Contrasting Reactions of 2,6-Dichloro-4-trichloromethylpyridine, 2,6-Dichloro-3-trichloromethylpyridine and their *N*-Oxides with Nucleophiles

Ronald S. Dainter, Hans Suschitzky,* and Basil J. Wakefield*
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT
Nigel Hughes* and Anthony J. Nelson
I.C.I. p.l.c., Organics Division, Research Department, Blackley, Manchester, M9 3DA

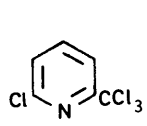
Various nucleophiles react with 2,6-dichloro-4-trichloromethylpyridine and 2-chloro-6-trichloromethylpyridine as expected, by displacement of ring chlorine atoms. But in the reactions of nucleophiles with 2,6-dichloro-3-trichloromethylpyridine and 2,6-difluoro-3-trifluoromethylpyridine, displacement of ring halogen atoms is accompanied or followed by multiple attack at the trihalogenomethyl group. The reactivity of the trihalogenomethyl groups is modified by *N*-oxidation. A mechanism for the peculiar reactivity of the trihalogenomethyl groups is proposed, involving loss of halide ion from the CX_3 group assisted by lone pairs on substituents or negative charge in Meisenheimer intermediates. Both geometrical isomers of 1,2-dichloro-1,2-bis(2,6-dichloro-3-pyridyl)ethene are described.

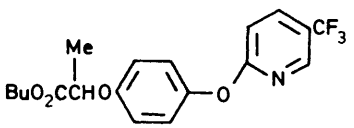
Many trihalogenomethylpyridine derivatives show potentially useful biological activity, and some have been developed commerically. The latter include 2-chloro-6-trichloromethylpyridine (**1**) (a nitrification inhibitor)[1] and the 2-aryloxy-5-trifluoromethylpyridine (**2**) (a herbicide).[2] It is thus surprising that so little has been published concerning the chemistry of trihalogenomethylpyridines which proves to have some interesting and unexpected features.

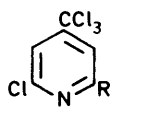
It has been reported in Patents[3] that various chlorinated 2- and 4-trichloromethylpyridines (**1**) and (**3**)—(**8**) react with nucleophiles as expected, *i.e.* by displacement of chlorine at a reactive 2- and/or 4-position, leaving the trichloromethyl group intact. We have confirmed these reports for 2,6-dichloro-4-trichloromethylpyridine (**3**). Thus, reaction with methoxide gave the monomethoxy compound (**9**), or, with an excess of the reagent, the dimethoxy compound (**10**). With butylamine or piperidine only the monoamines (**11**) and (**12**) were obtained even with an excess of the amine. We have also noted that 2-chloro-6-trichloromethylpyridine (**1**) undergoes replacement of the ring chlorine atom by methoxide, giving (**13**).

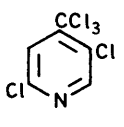
Surprisingly, although the Patents cited imply that the reactions disclosed in them are general for α-, β-, and γ-trichloromethylpyridines, the examples described concern almost exclusively the α- and γ-isomers. Our investigations reveal that the β-trichloromethylpyridines show quite different reactivity and reactions.

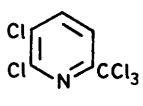
The complete reaction of 2,6-dichloro-3-trichloromethylpyridine (**14**) with an excess of sodium methoxide in methanol gave a mixture of two products. G.c.-m.s. revealed them to be isomers, each containing four methoxy groups and one chlorine atom, corresponding to the ortho esters (**15**) and (**16**). The major product was isolated in a pure state and its identity as (**15**) was confirmed by hydrolysis to the ester (**17**) from which the remaining chlorine was removed by hydrogenolysis. Subsequent hydrolysis of the ester group gave an acid identified as 6-methoxypyridine-3-carboxylic acid (**18**) by comparison with a sample derived from 2-chloro-5-trichloromethylpyridine (**19**).[4]

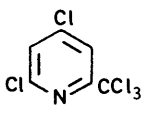

(**1**)

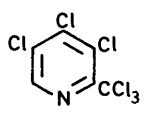

(**2**)

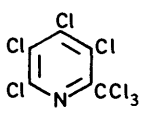

(**3**) R = Cl
(**9**) R = OMe
(**11**) R = NHBu
(**12**) R = NC_5H_{10}

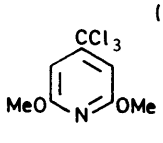

(**4**)

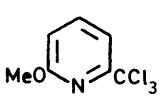

(**5**)

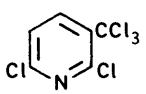

(**6**)

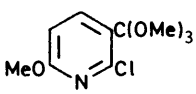

(**7**)

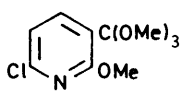

(**8**)

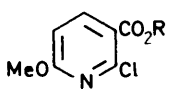

(**10**)

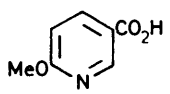

(**13**)

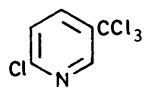

(**14**)

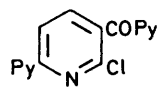

(**15**)

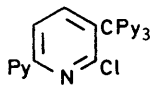

(**16**)


(**17**) R = Me
(**27**) R = H


(**18**)


(**19**)


(**20**)

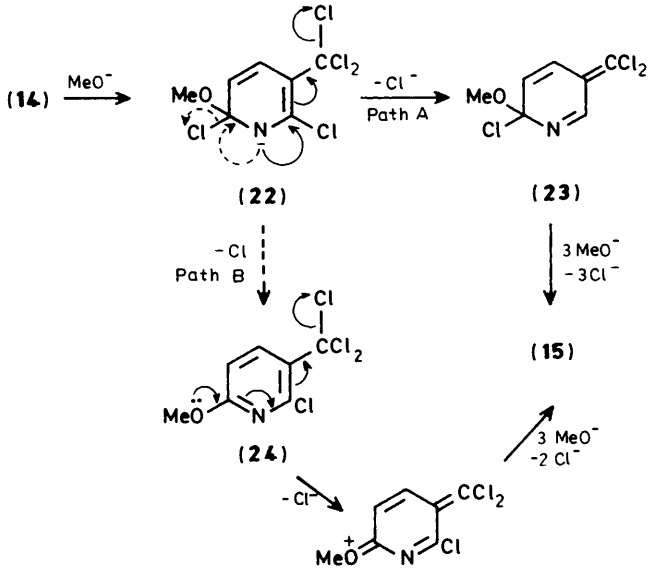

(**21**)

Py = piperidino

Thus in contrast to the 4-trichloromethyl isomer (**3**), the 3-trichloromethyl isomer (**14**) undergoes displacement of all three chlorines from the trichloromethyl group as well as a ring chlorine.

The reaction of 2,6-dichloro-3-trichloromethylpyridine (**14**) with butylamine proceeded rapidly, but only tars were obtained. However, with piperidine the amide (**20**) was obtained in 63% yield after hydrolytic work-up; no intermediate was isolated, but there was n.m.r. evidence (see Experimental section) for the presence of the orthoamide (**21**) before hydrolysis.

