Highly Selective Aromatic Chlorinations. Part 2.[1] The Chlorination of Substituted Phenols, Anisoles, Anilines, and Related Compounds with *N*-Chloroamines in Acidic Solution

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Phenols, anisoles, anilines, and related compounds are chlorinated in trifluoroacetic acid at room temperature by *N*-chlorodialkylamines and *N*-chlorotrialkylammonium salts. With monosubstituted compounds and their 2- and 3-substituted derivatives the reaction occurs efficiently and selectively at the 4-position. The reactivity of these substrates and the selectivity of their chlorinations are determined by electronic rather than steric effects of the substituent. Blocking the reaction with a substituent in the 4-position generally leads to only poor or moderate yields of the 2-chlorinated product. Evidence for radical and cation radical intermediates has been obtained in the reactions of some of the 4-substituted reactants and the mechanism of chlorination is discussed in the light of these findings. The reactions of selected substrates have been scaled up to give laboratory syntheses.

The chlorination of aromatic compounds is an important route to many fine chemicals, pharmaceuticals, and bio-active compounds.[2] For these purposes one isomeric chloro-aromatic is invariably the desired product. Thus, 4-chlorophenols are much more effective germicides than the 2-isomers.[3] By generating a mixture of products unselective chlorinations are at best a waste of raw materials, whilst at worst they may lead to difficult and expensive isomer separations to remove unwanted compounds. For these reasons controlling the site-selectivity of aromatic chlorinations is an important challenge in organic synthesis.

Most attempts to achieve site-selectivity in aromatic chlorination have been directed towards controlling the approach of the chlorinating agent and the substrate. These have used bulky[4] or micellar chlorinating agents,[5] complexes between substrate and chlorinating agent,[6] or reactions in the presence of heterogeneous inorganic oxides[7] or where the substrate is held in the cavity of α-cyclodextrin[8] or a zeolite.[9] However, very recently we have shown that remarkable selectivities can be obtained more simply by using *N*-chloroamines in acid solution.[1] In this way anisole and phenol are rapidly and efficiently mono-chlorinated in the 4-position. In a parallel study Olah and his co-workers have shown that similar selectivities can be obtained with *S*-chlorodimethylsulphonium chloride.[10]

In this paper we have extended our studies and we report the results from the chlorination of substituted phenols, anisoles, anilines, and related compounds with the *N*-chloroamine systems.

Results

Method.—Electron-rich aromatic compounds with a π-donor (+*M*) substituent are chlorinated when added to an equimolar quantity of an *N*-chlorodialkylamine or of *N*-chlorotriethylammonium chloride (NCTA) * in trifluoroacetic acid (TFA). As described previously[1] for anisole and phenol the extent of reaction can conveniently be monitored by ^{1}H n.m.r. spectroscopy and the product distributions measured by g.c. or h.p.l.c.

* The following abbreviations are used, NCTA, *N*-chlorotriethylammonium chloride; NCP, *N*-chloropiperidine; NCM, *N*-chloromorpholine; and TFA, trifluoroacetic acid.

Table 1. Chlorination of some electron-rich mono substituted aromatic compounds with an equimolar quantity of *N*-chlorinated amine in TFA

Substrate	Chlorinating agent	Monochloro-isomer distribution (%)[a] 2-	4-	Yield (%)[b]
Phenoxyacetic acid	NCM	1	99[c]	90
Phenyl acetate	NCM	20	80	80
Aniline	NCTA	4	96[d]	68
N,*N*-Dimethylaniline	NCTA	62	38[e]	89
Acetanilide	NCM	9	91	100
Anisole[f]	NCP or NCTA	1	99	97
Phenol[f]	NCP or NCTA	3	97	100

[a] Measured by g.c. following work-up of reactions. [b] Yield based on *N*-chlorinated amine. [c] Measured by h.p.l.c. [d] Product contained 72 mono- and 28% 2,4-di-chloroaniline. [e] Product contained 85 mono- and 15% di-chloro-*N*,*N*-dimethylaniline. [f] From ref. 1.

Monosubstituted Benzenoid Compounds with a +M Substituent.—The data in Table 1 show that for the majority of the monosubstituted benzene compounds 4-chlorination is the dominant reaction. The exception is *N*,*N*-dimethylaniline where 2-chlorination predominates.

2- *And* 3-*Substituted Phenols and Anisoles and* 3,5-*Dimethylphenol.*—2- And 3-substituted phenols and anisoles are selectively chlorinated at the 4-position relative to the hydroxy or methoxy substituent (Table 2). With the more reactive substrates, particularly those that are 1,3-disubstituted where the activating effects are reinforcing, 2,4-dichlorination is also observed. However, it is noteworthy that even with equimolar quantities of reactants this is only a minor reaction (<7%) for all but 1,3-dimethoxybenzene and 3,5-dimethylphenol. These two substrates which are strongly activated towards electrophilic substitution require an excess of substrate to reduce the yield of dichlorination below 10% (Table 2).

