Transformations of Trichloromethyl Groups During Reactions of 3-Trichloromethylpyridines with Methoxide

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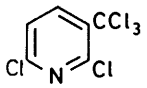
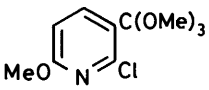
When methoxide ion attacks an unsubstituted 2- or 6-position of a 3-trichloromethylpyridine, a hydrogen shift leads to a methoxy-substituted 3-dichloromethylpyridine. Further reaction of the dichloromethyl group with methoxide gives the corresponding acetal. This type of reaction has been applied to several chlorinated 3-trichloromethylpyridines and to 3-trichloromethylpyridine itself; a convenient synthesis of the latter is described.

We have reported that the reaction of 2,6-dichloro-3-trichloromethylpyridine (**1**) with nucleophiles gives products in which all the chlorine atoms have been displaced from the trichloromethyl group. With methoxide, for example, the main product was the ortho ester (**2**).[1,2]

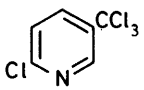
Our initial experiments on 2-chloro-5-trichloromethylpyridine (**3**) gave only products analogous to those from the 2,6-dichloro compounds (**1**). Thus, sodium methoxide in methanol gave the ester (**4**).† However, a reaction with sodium methoxide in tetrahydrofuran (THF), followed by aqueous work-up, gave, besides a poor yield of the acid (**5**), a compound which retained a chlorine atom and whose spectroscopic properties ($\nu_{max.}$ 1 680 cm^{-1}, singlet at δ 10.15) indicated that it was an aldehyde. We postulated structure (**6**) for the aldehyde, and this was subsequently confirmed (see below). Its formation must have involved attack of methoxide on the sterically hindered 6- rather than the 2-position, so we reasoned that analogous products might be more favoured in reactions of 2-chloro-3-trichloromethylpyridine (**8**).



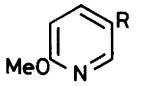
(**1**)



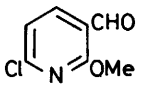
(**2**)



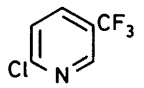
(**3**)



(**4**) R = CO_2Me
(**5**) R = CO_2H



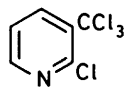
(**6**)



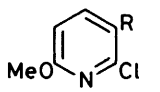
(**7**)

A reaction of 2-chloro-3-trichloromethylpyridine (**8**) with sodium methoxide in methanol gave the acetal (**9**) in 59% yield together with a little (9%) of the dimethoxy aldehyde (**10**). With sodium methoxide in THF the products isolated were the aldehydes (**11**) (35%) and (**10**) (9%). Once again an analogous reaction with the trifluoromethyl compound (**12**) proceeded 'normally' to give the ring-methoxy compound (**13**).

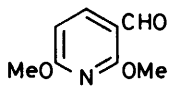
Since the acetal and aldehyde products were unexpected, and their structures in some cases ambiguous [for example, the data did not exclude (**14**) as an alternative to structure (**10**)], key products were synthesized by an alternative route. Reaction of 2,6-dichloro-3-cyanopyridine (**15**) with an excess of methoxide gave the dimethoxy compound (**16**), which on reduction with di-isobutylaluminium hydride gave the aldehyde (**10**). Reaction of the dichloro nitrile (**15**) with 1 equiv. of methoxide gave a mixture of nitriles (**17**) and (**18**) which we could not separate, but which on reduction gave a mixture of the isomeric aldehydes (**6**) and (**11**).



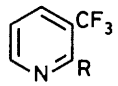
(**8**)



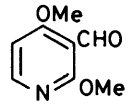
(**9**) R = $CH(OMe)_2$
(**11**) R = CHO



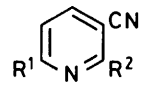
(**10**)



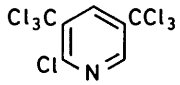
(**12**) R = Cl
(**13**) R = OMe



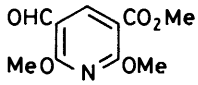
(**14**)



(**15**) $R^1 = R^2 = Cl$
(**16**) $R^1 = R^2 = OMe$
(**17**) $R^1 = Cl, R^2 = OMe$
(**18**) $R^1 = OMe, R^2 = Cl$