We have proposed two mechanisms to explain the high reactivity of the trichloromethyl group in 2,6-dichloro-3-trichloromethylpyridine (**14**);[6] they are summarised, for reactions with methoxide, in Scheme 1. In Path A (solid arrows), the



Scheme 1.

initial Meisenheimer-type adduct (**22**) eliminates chloride ion from the trichloromethyl group rather than the ring, to give the reactive intermediate (**23**), which can give the ortho ester (**15**) *via* attack of methoxide at the side-chain carbon and analogous repeated sequences. In Path B (dotted arrows), normal substitution of Cl–6 occurs, but the trichloromethyl group in the product is activated by the lone pair on oxygen as shown (**24**). Mechanisms analogous to Path A have been proposed to account for the abnormal reactivity of 3-trifluoromethylimidazoles,[8] and the high reactivity of *p*-hydroxy- and *p*-aminobenzotrifluoride has been accounted for by activation as in Path B[7,9] (and there is kinetic evidence for an analogous loss of bromide from a *p*-dibromomethylphenol[10]). Bunnett has recently postulated an analogous explanation for abnormal nucleophilic substitution reactions of 2- and 4-iodobenzotrifluoride by an S_{RN} process.[11]

When the course of the reaction of methoxide with 2,6-dichloro-3-trichloromethylpyridine (**14**) was investigated by gas chromatography it was possible to observe some intermediates. Attempts to isolate these after short reaction times were largely unsuccessful, but one of them was obtained *ca.* 80% pure. Mass

* It is claimed in a Patent[5] that the reaction of methoxide with methyl 2,6-dichloropyridine-3-carboxylate (**28**) gives the ester (**29**), and on subsequent hydrolysis, the acid (**30**). In view of the similarity of the reported m.p.s to those of (**17**) and (**27**) respectively the structures given in the Patent should be reinvestigated.

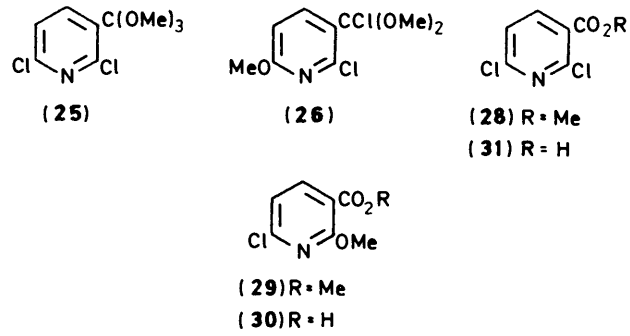
Table 1. Reaction of 2,6-dichloro-3-trichloromethylpyridine (**14**) with sodium methoxide in methanol

	Proposed structure	(**26**)	(**16**)	(**15**)	(**25**)
	t_R (min)	2.9	3.4	4.3	5.4
Reaction time		Area (% of total peak area)			
10 min		22	20	15	36
1 h		32	21	22	25
2 h		18	18	44	18
24 h		13	20	65	2

Table 2. Products of alkaline hydrolysis of reaction products shown in Table 1

	Structure	Unknown	(**27**)	(**30**)	(**31**)
	t_R (min)	5.9	8.07	10.46	12.03
Reaction time		Area (% of total peak area)			
10 min		8	42	20	21
24 h		0	71	0	17

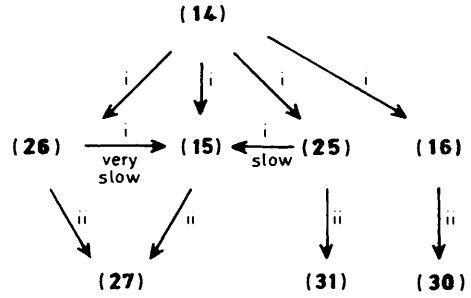
spectrometry revealed the presence of two chlorine atoms with a molecular ion corresponding to (**25**) or (**26**). A carboxylic acid isolated following hydrolysis of this impure product was identical with the one obtained by hydrolysis of the ester (**17**), *i.e.* compound (**27**),* and thus corresponded to structures (**26**). However, the ^{13}C n.m.r. spectrum of the impure product was more consistent with the alternative structure (**25**) as the major component of the mixture; in particular there was no strong



signal at $\delta > 160$, as expected for a 2,6-methoxypyridine. If this interpretation is correct, pathways for the reaction other than those shown in Scheme 1 must be considered.

Attempts to monitor the course of the reaction by g.c.-m.s. gave erratic results, owing to continuing reaction en route to or in the injection port. Even when samples were neutralised with acetic acid before analysis, some reaction with methanol continued, but under these conditions more consistent results were obtained. The relative proportions of the four main components of the reaction mixture after varying reaction times are shown in Table 1. The mass spectra of these components were consistent with the structures indicated in Table 1. Further confirmation of these proposed structures was obtained when the final reaction mixture, and the product of a similar reaction which had proceeded for only 10 min, were hydrolysed by dilution with aqueous sodium hydroxide followed by heating. The mixtures of acids thus obtained were analysed by h.p.l.c., and three of them were identified by comparison with authentic samples as 2-chloro-6-methoxypyridine-3-carboxylic acid (**27**), 2-chloro-6-methoxypyridine-5-carboxylic acid (**30**), and 2,6-dichloropyridine-3-carboxylic acid (**31**), in the proportions shown in Table 2. The unidentified minor component from the

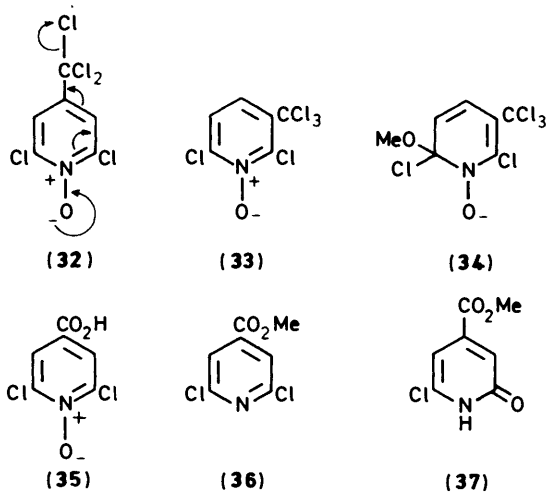
10 min reaction is thought to be a chlorohydroxypyridine-3-carboxylic acid formed by the action of hydroxide on the starting material. Acid (**27**) would have been formed from compounds (**15**) and (**26**), acid (**30**) from compound (**16**), and acid (**31**) from compound (**25**). The results listed in Table 2 are thus reasonably consistent with those listed in Table 1. The pathways followed are shown in Scheme 2. In summary, initial



Scheme 2. *Reagents:* i, NaOMe, MeOH; ii, OH^-

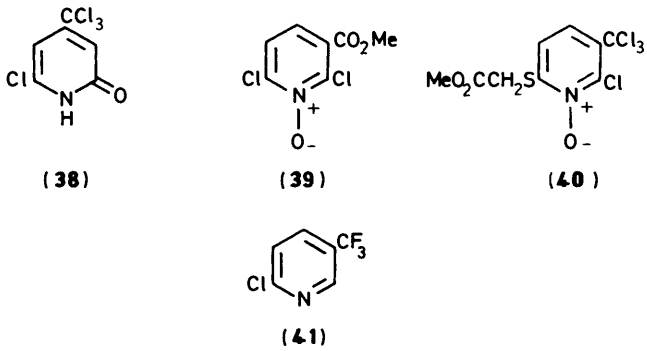
substitution by methoxide *either* at a ring carbon *or* at the side-chain carbon leads to further rapid reaction. In the former case the activation is as shown in Scheme 1. In the latter case, S_N1-like reaction is facilitated by stabilisation of carbocationic character at the side-chain carbon by the methoxy group attached to it.