4-*Substituted Derivatives of Phenol, Anisole, and Aniline and* 2,4,6-*Trisubstituted Phenols.*—4-*Chloroanisole and* 4-*chloroaniline* react very slowly with NCTA and TFA, the former reaction takes at least 2 weeks to reach completion (^{1}H n.m.r. analysis). The major product arises from 2-chlorination;

Table 2. Chlorination of 2- and 3-substituted anisoles and phenols with an equimolar quantity of *N*-chlorinated amine in TFA

Substrate	Chlorinating agent	Product(s)	Product distribution (%)[a]	Yield (%)[b]
1,2-Dimethoxybenzene	NCP	4-Chloro-1,2-dimethoxybenzene	93	66
		Dichloro-1,2-dimethoxybenzene	7	
2-Chloroanisole	NCTA	2,4-Dichloroanisole	100	83
2-Methylphenol	NCP or NCTA	4-Chloro-2-methylphenol	98	83
		6-Chloro-2-methylphenol	2	
Salicylic acid	NCM	5-Chlorosalicylic acid	96[c]	63
		3-Chlorosalicylic acid	4	
1,3-Dimethoxybenzene	NCP	4-Chloro-1,3-dimethoxybenzene	56[d]	79
		Dichloro-1,3-dimethoxybenzene	44[d]	
3-Methylanisole	NCP	4-Chloro-3-methylanisole	100	
3-Methylphenol	NCP	4-Chloro-3-methylphenol	98	89
		4,6-Dichloro-3-methylphenol	2	
3,5-Dimethylphenol	NCTA	4-Chloro-3,5-dimethylphenol	52[e]	95
		2,4-Dichloro-3,5-dimethylphenol	48[e]	

[a] Product distribution measured by g.c. following work-up of reactions. [b] Yield based on *N*-chlorinated amine. [c] Measured by h.p.l.c.; other minor products detected but not identified. [d] With a 5-fold excess of substrate the product distribution is 91 mono- and 9% di-chloro-1,3-dimethoxybenzene. [e] With a 2-fold excess of substrate at −17 °C the product distribution is 96 mono- and 4% di-chloro-3,5-dimethylphenol.

Table 3. Chlorination of some 4-substituted derivatives of anisole, phenol, and aniline with equimolar quantities of *N*-chlorinated amine in TFA

Substrate	Chlorinating agent	Product(s)[a]	Yield (%)[b]
4-Chloroaniline	NCTA	2,4-Dichloroaniline	42
		2,4,6-Trichloroaniline	3
		$Et_2N^+{=}CHCH_3$[c]	
4-Chloroanisole	NCTA	2,4-Dichloroanisole	34
		$Et_2N^+{=}CHMe$[c]	
1,4-Dimethoxybenzene	NCP or NCTA	2-Chloro-1,4-dimethoxybenzene	50—75
		Dichloro-1,4-dimethoxybenzene	Trace
4-Methylanisole	NCP	Monochloro-4-methylanisoles	
		Dichloro-4-methylanisoles	
		4-Methylphenol	
		2-Chloro-4-methylphenol	
		4-Chloro-4-methylcyclohexa-2,5-dien-1-one[c]	
4-Methylphenol	NCP	4-Chloro-4-methylcyclohexa-2,5-dien-1-one[d]	
		Monochloro-4-methylphenol	
4-Chlorophenol	NCP	2,4-Dichlorophenol	
4-Methoxyphenol	NCP	Monochloro-4-methoxyphenol	
4-Methyl-2,6-di-t-butylphenol	NCM	6-Chloro-4-methyl-2-t-butylphenol	89
		2,6-Dichloro-4-methylphenol	6
2,4,6-Tri-t-butylphenol	NCM	4-Chloro-2,6-di-t-butylphenol	

[a] Products detected and identified by g.c. and g.c.–m.s. [b] Yield based on *N*-chlorinated amine. [c] Detected by ^{1}H n.m.r. [d] Detected by ^{1}H and ^{13}C n.m.r.

however, this accounts for less than 50% of the NCTA. With the aniline a trace of dichlorination also occurs (Table 3). The ^{1}H n.m.r. spectra of the reactions of each substrate show small absorptions corresponding to those of *N,N*-diethylethylidene-iminium ion.[11]

1,4-*Dimethoxybenzene* reacts with NCTA or with NCP to give 2-chloro-1,4-dimethoxybenzene and a small amount of a dichlorinated product (Table 3). The most striking feature of these reactions is the complete absence of substrate and product ^{1}H n.m.r. absorptions in the first few minutes of the reaction. However, the conversion of *N*-chloroammonium ion into protonated amine is easily discernible (*e.g.* reaction of NCP [see Figure]. E.s.r. spectroscopy of the reaction with NCTA showed a strong broad signal attributable to the rapid one-electron transfer between 1,4-dimethoxybenzene and its radical cation. In agreement with this conclusion the reaction mixtures are dark green like those reported for the radical cation in nitromethane.[12]