(**19**)



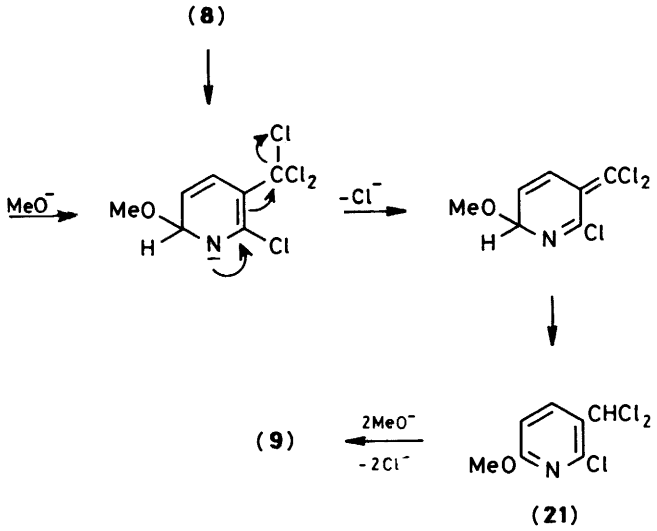
(**20**)

In all the reactions of 3-trichloromethylpyridines described above [and in the reactions of 2,6-dichloro-3-trichloromethylpyridine (**1**) reported previously[1]] the following generalisation holds good: introduction of a nucleophile at an α-position bearing chlorine is accompanied by ortho ester/ester formation,

† In contrast, the reported reactions of 2-chloro-5-trifluoromethylpyridine (**7**) with most nucleophiles proceed cleanly, by displacement of the ring chlorine atom, though with ammonia some 2-amino-5-cyanopyridine was obtained.[3]

whereas introduction of the nucleophile at an unsubstituted α-position results in acetal/aldehyde formation. This generalisation was neatly confirmed by the reaction of 2-chloro-3,5-bis(trichloromethyl)pyridine (**19**) with methoxide, which gave the formyl ester (**20**) in good yield.

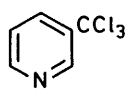
In our preliminary communication,[1] we proposed a mechanism for the formation of acetal, as represented by the Scheme. To be consistent with this Scheme, the following are



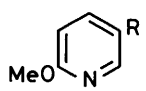
Scheme.

required: (*a*) the loss of the first chlorine atom from the side chain and the hydrogen shift follow (or accompany) the initial nucleophilic attack on the ring, and precede the displacement of the remaining chlorine atoms and (*b*) the hydrogen atom which appears in the side chain originates from the 6-position of the pyridine ring. Attempts to test these requirements by experiments on 2-chloro-3-trichloromethylpyridine (**8**) were only partially successful. After reactions of compound (**8**) with sodium methoxide in methanol for short reaction times, mixtures of products were obtained. One component of the mixtures was identified by n.m.r. and mass spectrometry as the key dichloromethyl intermediate (**21**), but it could not be obtained analytically pure; attempts to monitor the reaction by gas chromatography and mass spectrometry gave inconsistent results, probably owing to continuing reactions before analysis (*cf.* ref. 2). In an attempt to obtain evidence on the origin of the hydrogen atom introduced into the side-chain, and/or determine whether its transfer was intra- or inter-molecular, reactions were carried out in *O*-deuteriomethanol as solvent, but the n.m.r. spectrum of the multi-component mixture of products was too complex to allow firm deductions to be made. It was significant, however, that a singlet was present at δ 7.1, corresponding to the dichloromethyl group in (**21**); its presence suggested that any exchange was incomplete.

In order to obtain more definitive information we wished to investigate the simplest possible substrate *viz* 3-trichloromethylpyridine (**22**). Surprisingly, at the time of this work this



(**22**)



(**23**) R = CH(OMe)
(**24**) R = $CHCl_2$
(**25**) R = $CH(OEt)_2$

compound was reported in the literature only as a minor component of a mixture.[4] A possible route to this compound appeared to be the reaction of nicotinic acid with phosphorus pentachloride. According to literature precedent, such a reaction is only successful for carboxylic acid groups α- to the nitrogen in nitrogen heterocyclic aromatic compounds,[5] though we had reason to suppose that a reaction of nicotinic acid with a combination of phosphorus pentachloride and other phosphorus(v) chlorides might be successful.[6] In fact, reasonable yields (*ca.* 60% of 3-trichloromethylpyridine (**22**) were obtained with phosphorus pentachloride alone, provided that the reaction temperature was carefully controlled.