In the light of these hypotheses, we predicted that conversion of the trichloromethylpyridines (**3**) and (**14**) into their *N*-oxides, (**32**) and (**33**), might lead to a reversal of the relative reactivities of their trichloromethyl groups. Thus, in the case of the 4-trichloromethyl compound, loss of chloride ion from the trichloromethyl group would be facilitated, as shown by the *N*-oxide (**32**); and in the case of the Meisenheimer adduct (**34**) of the 3-trichloromethyl isomer (**33**), the ring nitrogen carries only a lone pair, rather than the negative charge of (**22**). The results of our experiments on the *N*-oxides were not clear-cut, owing to partial deoxygenation during the reactions, but they did give some indication of the correctness of our predictions.



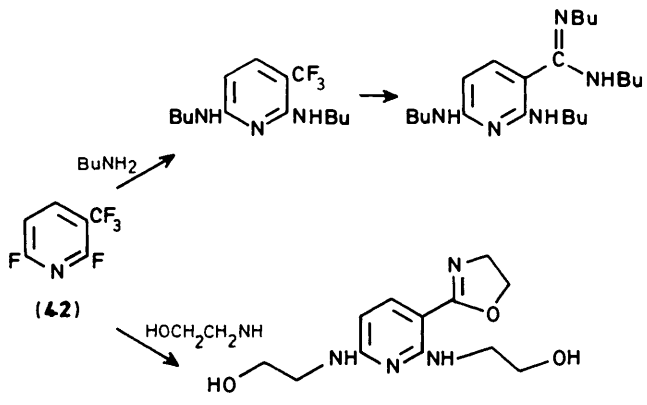
The *N*-oxides (**32**) and (**33**) were readily prepared by the Chivers-Suschitzky procedure.[12] In the case of the 4-trichloromethyl isomer (**32**), however, if the temperature was allowed to rise much above 0 °C when the reaction mixture was diluted prior to work-up, the carboxylic acid (**35**) was obtained, thus demonstrating the high reactivity of the trichloromethyl group. Similarly, whereas 2,6-dichloro-4-trichloromethylpyridine (**3**) yielded only the monosubstituted product (**12**) after extended reaction with an excess of piperdine at *ca.* 65 °C, the corresponding *N*-oxide reacted rapidly with piperidine at 0 °C, but gave only a tarry mixture, from which no pure product could be isolated. A reaction of the *N*-oxide (**32**) with sodium methoxide in methanol also gave a multi-component mixture, including deoxygenated products. In order to simplify the analysis, the mixture was treated with phosphorus trichloride to achieve complete deoxygenation. The products then isolated were deoxygenated starting material (9%), the ester (**36**) (5%), and the pyridones (**37**) and (**38**) (3 and 7%, respectively). Although the yields were low, the formation of the esters (**36**) and (**37**) again demonstrated the higher reactivity of the trichloromethyl group in the *N*-oxide (**32**) than in compound (**3**).

A reaction of the 3-trichloromethylpyridine *N*-oxide (**33**) with piperidine at room temperature gave only an intractable mixture of products, and, at higher temperatures, the deoxygenated amide previously obtained, (**20**). With 1 equivalent of sodium methoxide at room temperature a low yield of the ester (**39**) was obtained; when a five-fold excess of sodium methoxide was used, however, the deoxygenated ortho ester previously described, (**15**), was isolated in 66% yield. The greatest contrast between a reaction of 2,6-dichloro-3-trichloromethylpyridine (**14**) and its *N*-oxide (**33**) was shown by their reactions with methyl thioglycolate. The former gave only an intractable mixture of products even at 0 °C. The *N*-oxide (**33**), however,



reacted in boiling ethanol to give the *N*-oxide (**40**), in which a ring chlorine had been displaced, leaving the trichloromethyl group intact.

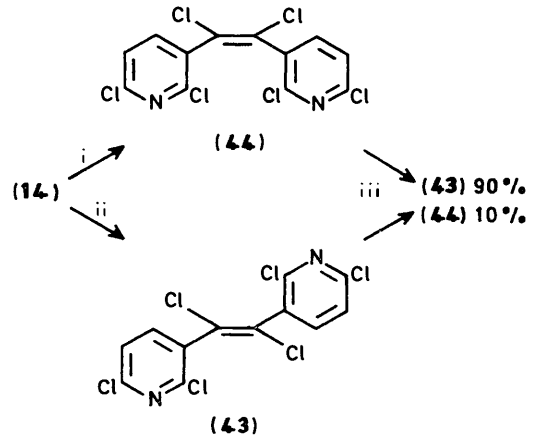
3-Trifluoromethylpyridines show much less activation of the trifluoromethyl group on, or following, nucleophilic substitution than do their trichloromethyl analogues. This is in accordance with our proposed mechanism, since fluoride is a much poorer leaving group than chloride. Japanese workers have reported that 2-chloro-5-trifluoromethylpyridine (**41**) undergoes nucleo-



Scheme 3.

philic substitution of the ring chlorine exclusively.[13] In the case of 2,6-difluoro-3-trifluoromethylpyridine (**42**), however, we observed some attack of the trifluoromethyl group under more vigorous conditions, as illustrated by the reactions with butylamine and ethanolamine shown in Scheme 3.