4-*Methylphenol* reacts cleanly to give 4-chloro-4-methylcyclohexa-2,5-dien-1-one and a small amount of 2-chloro-4-methylphenol. Since the cyclohexadienone is not amenable to g.c. analysis it was identified by comparison of its ^{13}C and ^{1}H n.m.r. spectra with those in the literature.[13]

4-*Chlorophenol* reacts slowly with NCP to give 2,4-dichlorophenol with, after 19 h, a 70% consumption of the chloroamine. A ^{1}H n.m.r. study of the reaction shows the conversion of the phenol and NCP to products occurs without the peak broadening observed with 1,4-dimethoxybenzene or the build-up of detectable amounts of intermediates or products such as 4,4-dichlorocyclohexa-2,5-dien-1-one.

4-*Methoxyphenol and* 4-*methylanisole* react rapidly (<5 min) with NCP and each substrate gives an intermediate that is more slowly (*ca.* 45 min) converted into products. ^{1}H N.m.r. spectroscopy shows that each intermediate has a characteristic singlet absorption at δ 3.7. The methoxyphenol yields a single monochlorinated product, probably 2-chloro-4-methoxyphenol, whilst the methylanisole gives a mixture of compounds from chlorination and *O*-demethylation. The identity of the chlorinated methylanisoles and whether they arise from ring or side-chain chlorination was not investigated further.

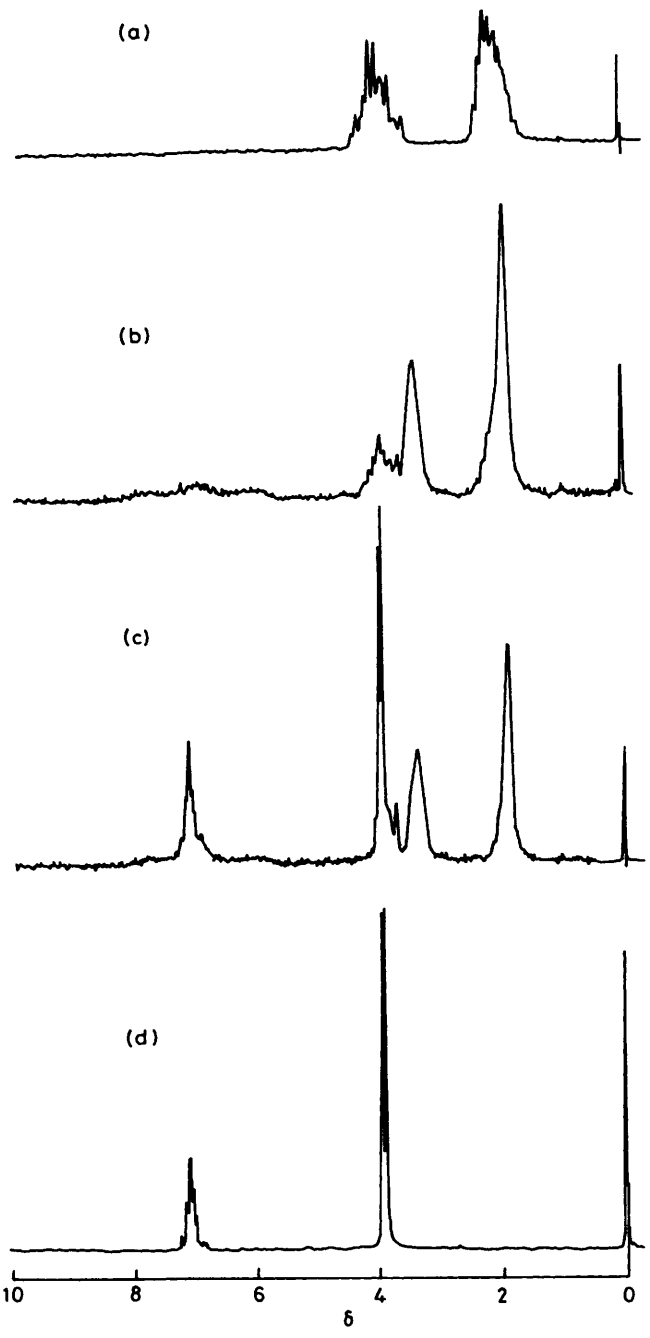


Figure. ^{1}H N.m.r. spectra of TFA solutions of (a) *N*-chloropiperidine, (b) an equimolar mixture of *N*-chloropiperidine and 1,4-dimethoxybenzene, 15 min after mixing, (c) mixture in (b) 24 h after mixing, and (d) 2-chloro-1,4-dimethoxybenzene