The reaction of 3-trichloromethylpyridine (**22**) with an excess of sodium methoxide in methanol gave the methoxy acetal (**23**) in good yield. With only 1.5 mol equiv. of sodium methoxide in THF, the main product was the dichloromethyl compound (**24**). It was further confirmed that the dichloromethyl compound (**24**) was an intermediate in the reaction when it was caused to react with an excess of methoxide [giving the acetal (**23**)] or ethoxide [giving the acetal (**25**)].

A reaction of 3-trichloromethylpyridine (**22**) in [$^2H_8$]-THF gave unlabelled dichloromethyl compound (**24**), thus excluding the possibility that the side-chain hydrogen atom arose from hydrogen abstraction from the solvent. The fact that the rearrangement took place in a protic solvent made a mechanism involving hydride ions unlikely. There remained two plausible mechanisms to consider: a concerted 1,5-hydrogen shift, and a prototropic process. The former seemed unlikely, since although a thermal 1,5-suprafacial shift is allowed, an s-*cis* conformation in the diene system is required for efficient orbital overlap.[7] With the intention of distinguishing between a concerted, intramolecular mechanism and a dissociative proton shift, a reaction was carried out in the presence of methan[^{2}H]ol. The result was ambiguous: the n.m.r. signal for the dichloromethyl proton was present in the product but its integration corresponded to only *ca.* 0.6 H.* Thus some, but not all, of the dichloromethyl group contained dueterium from the solvent. A concerted 1,5-shift in an s-*trans* diene system would be, as far as we are aware, unprecedented. We suggest, therefore, that a very rapid proton shift occurs, in which only a proportion of the protons escape from the solvent cage.

A search of the literature has revealed a few examples of reactions analogous to the ones described in this paper. They include reactions of nucleophiles with 3-(dichloromethyl)-nitrobenzenes,[8,9] with halogenomethylpyrazines,[10] and with 4-(chloroalkyl)pyridazines.[11] We suggest that similar reactions are likely to be general for aromatic compounds bearing halogenomethyl groups *meta* to anion-stabilising groups. Furthermore, in certain cases analogous reactions may occur even without the anion-stabilising group.[12,13] Finally, we draw attention to 'vicarious nucleophilic substitution of hydrogen',[14] and some abnormal reactions of nucleophiles with halogenomethyl derivatives of five-membered aromatic heterocycles (particularly furans),[15] which have some analogy with the types of reaction discussed above.

Experimental

I.r. spectra were of liquid films or Nujol mulls. N.m.r. spectra were recorded for solutions in deuteriochloroform unless otherwise stated. For mass spectra, the *m/z* values recorded are for ions containing ^{35}Cl only; the appropriate isotope patterns were observed. B.p.s for substances distilled on a small scale refer to the oven temperatures used for bulb-to-bulb distillation.

* Deuterium exchange in the product did not occur at a significant rate under the conditions of the experiment.

Reactions of 2-*Chloro*-5-*trichloromethylpyridine* (**3**).—(*a*) A solution of sodium (0.92 g, 40 mmol) in methanol (10 ml) was added to a solution of 2-chloro-5-trichloromethylpyridine (2.29 g, 10 mmol) in methanol (50 ml) and the mixture was stirred at room temperature for 18 h. The mixture was poured into ice–water (150 ml). Conventional work-up followed by distillation gave methyl 6-methoxypyridine-3-carboxylate (**4**) (1.38 g, 60%), low melting crystals, b.p. 92 °C/3.5 mmHg (lit.,[16] m.p. 42 °C, b.p. 256 °C); $\nu_{max.}$ 1 720 cm^{-1}; δ 4.05 (3 H, s), 4.15 (3 H, s), 6.7 (1 H, d), 8.25 (1 H, d), and 9.0 (1 H, d); *m/z* 167 (M^+).