We take this opportunity to report briefly some other reactions of 2,6-dichloro-3-trichloromethylpyridine (**14**), summarised in Scheme 4. The reaction of copper and other reagents



Scheme 4. *Reagents:* i, H_2, Pd/C; ii, Cu, pyridine; iii, *hν*

with perchlorotoluene was reported by Spanish workers to give a mixture of *E*- and *Z*-perchlorostilbenes;[14] they suggested that perchlorobenzyl radicals were intermediates, but (triplet) carbene or carbenoid intermediates would also seem to be possible. We, and Swiss workers,[15] independently found that the reaction of copper in pyridine with 2,6-dichloro-3-trichloromethylpyridine (**14**) gave a single 1,2-dichloro-1,2-bis-(2,6-dichloro-3-pyridyl)ethene, m.p. *ca.* 245 °C. On the other hand, hydrogenation of the trichloromethylpyridine (**14**), with palladium on carbon as the catalyst, also gave a single dichlorodipyridylethene, m.p. 172 °C. U.v. irradiation of either isomer led to a mixture of the two in a ratio of 1:9, the higher melting isomer predominating. Although absolute proof is lacking, we suggest that, by analogy with other geometrically isomeric alkenes, the higher melting compound is the *E*-isomer (**43**). The u.v. spectra of the isomers is uninformative, as both absorb at 277 nm. Ballester *et al.* report that the perchlorostilbenes also exhibit anomalous u.v. spectra.[14a] A simple inspection of models of these types of compounds reveals that it is difficult for either isomer to achieve planarity. In the case of the pyridyl derivatives, (**43**) and (**44**), computer analysis indicates that for both isomers the conformer with minimum energy has a dihedral angle between the rings of at least 45°, thus explaining why the chromophore is similar for each isomer.

Some remarkable reactions of 3-trichloromethylpyridines, unsubstituted in the 2- and/or 6-positions (*cf.* ref. 6) will be described in a later paper.

Experimental

I.r. spectra were of liquid films or of Nujol or hexachlorobutadiene mulls. N.m.r. spectra were recorded at 60, 80 or 90 MHz (^{1}H) or 20 MHz (^{13}C) for solutions in $CDCl_3$ with TMS as internal standard, unless otherwise stated. Mass spectra were measured using electron impact ionisation; the *m/z* values recorded are for ions containing ^{35}Cl only, the figure in parentheses being the number of chlorines appropriate to the isotope pattern observed. Gas chromatography was carried out by means of a Pye Unicam G.C.D. Chromatograph fitted with a Hewlett-Packard H.P. 3380A integrator, using 5 ft 5% OV17 on Celite column at the temperature stated, and a flow rate of nitrogen of 40 ml min^{-1}. H.p.l.c. was carried out by means of a Hewlett-Packard 1084B Chromatograph using a 10 cm × 4.9 mm ODS Hypersil column and a u.v. detector set at $\lambda_{max.}$ 270 nm. The eluant was a 30:70 mixture of (*a*) acetonitrile, and (*b*) water + 0.5% cetyltrimethylammonium bromide. Boiling points refer to the oven temperature for bulb-to bulb distillation.

The trichloromethylpyridines (**1**), (**3**), and (**14**) were obtained by vapourphase chlorination of the corresponding picolines.

Reactions of 2,6-*Dichloro*-4-*trichloromethylpyridine* (**3**).—(a) *With methoxide.* (i) 2,6-Dichloro-4-trichloromethylpyridine (3.98 g, 15.0 mmol) was added to the solution obtained from sodium (0.345 g, 15.0 mmol) in dry methanol (30 ml), and the mixture was stirred under reflux during 5 h. The solvent was evaporated under reduced pressure and the residual oil was distilled, to yield 2-chloro-6-methoxy-4-trichloromethylpyridine (**9**)[3a] (3.63 g, 93%), b.p. 242 °C; ^{1}H δ 3.8 (3 H, s), 6.9 (1 H, s), and 7.2 (1 H, s); ^{13}C δ 54.6 (OMe), 94.2 (CCl_3), 106.0 (C-5), 112.9 (C-3), 149.5 (C-4), 156.2 (C-2), and 164.1 (C-6); M^+ at *m/z* 259 (Cl_4) (Found: C, 32.4; H, 1.9; N, 5.1. Calc. for $C_7H_5Cl_4NO$: C, 32.2; H, 1.9; N, 5.4%).

(ii) 2,6-Dichloro-4-trichloromethylpyridine (2.66 g, 10.0 mmol) was added to a stirred solution of sodium (0.23 g, 10.0 mmol) in methanol (20 ml). The mixture was heated under reflux for 48 h, during which time sodium (0.69 g) was added in portions. The solvent was evaporated under reduced pressure and the solid residue was recrystallised from ethanol to yield 2,6-*dimethoxy*-4-*trichloromethylpyridine* (**10**) (2.05 g, 81%), m.p. 70—71 °C, ^{1}H δ 3.9 (6 H, s) and 6.7 (2 H, s); ^{13}C δ 53.7 (OMe), 95.9 (CCl_3), 98.3 (C-3,5), 159.9 (C-4), and 163.7 (C-2,6); M^+ at *m/z* 255 (Cl_3) (Found: C, 37.8; H, 3.0; N, 5.4. $C_8H_8Cl_3NO_2$ requires C, 37.5; H, 3.1; N, 5.5%).

(b) *With piperidine.* A mixture of 2,6-dichloro-4-trichloromethylpyridine (2.66 g, 10.0 mmol), piperidine (8.5 g, 0.1 mol), and methanol (50 ml) was heated under reflux for 3 h. The mixture was poured into ice–water (150 ml). Conventional work-up gave 2-*chloro*-6-*piperidino*-4-*trichloromethylpyridine* (**12**) (1.95, 63%), m.p. 73—75 °C (from methanol), ^{1}H δ 1.5 (6 H, m), 3.5 (4 H, m), and 6.85 (2 H, s); ^{13}C δ 24.5, 25.4, and 46.2 (all piperidine ring), 95.5 (CCl_3), 100.6 (C-5), 107.4 (C-3), 150.4 (C-4), 155.3 (C-2), and 158.9 (C-6); M^+ at *m/z* 312 (Cl_4) (Found: C, 43.0; H, 3.9; N, 9.0. $C_{11}H_{12}Cl_4N_2$ requires C, 42.1; H, 3.8; N, 8.9%).

(c) *With butylamine.* A mixture of 2,6-dichloro-4-trichloromethylpyridine (10.62 g, 40.0 mmol) and butylamine (29.2 g) was heated under reflux for 2 h, cooled, and poured into ice–water acidified with 2M hydrochloric acid. The mixture was extracted with chloroform, and the extract was washed with water, dried, and evaporated to leave an oily residue which solidified on cooling in ice–salt. Recrystallisation of the solid from ethanol gave crude 2-*butylamino*-6-*chloro*-4-*trichloromethylpyridine* (**11**) (10.2 g, 85%) which was purified for analysis by dry column chromatography (light petroleum, silica), m.p. 46—48 °C, $\nu_{max.}$ 3 290 cm^{-1} (NH str), ^{1}H δ 0.9 (3 H, t), 1.4 (4 H, br), 3.25 (2 H, br), 6.75 (1 H, s), 6.95 (1 H, s), and 7.4 (1 H, br s); ^{13}C δ 13.7, 19.8, 30.8, 40.7, 94.9, 102.8 (C-5), 105.2 (C-3), 149.9 (C-4), 153.5 (C-6), and 159.2 (C-2); M^+ at *m/z* 300 (Cl_4) (Found: C, 39.8; H, 4.0; N, 9.3. $C_{10}H_{12}Cl_4N_2$ requires C, 39.8; H, 4.0; N, 9.3%).

