	8.426	6.515	–	7.022	3.941, 3.964
3	8.925	7.381	8.505	6.675	6.869	–	3.895(5), 4.015(8)
7	–	7.201	8.360	6.513	–	6.949	3.919, 3.962
8	–	7.396	8.481	6.773	6.976	–	3.954[c]

Compound	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{6,7}$	$J_{6,8}$
Coupling constants (Hz)						
2	4.4	1.8	8.3	0.9	–	2.1
3	4.1	1.6	8.4	–	8.4	–
7	–	–	–	–	–	2.2
8	–	–	–	–	8.6	–

[a] ^{1}H NMR spectra of **4** and **5**, involving the Cl/OMe *peri*-couple, will be reported later
[b] MeO signals not specifically assigned, unless otherwise stated
[c] other MeO signal obscured

Table 3. 67 MHz ^{13}C NMR chemical shifts[a]

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8
2	150.91	118.12	130.71	161.20	99.58	155.95	98.13
3	149.58	120.82	130.76	148.53	103.52	106.74	149.34
7	151.56	118.70	133.67	162.25	99.22	155.99	98.38

	C-9	C-10	OMe[b]
2	150.33	116.83	55.56, 55.77
3	140.41	121.58	55.67(5), 55.96(8)
7	150.22	115.22	55.89, 55.82

[a] ^{13}C NMR chemical shifts of **4** and **5**, involving the Cl/OMe *peri*-couple, will be reported later
[b] MeO signals not specifically assigned, unless otherwise stated

Experimental

Sonochemical experiments were performed using a Kerry Pulsatron PU125 ultrasonic cleaning bath. Chromatographic separations were carried out using a Harrison Research model 7924T Chromatotron using ethyl acetate:light petroleum (b.p. 60–80 °C) = 1:4 as eluant. ^{1}H and ^{13}C NMR spectra were measured on a Jeol EX270 instrument. All spectra were recorded as dilute solutions in $CDCl_3$ containing *TMS* as internal reference, standard instrument operating settings were employed for 2D measurements. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by MEDAC Ltd., Chemistry Department, Brunel University.

2,4-Dichloroquinolines were synthesized by the "one pot" general procedure reported previously [8]. **6** 63% yield, M.p.: 65–66 °C, m.p. (lit.) 66–67 °C [16]; **4** colourless needles (from ethanol), 35% yield,

m.p.: 172–173 °C; Found C, 51.29; H, 3.43; N, 5.25; $C_{11}H_9Cl_2NO_2$ requires C, 51.19; H, 3.51; N, 5.43%; **5** 32% yield, m.p.: 130–131 °C, m.p. (lit.): 132–134 °C [9].

Sonochemical dehalogenation was performed as previously described [7] using dichloroquinoline (0.005 mol) and lithium wire (0.02 mol) in *THF* (25 ml). Progress of the reaction was monitored by 270 MHz ^{1}H NMR on separated aliquots (see Table 1). The reaction mixture was finally quenched in water (100 ml), extracted with either, dried ($MgSO_4$) and the solvent removed. The residue was the chromatographed with ethyl acetate:light petroleum.

From **6** was obtained **1**, b.p.: 238 °C, b.p. (lit.): 238.05 °C [17]; picrate: m.p.: 205–206 °C, m.p. (lit.): 207–208 °C [17]. From **4** was obtained **2**, colourless prisms (from hexane), m.p.: 34–35 °C. Found: C, 69.57; H, 6.13; N, 7.72; $C_{11}H_{11}NO_2$ requires C, 69.84; H, 5.83; N, 7.41%. Pure samples of **7** and **8** could not be isolated.

Skraup reactions were performed as previously described [18] using arsenic pentoxide as oxidizing agent and isolation by steam distillation. From freshly redistilled 2,5-dimethoxyaniline **3**, 12% yield was obtained as colourless prisms (from hexane), m.p.: 74–75 °C, m.p. (lit.): 75–76°C [4]. A similar reaction with 3,5-dimethoxyaniline furnished, after steam distillation, only a very low yield (*ca.* 1%) of an impure product which contained some **2** (by 270 MHz ^{1}H NMR) which was not isolated.

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