(*b*) 2-Chloro-5-trichloromethylpyridine (2.29 g, 10 mmol) was added to a suspension of sodium methoxide (2.16 g, 40 mmol) in tetrahydrofuran (50 ml) and the mixture was stirred at room temperature for 15 h. The mixture was poured into ice–water (100 ml). Conventional work-up followed by chromatography (silica, light petroleum–ethyl acetate, gradient elution) gave (i) 6-methoxypyridine-3-carboxylic acid (**5**) (0.23 g, 15%), m.p. 165—168 °C (lit.,[16] m.p. 173 °C); $\nu_{max.}$ 1 670 cm^{-1}; δ([$^2H_6$]-DMSO) 3.8 (3 H, s), 6.7 (1 H, d), 8.0 (1 H, d), and 8.6 (1 H, s); δ_C 53.8 (OMe), 110.5 (C-4), 120.5 (C-3), 139.9 (C-5), 149.5 (C-2), 166.2 (C-6), and 185.2 (CO_2H); *m/z* 153 (M^+) (Found: C, 55.0; H, 4.7; N, 9.2. Calc. for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.15%); and (ii) 6-*chloro*-2-*methoxypyridine*-3-*carbaldehyde* (**6**) (0.10 g, 6%), m.p. 62—64 °C; $\nu_{max.}$ 1 680 cm^{-1}; δ 4.0 (3 H, s), 6.95 (1 H, d), 7.95 (1 H, d), and 10.15 (1 H, s); *m/z* 171 (M^+, Cl) (Found: C, 48.7; H, 3.5; N, 8.2. $C_7H_6ClNO_2$ requires C, 48.9; H, 3.4; N, 8.1%).

Reactions of 2-*Chloro*-3-*trichloromethylpyridine* (**8**).—(*a*) 2-Chloro-3-trichloromethylpyridine (2.29 g, 10 mmol) was added to a solution of sodium (0.92 g, 40 mmol) in methanol (30 ml). The mixture was heated under reflux for 6 h. Conventional work-up followed by chromatography (silica, light petroleum–ethyl acetate, gradient elution) gave (i) 2-*chloro*-3-(*dimethoxymethyl*)-6-*methoxypyridine* (**9**) (1.27 g, 59%), b.p. 94 °C/0.01 mmHg; $\nu_{max.}$ 2 940 and 2 840 cm^{-1}; δ 3.35 (6 H, s), 3.9 (3 H, s), 5.55 (1 H, s), 6.7 (1 H, d), and 7.8 (1 H, d); *m/z* 217 (M^+, Cl) (Found: C, 49.6; H, 5.5; N, 6.4. $C_9H_{12}ClNO_3$ requires C, 49.7; H, 5.6; N, 6.4%); and (ii) 2,6-dimethoxypyridine-3-carbaldehyde (**11**) (0.15 g, 9%), m.p. 53—55 °C (for properties, see below).

(*b*) 2-Chloro-3-trichloromethylpyridine (2.29 g, 10 mmol) was added to a suspension of sodium methoxide (2.16 g, 40 mmol) in tetrahydrofuran (30 ml) and the mixture was stirred and heated under reflux for 15 h. Conventional work-up followed by chromatography (silica, light petroleum–ethyl acetate, gradient elution) gave (i) 2-*chloro*-6-*methoxypyridine*-3-*carbaldehyde* (**11**) (0.59 g, 35%), m.p. 117—119 °C; $\nu_{max.}$ 1 690 cm^{-1}; δ 4.0 (3 H, s), 6.8 (1 H, d), 8.2 (1 H, d), and 10.4 (1 H, s): δ_C 54.8 (OMe), 110.6 (C-5), 122.9 (C-3), 139.6 (C-4), 153.1 (C-2), 166.4 (C-6), and 188.1 (CHO); *m/z* 171 (M^+, Cl) (Found: C, 48.8; H, 3.7; N, 8.25. $C_7H_6ClNO_2$ requires C, 48.9; H, 3.8; N, 8.1%); and (ii) 2,6-dimethoxypyridine-3-carbaldehyde (**10**) (0.15 g, 9%), m.p. 53—55 °C (lit.,[17] m.p. 70—71 °C); $\nu_{max.}$ 1 680 cm^{-1}; δ 4.05 (3 H, s), 4.15 (3 H, s), 6.4 (1 H, d), 8.1 (1 H, d), and 10.25 (1 H, s) (Found: *m/z* 167.058 $C_8H_9NO_3$ requires *m/z* 167.058).