2-*Methoxy*-6-*trichloromethylpyridine* (**13**).—A solution of 2-chloro-6-trichloromethylpyridine (2.29 g, 10.0 mmol) in methanol (25 ml) was added to a solution from sodium (2.3 g, 0.1 mol) in methanol (25 ml) and the mixture was stirred under reflux for 15 h. Conventional work-up followed by chromatography (silica, light petroleum–ethyl acetate) gave the *title*

compound (0.97 g, 44%, b.p. 80 °C/0.4 mmHg, $\lambda_{max.}$ 279 nm; ^{1}H δ 3.9 (3 H, s), 6.65 (1 H, d), and 7.5 (2 H, m); ^{13}C δ 53.6 (OMe), 96.9 (CCl_3), 111.6 and 112.5 (C-3 and C-5), 139.3 (C-4), 155.9 (C-6), and 162.9 (C-2); M^+ at *m/z* 226 (Cl_3) (Found: C, 37.1; H, 2.7; N, 6.1. $C_7H_6Cl_3NO$ requires C, 37.1; H, 2.7; N, 6.2%).

Reactions of 2,6-*Dichloro*-3-*trichloromethylpyridine* (**14**) *with Methoxide*.—(a) *Complete reaction*. 2,6-Dichloro-3-trichloromethylpyridine (5.31 g, 20 mmol) was added to a solution of potassium hydroxide (5.6 g, 100 mmol) in methanol (50 ml). The mixture was heated under reflux during 6 h, cooled, and poured into water (100 ml). The resulting suspension was extracted with ether (3 × 50 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to dryness. The white solid residue was recyrstallised from light petroleum (b.p. 60—80 °C; 15 ml) to give 2-*chloro*-6-*methoxy*-3-(*trimethoxymethyl*)*pyridine* (**15**), white solid, m.p. 69 °C, ^{1}H δ 3.18 (9 H, s, ortho ester OCH_3), 3.98 (3 H, s, 6-OCH_3), 6.7 (1 H, d, 5-H), and 8.06 (1 H, d, 4-H); ^{13}C δ 49.55 (ortho ester OCH_3), 54.1 (6-OCH_3), 108.4 (C-5), 113.7 (ortho ester C), 122.3 (C-3), 142.8 (C-4), 146.9 (C-2), and 163.5 (C-6); *m/z* 247 (Cl) (M^+), 216 (Cl), 170 (Cl), 136, and 105 (Found: C, 48.5; H, 5.8; Cl, 14.3 N, 5.9. $C_{10}H_{14}ClNO_4$ requires C, 48.5; H, 5.65; Cl, 14.3; N, 5.65%).

A sample of the mother liquor was examined by g.c.-m.s. which revealed two major components, t_R 2.36 and 2.93 min. (190 °C), the latter corresponding to the ortho ester (**15**) described above. The m.s. of the former component showed it to be an isomer, and the ^{13}C n.m.r. of the mixture showed signals appropriate for 6-chloro-2-methoxy-3-(trimethoxymethyl)pyridine (**16**): δ 49.6, 54.4, 113.45, 115.8, 122.3, 142.55, 149.0, and 160.7.

The ortho ester (**15**) (4.0 g, 16.2 mmol) was dissolved in a mixture of methanol (20 ml) and 2M hydrochloric acid (5 ml). The mixture was heated under reflux during 15 min, cooled, and diluted with water (30 ml). The white crystalline precipitate was washed with water and dried, giving crude *methyl* 2-*chloro*-6-*methoxypyridine*-3-*carboxylate* (**17**) (2.8 g, 86%), m.p. 65 °C; recrystallisation from light petroleum (b.p. 60—80 °C; 12 ml) gave 2.07 g, m.p. 68.5 °C, δ 3.92 (3 H, s, CO_2CH_3), 4.0 (3 H, s, 6-OCH_3), 6.71 (1 H, d, 5-H), and 8.14 (1 H, d, 4-H) (Found: C, 47.8; H, 4.1; Cl, 17.8; N, 7.0. $C_8H_8ClNO_3$ requires C, 47.6; H, 4.0; Cl, 17.6; N, 6.9%).

(b) *Characterising reactions of methyl* 2-*chloro*-6-*methoxypyridine*-3-*carboxylate* (**17**). (i) Hydrolysis. A small sample of the ester (**17**) was dissolved in a mixture of methanol and 2M sodium hydroxide, and the solution was heated under reflux during 30 min. The solution was cooled, acidified, and filtered, to give 2-*chloro*-6-*methoxypyridine*-3-*carboxylic acid* (**27**), m.p. 235 °C, ^{1}H ([$^2H_6$]DMSO) δ 3.95 (3 H, s, OCH_3), 6.95 (1 H, d, 5-H), 8.22 (1 H, d, 4-H), and 13.2 (1 H, d, CO_2H): ^{13}C δ 54.4 (OCH_3), 109.3 (C-5), 119.55 (C-3), 143.3 (C-4), 147.3 (C-2), 164.1 (C-6), and 165.1 (CO_2H); *m/z* 187 (Cl) (M^+), 170 (Cl), and 157 (Cl) (Found: C, 44.5; H, 2.7; Cl, 18.9; N, 7.2. $C_7H_6ClNO_3$ requires C, 44.8; H, 3.2; Cl, 18.7; N, 7.5%).

(ii) Hydrogenolysis. The ester (**17**) (1.0 g, 5 mmol) was dissolved in methanol (30 ml) and hydrogenated at room temperature and pressure over palladium (5% on charcoal, 0.2 g) in the presence of potassium acetate (0.2 g). When the uptake of hydrogen ceased the solution was separated from the catalyst and evaporated to dryness. The solid residue was extracted with light petroleum (b.p. 40—60 °C), and the suspended inorganic solids were filtered off. Cooling and filtration of the filtrate gave *methyl* 6-*methoxypyridine*-3-*carboxylate* (0.70 g, 84%), m.p. 50.5 °C, δ 3.7 (3 H, s, CO_2CH_3), 3.8 (3 H, s, 6-OCH_3), 6.5 (1 H, d, *J* 8 Hz, 5-H), 7.85 (1 H, dd, *J* 8 Hz and 2 Hz, 4-H), and 8.5 (1 H, d, *J* 2 Hz, 2-H) (Found: C, 57.5; H, 5.5; N, 8.4. $C_8H_9NO_3$ required C, 57.4; H, 5.4; N, 8.4%).

A small sample of this ester was hydrolysed as described under (i) to give 6-*methoxypyridine*-3-*carboxylic acid* (**18**), m.p. 173—174 °C, (lit.,[4] 165—168 °C), ^{1}H δ 3.95 (3 H, s, OCH_3), 6.92 (1 H, d, 5-H), 8.18 (1 H, dd, 4-H), 8.78 (1 H, d, 2-H), and 12.97 (CO_2H); ^{13}C δ 53.7 (OCH_3), 110.4 (C-5), 120.3 (C-3), 139.8 (C-4), 149.4 (C-2), and 166.04 and 166.09 (C-6 and CO_2H); *m/z* 153 (Cl) (M^+) (Found: C, 54.7; H, 4.6; N, 9.1. $C_7H_7NO_3$ requires C, 54.9; H, 4.6; N, 9.1%).