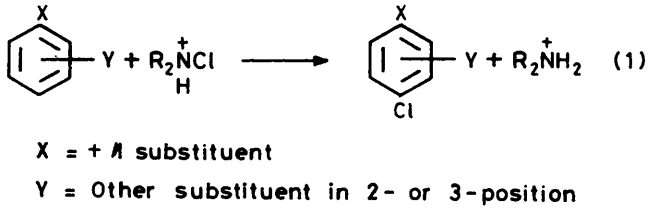
4-*Methyl*-2,6-*di-t-butylphenol* reacts very rapidly with NCM (<1 min) to give 6-chloro-4-methyl-2-t-butylphenol and a small amount of 2,6-dichloro-4-methylphenol. To check that these products do not arise from an acid-catalysed de-t-butylation followed by chlorination, the stability of the substrate in TFA was investigated. A solution of 2,6-di-t-butyl-4-methylphenol in TFA at room temperature is approximately 7% de-t-butylated within 3 min of mixing. Leaving the chlorination reaction mixtures in TFA to stand for several days leads to changes in the products arising from de-t-butylation of the 6-chloro-4-methyl-2-t-butylphenol and unchanged starting material.

2,4,6-*Tri-t-butylphenol* is rapidly chloro-de-t-butylated by NCM to a monochlorinated product presumed to be 4-chloro-2,6-di-t-butylphenol (g.c.–m.s. analysis).

Laboratory-scale Chlorinations.—The feasibility of using these chlorinations for laboratory-scale syntheses (*ca.* 20 g of substrate) has been investigated with four substrates, namely phenol, anisole, 2-methylphenol, and 2-chloroanisole. The reactions were carried out using equimolar amounts of substrate and chlorinating agent in aqueous sulphuric acid or TFA. The best results are obtained with a reactive chloroamine, such as NCM, in 80% (v/v) aqueous sulphuric acid or in TFA (Table 4). The inhomogeneity of the sulphuric acid reactions is not a problem if the mixtures are stirred vigorously. The major disadvantage from using sulphuric acid arises from aromatic sulphonation competing with the chlorination with the most reactive substrates. The former can be reduced to a minor side reaction by keeping the reaction mixtures cold (< 8 °C). Under these conditions the chlorination competes very effectively with sulphonation.

Discussion

Our studies on the chlorination of anisole and phenol with acidic solutions of *N*-chlorinated alkylamines[1] have been extended to a selection of phenols, anisoles, anilines, and related compounds. The high site-selectivity for 4-chlorination noted previously occurs generally with other electron-rich aromatic compounds provided they have a π-donor (+*M*) substituent with a free 4-position [see equation (1)].



The 4-chlorination of aniline competes effectively with protonation and the consequent deactivation of the substrate. However, significant dichlorination occurs with this substrate because the amino group is a very effective π-donor (*cf.* σ^+ values for 4-OMe and 4-NH_2 are −0.78 and −1.3, respectively[14]) and possibly also because 4-chloroaniline being a weaker base than aniline is less extensively protonated in TFA.[15] Interestingly the rapid reaction of *N,N*-dimethylaniline leads to mainly 2-chlorination. This is the only electron-rich monosubstituted benzenoid compound where we have observed more 2- than 4-chlorination. The reason for this anomaly is unclear; however, the chlorination of *N,N*-dimethylaniline with either chlorine[16] or *N*-chlorosuccinimide[17] also gives predominantly 2-chlorination. Neale *et al.*,[17] who studied the latter reaction, suggested that chlorination might occur initially on the aniline nitrogen followed by rearrangement of the *N*-chloro-*N,N*-dimethylanilinium ion preferentially to 2-chloro-*N,N*-dimethylaniline. A similar explanation might account for our results.

The selectivity for 4-chlorination with the monosubstituted benzenes can be correlated very roughly with the π-donor ability, but not the bulk, of the substituent. (Unfortunately we have been unable to find a comprehensive scale measuring π-donor effects, *e.g.* σ^+ or σ_R^+, for all the substituents used in this study[14,18].) Thus for example with good π-donors such as –OMe and $-OCH_2CO_2H$ there is a large 4/2 chlorination selectivity of ~100 whilst with –OCOMe, which is a poorer

Table 4. Laboratory-scale chlorination of phenol, anisole, 2-methylphenol, and 2-chloroanisole with *N*-chloroamines in acidic media

Substrate	Chlorinating agent	Reaction conditions	Product distribution (%)	Yield (%)
2-Chloroanisole	NCM	80% (v/v) H_2SO_4/1 h	2,4-Dichloroanisole (99.5) 2,6-Dichloroanisole (0.3) 2,4,6-Trichloroanisole (0.2)	88[a]
2-Chloroanisole	NCM	TFA/1 h	2,4-Dichloroanisole (98.7) 2,6-Dichloroanisole (0.4) 2,4,6-Trichloroanisole (0.9)	95[a]
Anisole	NCM	80% (v/v) H_2SO_4/25 min	2-Chloroanisole (6) 4-Chloroanisole (94)	75[a]
Phenol	NCM	80% (v/v) H_2SO_4/15 min	2-Chlorophenol (7) 4-Chlorophenol (93)	78[b]
2-Methylphenol	NCM	80% (v/v) H_2SO_4/15 min	4-Chloro-2-methylphenol (95) 6-Chloro-2-methylphenol (5)	98[b]

[a] Isolated yield based on oxidant with product composition shown. [b] Yield based on oxidant measured by g.c.