(*c*) 2-Chloro-3-trichloromethylpyridine (2.62 g, 11.4 mmol) was added to a solution of sodium (0.46 g, 20 mmol) in methanol (30 ml) and the mixture was heated under reflux for 2 h. Conventional work-up followed by chromatography [neutral alumina, light petroleum–ethyl acetate (4:1)] gave (i) 2-chloro-3-dichloromethyl-6-methoxypyridine (**21**) (0.58 g, 22%), pale yellow oil which darkened rapidly with time; δ 4.0 (3 H, s), 6.82 (1 H, d), 7.10 (1 H, s), and 8.17 (1 H, d); *m/z* 225 (M^+, Cl_3) and (ii) a mixture of (0.34 g) of starting material and 2-chloro-3-(dimethoxymethyl)-6-methoxypyridine (**9**), identified by n.m.r. and g.c.–m.s.

(*d*) 2-Chloro-3-trichloromethylpyridine (0.5 g) was dissolved in methan[^{2}H]ol (5 ml). A small amount of anhydrous potassium carbonate was added and the mixture was heated for 15 h. The solvent was evaporated under reduced pressure and the residue was extracted with deuteriochloroform. The ^{1}H n.m.r. spectrum of the mixture showed peaks at, *inter alia*, δ 6.8 (d), 7.1 (s), and 8.2 (s); the integrations of the first two were in the ratio of *ca.* 2:1.

Reaction of 2-*Chloro*-3-*trifluoromethylpyridine* (**12**).—2-Chloro-3-trifluoromethylpyridine (2.92 g, 12.6 mmol) was added to a solution of sodium (0.92 g, 40 mmol) in methanol (30 ml) and the mixture was heated under reflux for 6 h. Conventional work-up followed by chromatography (silica, ethyl acetate–light petroleum) gave 2-*methoxy*-3-*trifluoromethylpyridine* (**13**) (0.60 g, 67%), b.p. 150 °C (Kugelrohr); δ 3.9 (3 H, s), 6.8 (1 H, dd), 7.8 (1 H, d), and 8.2 (1 H, d); *m/z* 177 (M^+) (Found: C, 47.2; H, 3.5; N, 8.0. $C_7H_6F_3NO$ requires C, 47.4; H, 3.3; N, 7.8%).

Reactions of 2,6-*Dichloro*-3-*cyanopyridine* (**15**).—(*a*) A solution of 2,6-dichloro-3-cyanopyridine (1.72 g, 10 mmol) in methanol (25 ml) was added to a solution of sodium (0.46 g, 20 mmol) in methanol (20 ml) and the mixture was stirred at room temperature for 1 h. Conventional work-up gave 2,6-*dimethoxy*-3-*cyanopyridine* (**16**) (1.16 g, 71%), m.p. 89.5—90 °C (from light petroleum), $\nu_{max.}$ 2 220 cm^{-1}; δ 3.85 (3 H, s), 3.95 (3 H, s), 6.3 (1 H, d), 7.7 (1 H, d); ^{13}C δ 53.9 (2 × OMe), 86.5 (C-3), 102.5 (C-5), 115.7 (CN), 143.9 (C-4), 164.5 (C-6), 165.5 (C-2); *m/z* 164 (M^+) (Found: C, 58.3; H, 4.8; N, 17.0. $C_8H_8N_2O_2$ requires C, 58.5; H, 4.9; N, 17.1%).

(*b*) A similar reaction, but with only 1 mol equiv. of sodium methoxide, gave an inseparable mixture (1.55 g, 93%), m.p. 89—90 °C, of 2-chloro-3-cyano-6-methoxypyridine (**18**) and 6-chloro-3-cyano-2-methoxypyridine (**17**), $\nu_{max.}$ 2 230 cm^{-1}; δ 4.0 (s), 4.1 (s), 6.8 (d), 7.1 (d), 7.85 (d), and 7.9 (d) (Found: C, 49.7; H, 3.0; N, 16.7. $C_7H_5ClN_2O$ requires C, 49.9; H, 3.0; N, 16.6%).