(c) *Incomplete reactions*. (i) Sodium (1.4 g, 60 mmol) was dissolved in methanol (100 ml). 2,6-Dichloro-3-trichloromethylpyridine (5.2 g, 20 mmol) was added, and the mixture was heated under reflux during 10 min and then cooled rapidly in an ice-bath. The mixture was freeze-dried *in vacuo* and the residual gummy solid was slurried with cold water. The slurry was extracted with ether. The extract was dried ($MgSO_4$) and evaporated to dryness, leaving an oil which slowly crystallised. The solid was triturated with light petroleum, b.p. 60—80 °C, collected by filtration, and dried. Examination by g.c. (190 °C) revealed two major components. The minor component (20% of peak area) corresponded to 2-chloro-6-methoxy-3-(trimethoxymethyl)pyridine (**15**). The major component (80% of area) could not be purified by crystallisation, but was identified by g.c.-m.s., *m/z* 251 (Cl_2) (M^+), 220 (Cl_2) (base peak, $M - OCH_2$), and ^{13}C n.m.r.; δ 49.8 (OCH_3), 113.1 (ortho ester C), 122.45 (C-5), 129.4 (C-3), 143.0 (C-4), 148.5 (C-2), and 150.5 (C-6), as 2,6-dichloro-3-(trimethoxymethyl)pyridine (**25**). However, hydrolysis of the impure product gave 2-chloro-6-methoxypyridine-3-carboxylic acid (**27**), m.p. 235 °C, identified by comparison with the compound described above.

(ii) Sodium (0.53 g) was dissolved in methanol (25 ml). The solution was cooled, finely powdered 2,6-dichloro-3-trichloromethylpyridine (1.325 g) was added, and the mixture was heated under reflux. Samples were removed at intervals, diluted with methanol, made slightly acid by the addition of acetic acid, and examined by g.c. (175 °C); the results are shown in Table 1.

The final products of this reaction, and of a similar reaction which had only been allowed to proceed for 10 min, were each diluted with 2M sodium hydroxide (10 ml) and heated under reflux during 1 h. The resulting mixtures were examined by h.p.l.c., authentic specimens of 2-chloro-6-methoxypyridine-3-carboxylic acid (**27**), 6-chloro-2-methoxypyridine-3-carboxylic acid (**30**), and 2,6-dichloropyridine-3-carboxylic acid (**31**) being used for identifying peaks; the results are shown in Table 2.

Reactions of 2,6-*Dichloro*-3-*trichloromethylpyridine* (**14**) *with Piperidine*.—A mixture of 2,6-dichloro-3-trichloromethylpyridine (2.66 g, 10 mmol), piperidine (8.5 g, 0.1 mol) and methanol (30 ml) was stirred at room temperature for 15 h. Conventional work-up gave N-(2-*chloro*-6-*piperidino*-3-*pyridylcarbonyl*)*piperidine* (**20**) (1.91 g, 63%), m.p. 158—160 °C [from light petroleum, (b.p. 100—120 °C)], $\nu_{max.}$ 1 620 cm^{-1}; ^{1}H δ 1.6 (12 H, m), 3.5 (8 H, m), 6.4 (1 H, d), and 7.25 (1 H, d); ^{13}C δ 25.0, 25.9, 42.3, 45.5, 46.6, 47.7, 104.1, 118.4, 137.9, 144.7, 158.1, and 166.0; M^+, at *m/z* 307 (Cl) (Found: C, 62.6; H, 7.2; Cl, 11.9; N, 13.5. $C_{16}H_{22}ClN_3O$ requires C, 62.4; H, 7.2; Cl, 11.9; N, 13.7%).

In another experiment, dry *N*,*N*-dimethylformamide was used as solvent in place of methanol. On completion of the reaction, solvent and excess piperidine were removed as completely as possible *in vacuo*. The ^{1}H n.m.r. spectrum of the product indicated a ratio of aromatic to non-aromatic protons of *ca.* 1:20.

Reactions of 2,6-*Difluoro*-3-*trifluoromethylpyridine* (**42**).—(a) *With butylamine*. (i) Butylamine (2.92 g, 40 mmol) was added to a solution of 2,6-difluoro-3-trifluoromethylpyridine (1.83 g, 10 mmol) in dichloromethane (10 ml). When the resulting exothermic reaction had subsided the solvent was distilled, butylamine (2.92 g) was added, and the mixture was heated under reflux for 5 h. Water (25 ml) was added, and the pH was

adjusted to 3—4 by the addition of 2M HCl, then to 7 by the addition of aqueous sodium hydrogen carbonate. The resulting mixture was extracted with ether (50 ml) and the extract was dried and evaporated to leave a yellow oil containing some solid. Digestion with light petroleum, filtration, and evaporation of solvent gave 2,6-bis(butylamino)-3-trifluoromethylpyridine (2.35 g, 81%) as a clear yellow oil, ^{1}H δ 1.2 (14 H, m), 3.3 (4 H, m), 4.6 (2 H, br), 5.6 (1 H, d), and 7.3 (1 H, d), which decomposed with time. Coupling with diazotised *p*-chloroaniline gave 2,6-bis(*butylamino*)-3-(p-*chlorophenylazo*)-5-(*trifluoromethyl*)*pyridine*, m.p. 75—75.5 °C, δ 1.3 (14 H, m), 3.5 (4 H, m), 5.2 (1 H, br), 7.35, 7.85 (1 H, s), and 9.9 (1 H, br) (Found: C, 56.2; H, 5.5; Cl, 8.3; N, 16.4. $C_{20}H_{25}ClF_3N$ requires C, 56.1; H, 5.9; Cl, 8.3; N, 16.4%).

(ii) In an otherwise similar experiment, the second addition was of butylamine (6.57 g, 90 mmol) and the subsequent reflux period was 24 h. The reaction mixture was cooled, and the resulting semi-solid was treated with water (50 ml) and the mixture adjusted to pH 7 as before. Ether (50 ml) was added, and the sticky insoluble material was filtered off, washed with ether, and dried to give N^{1}N^2-*dibutyl*[2,6-bis(*butylamino*)-3-*pyridyl*]*amidine* (2.2 g, 53%), m.p. 156.5—157.5 °C, $\nu_{max.}$ 3 280, 3 180, and 1 605 cm^{-1}, ^{1}H δ([$^2H_6$]DMSO) 1.2 (m, 28-H), 3.25 (8 H, br), 5.7 (1 H, d), 6.1 (1 H, br t), 6.9 (1 H, d), 6.95 (1 H, br), and 9.0 (1 H, br); M^+ at *m/z* 375. Coupling with diazotised *p*-chloroaniline gave the corresponding *azo dye*, (Found: C, 61.2; H, 8.3; Cl, 13.0; N, 17.6. $C_{28}H_{45}Cl_2N_7$ requires C, 61.1; H, 8.2; Cl, 12.9; N, 17.8%).