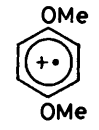
π-donor, this ratio becomes ~4—6. An analogous change is seen when the 4/2 chlorination selectivities of aniline and acetanilide are compared.

Substituents in the 2- and 3-positions of phenol and anisole have a negligible effect on the site-selectivity of the chlorinations although they do influence the reactivity of the substrates. Electron-withdrawing substituents, such as chlorine and carboxyl, slow down the chlorination whilst electron-donating groups, particularly in the 3-position, increase reactivity and can in some instances lead to significant dichlorination occurring. The substituent effects will be discussed in more detail with the mechanism in a subsequent paper in this series. It is noteworthy that a 3-substituent influences a substrate's reactivity predominantly through its electronic effect. There is no evidence that the bulk of a substituent in the 3-position hinders 4-chlorination.

The reactions of 4-substituted phenols, anisoles, and anilines are more complicated than those of the 2- and 3-isomers. However, with the majority of these substrates 2-chlorination occurs in poor–moderate yield. The relatively poor yields of 2-chloro products are explicable in terms of the very high preference that *N*-chloroamines have for 4-chlorination; when this route is blocked alternative pathways are able to compete effectively with the less favoured 2-chlorination. The study of these alternative reactions and their products reveals information on the mechanism of the *N*-chloroamine chlorinations.

Blocking the 4-position of anisole with a methoxy group slows down the rate of chlorination and stabilises a radical intermediate. Although the structure of the intermediate has not been unambiguously confirmed, it is most likely to be the 1,4-dimethoxybenzene radical cation (**1**), from the ready one-electron oxidation of the substrate. Rapid one-electron exchange between 1,4-dimethoxybenzene and its radical cation[19] would account for the paramagnetic broadening of the ^{1}H n.m.r. spectra and the broad signal in e.s.r. spectra of the reaction mixtures. Competing dimerisation to give the tetramethoxybiphenyl (**2**), a known product from this radical cation,[12] could account for the relatively low yields of 2-chloro-1,4-dimethoxybenzene.

4-Chloroanisole is less readily oxidised than 1,4-dimethoxybenzene and, not unexpectedly, the ^{1}H n.m.r. spectra of its reactions with NCTA show no paramagnetic broadening effects. However, the *N*-chloroammonium ion is not converted quantitatively into protonated amine; the 4-chloro substituent diverts some of the chlorinating agent into *N*,*N*-diethylethylideneiminium cation. Similar results are obtained with 4-chloroaniline. Our studies show that the iminium ion does not



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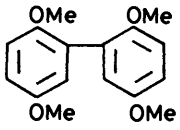

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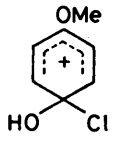

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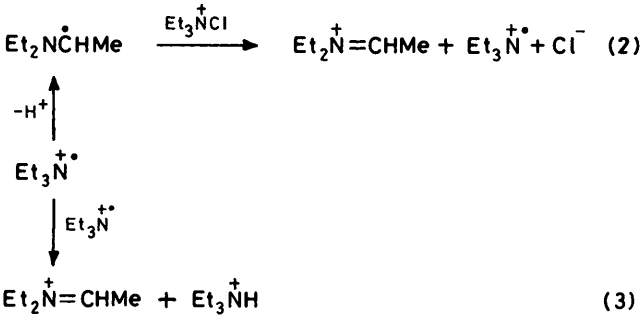
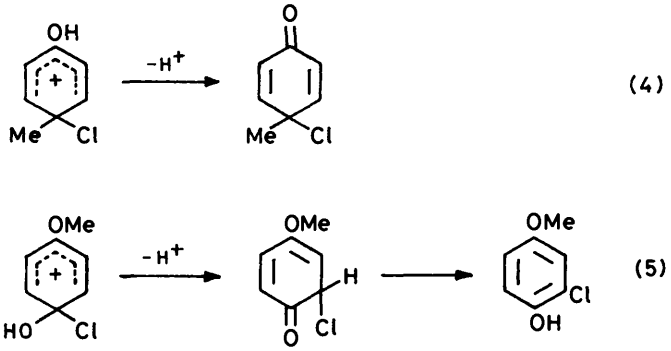
(4)

arise from the thermal decomposition of NCTA. A likely alternative route to this compound is the decomposition of the triethylaminium radical [see equations (2)[11] and (3)[20]].