Reduction of Nitriles.—(*a*) Di-isobutylaluminium hydride (1M in toluene; 6 ml) was added to a solution of 2,6-dimethoxy-3-cyanopyridine (**16**) (1.00 g, 6 mmol) in toluene (25 ml) and the mixture was stirred at room temperature for 1 h. Methanol (10 ml) and 20% sulphuric acid (30 ml) were added and the mixture was stirred for 1 h. Conventional work-up gave 2,6-dimethoxypyridine-3-carbaldehyde (**10**), identical with the product from reaction (*b*) of 2-chloro-3-trichloromethylpyridine.

(*b*) A similar reduction of the mixture of 2-chloro-3-cyano-6-methoxypyridine and 6-chloro-3-cyano-2-methoxypyridine gave, following chromatography (silica, ethyl acetate–light petroleum, gradient elution), (i) a mixture (0.54 g, 41%), m.p. 98—100 °C, of 2-chloro-6-methoxypyridine-3-carbaldehyde (**11**) and 6-chloro-2-methoxypyridine-3-carbaldehyde (**6**), $\nu_{max.}$ 1 690 cm^{-1}; δ 4.0 (s), 4.1 (s), 6.75 (d), 7.0 (d), 8.05 (d), 8.1 (d), and 10.4 (s) (Found: C, 49.1; H, 3.6; N, 8.05. $C_7H_6ClNO_2$ requires C, 49.0; H, 3.5; N, 8.2%), and (ii) starting material (0.25 g, 19%).

Reaction of 2-*chloro*-3,5-*bis*(*trichloromethyl*)*pyridine* (**19**).—2-Chloro-3,5-bis(trichloromethyl)pyridine (8.70 g) was added to a solution of sodium methoxide, prepared by dissolving sodium (4.0 g) in methanol (200 ml). The mixture was heated under reflux for 3 h. Concentrated HCl (sufficient to neutralise, then 5 ml excess) was added and the mixture was heated under reflux for 15 min. Sufficient water just to dissolve suspended sodium chloride was added, and the solution was cooled in ice. The resulting crystalline precipitate was collected by filtration and washed with water to give *methyl* 5-*formyl*-2,6-*dimethoxypyridine*-3-*carboxylate* (**20**) (1.82 g, 32%), m.p. 143—144 °C (from ethanol), $\nu_{max.}$ 1 700 and 1 675 cm^{-1}; δ 3.9 (3 H, s), 4.1 (6 H, s), 8.7 (1 H, s), and 10.2 (1 H, s); *m/z* 225 (M^+) (Found: C, 51.9; H, 4.4; N, 6.1. $C_{10}H_{11}NO_5$ requires C, 53.3; H, 4.9; N, 6.2%). 4-*Nitrophenylhydrazone*, m.p. 267—268 °C (decomp.) (from 2-

methoxyethanol) (Found: C, 52.6; H, 4.0; N, 15.2. $C_{16}H_{16}N_4O_6$ requires C, 53.3; H, 4.4; N, 15.5%).

3-*Trichloromethylpyridine* (**22**).—Nicotinic acid (36.6 g, 0.3 mol) and phosphorus pentachloride (125 g, 0.9 mol) were mixed thoroughly and heated at 115 °C for 72 h. Phosphorus oxychloride was distilled off under reduced pressure and the remaining oil was slowly added to ice (400 g). The resulting mixture was kept at 0 °C while it was basified with 2M sodium hydroxide. The mixture was extracted with dichloromethane (3 × 80 ml). The combined extracts were dried ($MgSO_4$) and the solvent evaporated. The residual oil was distilled to give 3-*trichloromethylpyridine* (37.5 g, 64%), b.p. 62—64 °C/0.07 mmHg; δ 7.40 (1 H, dd, *J* 8 and 6-Hz, 5 H), 8.24 (1 H, dd, *J* 8 and 2 Hz; 4-H), 8.70 (1 H, d, *J* 6 Hz, 6-H), and 9.22 (1 H, d, *J* 2 Hz; 2-H) (Found: C, 36.8; H, 2.1; N, 7.4. $C_6H_4Cl_3N$ requires C, 36.7; H, 2.05; N, 7.1%).