(d) *With* 2-*aminoethanol*. 2-Aminoethanol (3.66 g, 60 mmol) was added dropwise to a solution of 2,6-difluoro-3-trifluoromethylpyridine (1.71 g, 9.3 mmol) in dichloromethane (10 ml). The exothermic reaction caused refluxing for 5 min. The solvent was distilled off, and the remaining mixture was heated at 90 °C for 7 h. The resulting suspension was treated with water (50 ml) and dichloromethane (20 ml) and filtered. The resulting solid was washed with water and dried to give 2,6-*bis*(2-*hydroxyethylamino*)-3-*oxazolin*-2-*ylpyridine* (0.9 g, 36%), m.p. 131—132 °C (from water), $\nu_{max.}$ 3 400, 3 160, 1 660, and 1 605 cm^{-1}; ^{1}H δ([$^2H_6$]DMSO), 3.5 (8 H, m), 4.0 (4 H, m), 4.6 (2 H, br), 5.65 (1 H, d), 6.6 (1 H, br), 7.4 (1 H, d), and 8.65 (1 H, br); M^+ at *m/z* 266 (Found: C, 54.5; H, 6.6; N, 20.9. $C_{12}H_{18}N_4O_3$ requires C, 54.1; H, 6.8; N, 21.0%).

2,6-*Dichloro*-4-*trichloromethylpyridine* N-*Oxide* (**32**).—2,6-Dichloro-4-trichloromethylpyridine (2.65 g, 10.0 mmol) was dissolved in a mixture of acetic acid (50 ml) and conc. sulphuric acid (25 ml). The mixture was cooled in an ice-bath as 86% hydrogen peroxide was added; it was then stirred at *ca.* 0 °C for 48 h, and then added slowly to ice–water. The resulting suspension was filtered. The filtrate was carefully neutralised at 0 °C and the resulting suspension was filtered. The combined precipitates were recrystallised from chloroform to give the *title compound* (2.04 g, 73%), m.p. 90—91.5 °C, δ 8.5 s; M^+ at *m/z* 279 (Cl_5) (Found: C, 25.75; H, 0.8; N, 5.0. $C_6H_2Cl_5NO$ requires C, 25.6; H, 0.7; N, 5.0%).

In an otherwise similar experiment the reaction mixture was poured into water and neutralised with concentrated aqueous sodium hydroxide, without special care to keep the mixture cold. The product was 2,6-*dichloro*-1-*oxidopyridine*-4-*carboxylic acid* (**15**) (1.6 g, 77%), m.p. 199—200 °C, ^{1}H δ([$^2H_6$]DMSO), 8.1; ^{13}C δ 125.2 (C-3), 126.9 (C-4), 142.4 (C-4), and 163.4 (CO_2H); M^+ at *m/z* 207 (Cl_2) (Found: C, 34.85; H, 1.6; N, 6.6. $C_6H_3Cl_2NO_3$ requires C, 34.65; H, 1.6; N, 6.7%).

2,6-*Dichloro*-3-*trichloromethylpyridine* N-*Oxide* (**33**).—This *compound* was prepared (92%) as described for its 4-trichloromethyl analogue, and had m.p. 133—135 °C (from chloroform), ^{1}H δ 7.6 (1 H, d) and 8.0 (1 H, d); ^{13}C δ 91.9 (CCl_3), 121.5 (C-5), 122.5 (C-4), 138.2 (C-3), 142.9 (C-6), and 143.8 (C-2); M^+ at *m/z* 279 (Cl_5) (Found: C, 25.8; H, 0.8; N, 4.8. $C_6H_2Cl_5NO$ requires C, 25.6; H, 0.7; N, 5.0%).

Reaction of 2,6-*Dichloro*-4-*trichloromethylpyridine* N-*Oxide* (**32**) *with Methoxide*.—2,6-Dichloro-4-trichloromethylpyridine *N*-oxide (1.4 g, 5.0 mmol) was added to a solution of sodium (0.115 g, 5.0 mmol) in methanol (50 ml) and the mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure, the residue was dissolved in chloroform, and an excess of phosphorus trichloride was added. The resulting mixture was heated under reflux for 3 h, then cooled, washed with water (100 ml), dried, and evaporated to give a residue which was subjected to chromatography (silica, gradient elution with ethyl acetate–light petroleum) to give (i) 2,6-dichloro-4-trichloromethylpyridine (**3**) (0.13 g, 9%); (ii) methyl 2,6-dichloropyridine-4-carboxylate (**36**) (0.09 g, 5%), m.p. 79—81.5 °C (lit.,[16] m.p. 81 °C), $\nu_{max.}$ 1 740 cm^{-1}; ^{1}H δ 3.9 (3 H, s) and 7.75 (2 H, s); ^{13}C δ 53.1 (CH_3), 122.5 (C-3,5), 142.3 (C-4), 151.4 (C-2,6), and 163.1 (C=O); M^+ at *m/z* 205 (Cl_2) (Found: C, 40.9; H, 2.5; N, 6.7. Calc. for $C_7H_5Cl_2NO_2$ C, 40.8; H, 2.45; N, 6.8%): (iii) 2-*Chloro*-4-*trichloromethylpyridin*-6-*one* (**38**) (0.17 g, 7%), yellow crystals, m.p. 120—123 °C, ^{1}H δ 7.15 (s); ^{13}C δ 93.8 (CCl_3), 108.3 (C-3), 110.4 (C-5), 145.0 (C-4), 157.4 (C-2), and 164.7 (C-6); M^+ at *m/z* 245 (Cl_4) (Found: C, 29.3; H, 1.3; N, 5.55. $C_6H_3Cl_4NO$ requires C, 29.2; H, 1.2; N, 5.7%): (iv) Methyl 2-chloro-6-oxopyridine-3-carboxylate (**37**) (0.05 g, 3%), m.p. 190—192 °C, $\nu_{max.}$ 1 735 cm^{-1}; ^{1}H δ 3.9 (3 H, s) and 7.3 (2 H, s); M^+ at *m/z* 187 (Cl) (Found: C, 44.5; H, 3.35; N, 7.6. $C_7H_6ClNO_3$ requires C, 44.8; H, 3.2; N, 7.5%).

Reactions of 2,6-*Dichloro*-3-*trichloromethylpyridine* N-*Oxide* (**33**).—(a) *With methoxide*. (i) A solution of 2,6-dichloro-3-trichloromethylpyridine *N*-oxide (1.4 g, 5.0 mmol) and sodium (0.13 g, 5.0 mmol) in methanol (30 ml) was stirred at room temperature for 48 h. Conventional work-up followed by chromatography (silica, gradient elution with ethyl acetate–light petroleum) gave recovered *N*-oxide (0.26 g, 19%), followed by *methyl* 2,6-*dichloro*-1-*oxidopyridine*-3-*carboxylate* (**39**) (0.12 g, 19%), m.p. 112—114 °C (from light petroleum), $\nu_{max.}$ 1 730 cm^{-1}; ^{1}H δ 4.0 (3 H, s) and 7.5 (2 H, s) (Found: M^+ at *m/z* 220.9646. $C_7H_5Cl_2NO_3$ requires M^+ at 220.9646).