The ^{1}H n.m.r. spectra of the reaction of 4-methoxyphenol and 4-methylanisole do not show paramagnetic broadening effects. Instead they indicate that with each substrate the chloroamine is consumed rapidly to give an intermediate that is converted more slowly into products. The identities of the intermediates are uncertain but the common absorption at δ 3.7, the strong propensity for *N*-chloroamines to give 4-chlorination, and the acidic reaction medium point to cations (**3**) and (**4**), respectively. In the reaction of 4-methylphenol the intermediate equivalent to (**4**) would readily lose a proton to give 4-chloro-4-methylcyclohexa-2,5-dien-1-one [equation (4)] and consequently is not detected by ^{1}H n.m.r. spectroscopy.

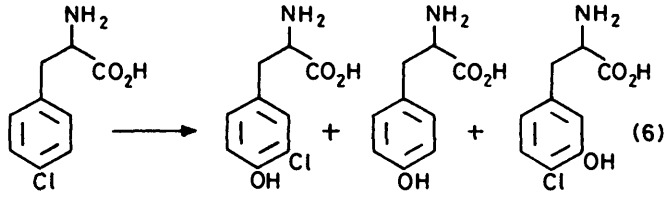
The most likely fate of intermediate (**3**) is intramolecular rearrangement and loss of a proton to give 2-chloro-4-methoxyphenol [equation (5)]. This type of rearrangement



(4)

(5)

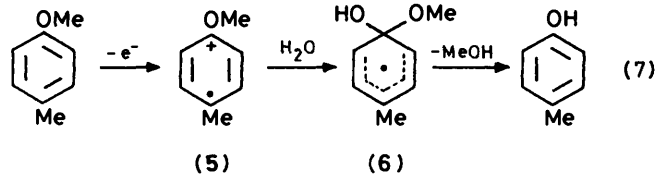
(known as an NIH shift[21]), which has been reported in the biological hydroxylation of such compounds as 4-chlorophenylalanine[22] [equation (6)] and of 2,4-dichlorophenoxyacetic acid,[23] is thought to occur *via* intermediates analogous to (**3**).[21b]



(6)

Production distribution (%)	85	10	5

The reaction of 4-methylanisole gives intermediate (**4**) which reacts further to a mixture of ring- and/or side-chain-chlorinated methylanisoles (detected by g.c.–m.s. but not identified). The route to the products from *O*-demethylation is unclear but could involve the radical cation (**5**) reacting with traces of water in the reaction mixture [equation (7)]. Such a mechanism was proposed by Torii *et al.*[24] for the Ce^{IV} oxidation of this substrate. Intermediates such as (**6**) formed by the *ipso*-hydroxylation of methoxybenzenes are known to lead to phenols by loss of methanol.[25]

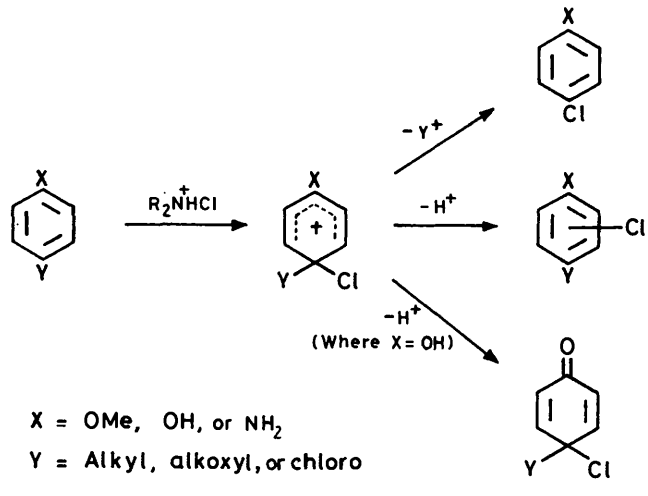


(7)

(5) (6)

In a brief study on two hindered trialkylphenols, 4-methyl-2,6-di-t-butylphenol and 2,4,6-tri-t-butylphenol, we observed that both substrates were rapidly chlorinated with loss of a t-butyl group. Unlike 4-methylphenol, in neither reaction could we find evidence for 4-chloro-2,5-dienone formation. Presumably the ready loss of a t-butyl cation prevents the build-up of the dienone in these reactions.

The reactions described above were, for reasons of economy, carried out on a small scale (< 1 g of substrate). Also to aid ^1H n.m.r. analyses and to ensure homogeneous mixtures TFA was used as the solvent throughout. Some of the reactions have been scaled up to use ~ 20 g of substrate and for these we used either TFA or aqueous sulphuric acid. The latter reaction medium is cheaper, less toxic than TFA, and has been used in the small-scale chlorination of anisole and phenol.[1] For laboratory-scale reactions we find that TFA and 80% (v/v) aqueous sulphuric acid give very comparable results, although with the latter



Scheme.

sulphonation can be a competing side reaction with reactive substrates. The results for the four substrates shown in Table 4 suggest that *N*-chloroamines could provide a valuable new selective route to 4-chlorinated aromatics. In this respect the full details of the synthesis of 2,4-dichloroanisole from 2-chloroanisole will be reported elsewhere.[26]

In conclusion, *N*-chlorodialkylamines and *N*-chlorotrialkylammonium ions will chlorinate a selection of electron-rich aromatic compounds with a π-donor (+*M*) substituent. The reactions show a pronounced selectivity for the 4-position, relative to the +*M* substituent, and a strong preference for monochlorination. The high site-selectivity does not arise from steric control of the reaction since 4-chlorination is not hindered by substituents in the 3- and 5-position and can even occur with substrates such as 4-methylphenol and 2,4,6-tri-t-butylphenol. Indeed it is possible that with all the substrates the initial attack occurs at the 4-position. Compounds with a substituent already in the 4-position are then aromatised by rearrangement of the chlorine or by loss of the substituent or, in the case of phenols, they can form 2,5-dienones (see Scheme). Finally there is evidence for the participation of radical cations in the chlorinations of some substrates. This and the origin of the selectivity will be discussed in a subsequent paper on the mechanism of these chlorinations.

Experimental

Materials.—All the materials were commercial reagent grade unless otherwise stated and were obtained from Aldrich Chemical Co. Ltd., B.D.H. Ltd., Fisons Scientific Apparatus Ltd., or Lancaster Synthesis Ltd.

6-Chloro-2-methylphenol, 4-chloro-3-methylphenol, 4,6-dichloro-3-methylphenol, 3,5-dimethylphenol, 4-chloro-3,5-dimethylphenol, and 2,4-dichloro-3,5-dimethylphenol were kindly provided by Croda Synthetic Chemicals Ltd.

2-, 3-, And 4-chloro-*N*,*N*-dimethylaniline were prepared by the methylation of the chloroaniline with trimethylphosphate following the method of Vogel[27] and had the b.p.s and ^1H n.m.r. absorptions given below.

2-Chloro-*N*,*N*-dimethylaniline, b.p. 206—208 °C at 760 mmHg (lit.,[28] 207—208 °C at 760 mmHg); δ($CDCl_3$) 2.80 (s, 6 H) and 6.84—7.48 (m, 4 H).

3-Chloro-*N*,*N*-dimethylaniline, b.p. 232—234 °C at 760 mmHg (lit.,[28] 234 °C at 760 mmHg); δ($CDCl_3$) 2.88 (s, 6 H), 6.48—6.80 (m, 3 H), and 7.04—7.12 (m, 1 H).

4-Chloro-*N*,*N*-dimethylaniline, b.p. 229—231 °C at 760 mmHg (lit.,[28] 231 °C at 760 mmHg); δ($CDCl_3$) 2.86 (s, 6 H), 6.64 (d, 2 H), and 7.18 (d, 2 H).

4-Chloro-1,3-dimethoxybenzene and 2,4-dichloroanisole were prepared by methylation of the corresponding phenol with dimethyl sulphate following the method of Vogel[29] and had the physical properties and ^{1}H n.m.r. absorptions given below.

4-Chloro-1,3-dimethoxybenzene, b.p. 136—137 °C at 17 mmHg (lit.,[28] 135—137 °C at 17 mmHg); δ($CDCl_3$) 3.72 (s, 3 H), 3.82 (s, 3 H), 6.20—6.40 (m, 2 H), and 7.06—7.20 (m, 1 H).

2,4-Dichloroanisole, m.p. 26.5—27.0 °C (lit.,[28] 28 °C); δ($CDCl_3$) 3.88 (s, 3 H), 6.84 (d, *J* 8 Hz, 1 H), 7.20 (dd, *J* 8 and 2 Hz, 1 H), and 7.38 (d, *J* 2 Hz, 1 H).

2-Chloroacetanilide was prepared by acetylation of 2-chloroaniline and had m.p. 86—88 °C (lit.,[28] 87—88 °C).

N-Chloroamines and *N*-chloroammonium salts were prepared as described previously.[1]

Methods.—The ^{1}H and ^{13}C n.m.r. spectroscopic and gas chromatographic procedures were described in the previous study.[1] E.s.r. spectra were obtained with a Varian E104 spectrometer. H.p.l.c. used Knauer h.p.l.c. pumps, type 364, and a Shandon ODS Hypersil column (25 cm, 4 mm) coupled to a Cecil CE212 variable-wavelength u.v. detector. All analyses were isocratic and used mixtures of methanol and water containing 1% acetic acid as eluant.

The small-scale chlorinations in TFA were performed and monitored by ^{1}H n.m.r. spectroscopy, as described for anisole,[1] although the following modified work-up was employed for reactions of aromatic amines. The product mixture was added dropwise to cooled water, basified with sodium carbonate, and then extracted with diethyl ether. The ether solution was dried ($MgSO_4$).

The reaction mixture from 1,4-dimethoxybenzene and NCTA was also studied by e.s.r. spectroscopy using a flattened aqueous sample cell to minimise dielectric loss from the solvent.