(ii) A solution of 2,6-dichloro-3-trichloromethylpyridine *N*-oxide (0.56 g, 2.0 mmol) and sodium (0.23 g, 10.0 mmol) in methanol (30 ml) was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure. Chromatography of the residue (silica, ethyl acetate–light petroleum) followed by distillation gave 2-chloro-6-methoxy-3-trimethoxymethylpyridine (**15**) (0.32 g, 65%) identified by its n.m.r. spectrum and hydrolysis to methyl 2-chloro-6-methoxypyridine-3-carboxylate (**17**).

(b) *With methyl thioglycolate*. 2,6-Dichloro-3-trichloromethylpyridine *N*-oxide (1.25 g, 4.5 mmol) and methyl thioglycolate (0.477 g, 4.5 mmol) were dissolved in ethanol (50 ml). A little anhydrous potassium carbonate was added and the mixture was heated under reflux for 5 h. The cooled reaction mixture was poured into ice–water (100 ml) and the resulting precipitate was filtered off dried, recrystallised from ethanol, and identified as *methyl* (6-*chloro*-1-*oxido*-5-*trichloromethyl*-2-*pyridylthio*)*acetate* (**40**) (1.35 g, 86%), m.p. 198.5—200 °C (decomp.), $\nu_{max.}$ 1 730 cm^{-1}; ^{1}H δ 3.8 (5 H, s), 7.5 (1 H, d), and 8.1 (1 H, d); ^{13}C δ 33.2 (SCH_2), 53.0 (OMe), 92.8 (CCl_3), 116.7 (C-5), 122.5 (C-4), 134.5 (C-3), 154.6 (C-2), 168.2 (C-6), and 202.1 (C=O); M^+ at *m/z* 349 (Cl_4) (Found: C, 30.7; H, 2.1; N, 4.15. $C_9H_7Cl_4NO_3S$ requires C, 30.8; H, 2.0; N, 4.0%).

1,2-*Dichloro*-1,2-*bis*(2,6-*dichloro*-3-*pyridyl*)*ethene* (**44**).—(*a*) A solution of 2,6-dichloro-3-trichloromethylpyridine (**14**) (2.65

g, 9.5 mmol) was hydrogenated at room temperature and atmospheric pressure over palladium (5% on charcoal, 0.2 g). During *ca.* 30 min., 270 ml of hydrogen were absorbed and uptake then ceased. The filtered solution was examined by g.c. (280 °C), which showed that the product consisted of essentially one compound. The solution was evaporated to dryness, and the residue recrystallised from light petroleum (b.p. 80—100 °C) to give *Z*-1,2-*dichloro*-1,2-*bis*(2,6-*dichloro*-3-*pyridyl*)*ethene* (**44**) (1.50 g, 75%), m.p. 172 °C, $\lambda_{max.}$ (isopropyl alcohol) 277 nm; ^{1}H δ 7.24 (d, *J* 8.2 Hz, 5-H) and 7.67 (d, *J* 8.2 Hz, 4-H); ^{13}C δ 123.6 (C-5), 129.0 (C-7 or C-3), 130.4 (C-3 or C-7), 140.8 (C-4), 148.6 (C-2), and 151.8 (C-6); M^+ at *m*/*z* 386 (Cl_6) (Found: C, 36.8; H, 0.9; Cl 53.3; N, 7.2. $C_{12}H_4Cl_6N_2$ requires C, 37.0; H, 1.0; Cl, 54.75; N, 7.2%).

(*b*) Treatment of 2,6-dichloro-3-trichloromethylpyridine with copper in pyridine as described in ref. 15 gave (*E*)-1,2-dichloro-1,2-bis(2,6-dichloro-3-pyridyl)ethene (**43**), m.p. 242 °C (lit.,[15] m.p. 245—246 °C), $\lambda_{max.}$ (isopropyl alcohol) 277 nm [lit.,[15] $\lambda_{max.}$(MeOH) 274.5 nm].

(*c*) Solutions of the *Z*- and *E*-isomers were separately irradiated during 5 h in isopropyl alcohol solution through quartz by means of a medium-pressure mercury lamp. The solutions were then analysed by g.c. (280 °C), and each was found to contain the *Z*- and *E*-isomers, in a ratio of 1:9.

Acknowledgements

We thank I.C.I. p.l.c. for a J.R.S. award; Dr. J. Clark, Mrs. R. Howard, and Dr. T. M. Williams for mass spectrometry, and Dr. A. M. Chippendale and Mr. R. Hayes for n.m.r. spectroscopy, and Dr. J. O. Morley for computer molecular modelling.

References

1 Belg. 624,800 (1983) (Dow Chemical Co.) (*Chem. Abstr.*, 1964, **61**, P1841).
2 *Weeds Today*, 1983, **14**, 3.
3 (*a*) H. Johnston and M. S. Tomita, U.S.P. 3,244,722/1966; (*b*) F. E. Torba, U.S.P. 3,705,170/1972.
4 R. S. Dainter, Ph.D. Thesis, Salford, 1983.
5 B.P. 1,552,682/1980 (Ciba Geigy).
6 R. S. Dainter, H. Suschitzky, B. J. Wakefield, N. Hughes, and A. J. Nelson, *Tetrahedron Lett.*, 1984, **25**, 5693.
7 Y. Kobayashi and I. Kumada, *Acc. Chem. Res.*, 1978, **11**, 197.
8 H. Kimoto and L. A. Cohen, *J. Org. Chem.*, 1979, **44**, 2902 and 1980, **45**, 3831; see also I. G. Moores, R. K. Smalley, and H. Suschitzky, *J. Fluorine Chem.*, 1982, **20**, 573.
9 R. Belcher, M. Stacey, A. Sykes, and J. C. Tatlow, *J. Chem. Soc.*, 1954, 3846.
10 P. B. de la Mare and P. A. Newman, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1797; see also G. Stein, H. Kammerer, and V. Bohmer, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1285.
11 J. F. Bunnett and C. Galli, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2515.
12 G. E. Chivers and H. Suschitzky, *J. Chem. Soc. C*, 1971, 2867.
13 T. Hago, K.-i. Fujikawa, T. Koyanagi, T. Nakajima, and K. Hayashi, *Heterocycles*, 1984, **22**, 117.
14 M. Ballester, C. Molinet, and J. Rosa, *Tetrahedron*, 1959, **6**, 109; M. Ballester and J. Castaner, *An. Fis. Quim.*, 1966, **62**, 397; S. Olivella, M. Ballester, and J. Castaner, *Tetrahedron Lett.*, 1974, 587.
15 U. Horn. F. Mutterer, and C. D. Weis, *Helv. Chim. Acta*, 1976, **59**, 190.
16 C. Dufour and S. Perret, Ger. Offen., 2 263 026/1973.

Received 28*th January* 1987; *Paper* 7/142