The product mixtures were analysed by g.c., except for those from phenoxyacetic and salicylic acid where h.p.l.c. was employed.

The products were identified by ^{1}H n.m.r. spectra of reaction mixtures, by comparison of retention times with those of authentic materials and by combined g.c.–m.s. When authentic materials were unavailable the products were examined by g.c.–m.s. The mass spectra and tentative identifications of these materials are given below. Monochlorinated products from reaction of:

(a) 4-Methylanisole, probably ring and side-chain isomers, *m/z* 158 (31%), 156 (M^+, 100), 121 (50), 91 (13), and 77(17); and *m/z* 158 (32%), 156 (M^+, 100), 143 (11), 141 (38), 121 (58), 113 (23), 91 (17), and 77 (75).

(b) 4-Methoxyphenol, probably 2-chloro-4-methoxyphenol, *m/z* 160 (29%), 158 (M^+, 88), 145 (33), 143 (100), 107 (37), 79 (22), 53 (17), and 57 (18).

(c) 4-Methylphenol, probably 2-chloro-4-methylphenol, *m/z* 144 (10%), 142 (M^+, 30), 141 (12), 107 (100), and 77 (35).

(d) 4-Methyl-2,6-di-t-butylphenol, probably 6-chloro-4-methyl-2-t-butylphenol, *m/z* 200 (10%), 198 (M^+, 31), 185 (32), 184 (13), 183 (100), 157 (14), 155 (40), and 77 (8).

(e) 2,4,6-Tri-t-butylphenol, probably 4-chloro-2,6-di-t-butylphenol, *m/z* 242 (8%), 240 (M^+, 24), 227 (33), 226 (13), 225 (100), 197 (18), 125 (18), and 57 (24).

Dichlorinated products from reaction of.

(a) 1,2-Dimethoxybenzene, probably 4,6-dichloro-1,2-dimethoxybenzene, *m/z* 210 (11%), 209 (26), 208 (74), 207 (63), 206 (M^+, 100), 195 (11), 193 (63), and 191 (69).

(b) 1,3-Dimethoxybenzene, probably 4,6-dichloro-1,3-dimethoxybenzene, *m/z* 210 (10%), 208 (67), 206 (M^+, 95), 193 (24), 191 (33), 165 (67), and 163 (100).

(c) 1,4-Dimethoxybenzene, probably 2,5-dichloro-1,4-dimethoxybenzene, *m/z* 210 (5%), 208 (30), 206 (M^+, 40), 195 (13), 193 (65), and 91 (100).

(d) 4-Methylanisole, *m/z* 194 (10%), 192 (57), 190 (M^+, 100), 177 (15), 175 (23), 155 (44), 147 (17), and 111 (38).

(e) *N*,*N*-Dimethylaniline, *m/z* 193 (9%), 192 (17), 191 (43), 190 (62), 189 (M^+, 70), 188 (100), 173 (19), and 172 (17).

4-Chloro-4-methylcyclohexa-2,5-dien-1-one was identified in the reactions of 4-methylphenol and 4-methylanisole by removal of solvent, and then dissolving the residue in deuteriochloroform and recording ^{1}H and ^{13}C n.m.r. spectra. The dienone had δ_H($CDCl_3$) 1.84 (s, 3 H), 6.25 (d, *J* 10 Hz, 2 H), and 7.0 (d, *J* 10 Hz, 2 H) [lit.,[13a] 1.85 (s, 3 H), 6.16 (d, *J* 10 Hz, 2 H), and 6.97 (d, *J* 10 Hz, 2 H)]; δ_C($CDCl_3$) (couplings in off-resonance spectrum) 29.3 (q), 59.6 (s), 126.3 (d), 150.9 (d), and 185.4 (s) [lit.,[13b] 29.4 (q), 59.9 (s), 126.5 (d), 149.5 (d), and 184.1 (s)].

Laboratory-scale Chlorinations.—The substrate (0.11 mol) was added with stirring to cooled 80% (v/v) sulphuric acid (250 cm^3). Stirring and cooling were continued while NCM (0.12 mol) was added dropwise at such a rate as to keep the reaction temperature below 8 °C. The cooling was then discontinued. After 1 h the stirred reaction mixture was poured into water (150 cm^3) containing ice (100 g) and the products were extracted into diethyl ether. The combined ether extracts were washed with water (100 cm^3) containing potassium iodide (0.5 g), sodium thiosulphate (2 g), and acetic acid (2 cm^3), followed by 8% (w/v) sodium hydroxide (50 cm^3) before they were dried ($MgSO_4$). Removal of the ether gave the crude product which was purified by distillation under reduced pressure.

The reactions were also carried out with TFA (100 cm^3) in place of the 80% (v/v) sulphuric acid. When this solvent was used the reactions were worked up by adding the product mixture carefully to cold aqueous sodium hydroxide (50 g in 150 cm^3). Extraction into diethyl ether and product isolation was then as described above.

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