Reactions of 3-*Trichloromethylpyridine*.—(*a*) A solution of 3-trichloromethylpyridine (1.0 g, 5.0 mmol) in dry methanol (15 ml) was added to a solution of sodium methoxide [sodium (0.46 g, 20 mmol) in dry methanol (25 ml)] and the mixture was heated under reflux under nitrogen for 6 h. The resulting suspension was cooled, poured into water and the solution extracted with ether (3 × 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The residual oil was purified by flash chromatography (silica, ethyl acetate–light petroleum, 1:6 with 5% triethylamine) to give 3-*dimethoxymethyl*-6-*methoxypyridine* (**23**) (0.68 g, 73%), b.p. 60—62 °C/0.03 mmHg, $\lambda_{max.}$ 273 nm; δ 3.25 [6 H, s, acetal $(OCH_3)_2$], 3.87 (3 H, s, 6-OCH_3), 5.3 (1 H, s, acetal CH), 6.67 (1 H, d, 5-H), 7.58 (1 H, dd, 4-H), and 8.15 (1 H, d, 2-H); δ_C 52.5 (2 × OCH_3), 53.3 (OCH_3), 101.6 (acetal C), 110.4 (C-5), 126.6 (C-3), 137.2 (C-4), 145.7 (C-2), and 164.3 (C-6) (Found: C, 58.9; H, 7.2; N, 7.5. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.1; N, 7.6%].

Hydrolysis of a sample of the acetal (**23**) (warm concentrated HCl, THF, 5 min) gave 6-methoxypyridine-3-carbaldehyde, m.p. 43—44 °C (lit.,[16] b.p. 65—70 °C/12 mm Hg), with i.r. and n.m.r. spectra in agreement with literature data.[17]

(*b*) Sodium methoxide (0.4 g, 7.5 mmol) was added to a stirred solution of 3-trichloromethylpyridine (1 g, 5 mmol) in dry tetrahydrofuran (25 ml) under nitrogen. The resulting suspension was stirred at room temperature for 48 h, filtered, and the solvent evaporated under reduced pressure. The solid residue was subjected to flash chromatography [silica, ethyl acetate–light petroleum (1:19) with 5% triethylamine] to give in the first fraction 3-*dichloromethyl*-6-*methoxypyridine* (**24**) (0.6 g, 61%), m.p. 48—50 °C after sublimation (66 °C/0.02 mmHg); δ 3.9 (3 H, s, OCH_3), 6.67 (1 H, s, acetal CH), 6.78 (1 H, d, 5-H), 7.84 (1 H, dd, 4-H), and 8.19 (1 H, d, 2-H); δ_C 53.8 (OCH_3), 69.5 acetal C), 111.7 (C-5), 129.6 (C-3), 136.9 (C-4), 144.0 (C-2), and 165 (C-6); *m/z* (CI) 192 (*M* + 1) (Cl_2) (Found: 43.5; H, 3.6; N, 7.1. $C_7H_7Cl_2NO$ requires C, 43.8; H, 3.7; N, 7.3%). The second fraction gave 3-trichloromethylpyridine (**22**) (0.2 g, 20%).

(*c*) 3-Trichloromethylpyridine (0.3 g, 1.5 mmol) and sodium methoxide (0.1 g, 2.2 mmol) were weighed and added to [$^2H_8$]tetrahydrofuran (2 ml) under argon in a dry box. The mixture was stirred at room temperature for 48 h and then filtered. The precipitated sodium chloride was washed with dichloromethane. The combined filtrate and washings were evaporated to leave an oily residue which solidified on cooling in ice–salt. Sublimation (66 °C/0.02 mmHg) gave 3-dichloromethyl-6-methoxypyridine (**24**), (0.25 g, 80%), white needles with ^1H n.m.r. spectrum identical with that reported in (*b*).

(*d*) A mixture of 3-trichloromethylpyridine (0.3 g, 1.52 mmol), methan[^2H]ol (0.5 ml), sodium methoxide (0.12 g, 2.3 mmol), and dry THF (4 ml) was stirred at room temperature for 24 h, under nitrogen. The ^1H n.m.r. spectrum of the filtered mixture showed the following signals (δ 5 to 10 only; integration based on signal at δ 6.8 = 1): δ 6.8 (d, 1 H), 7.1 (s, 0.6 H), 7.9 (dd, 1 H), and 8.25 (m, 1 H). After 6 h at *ca.* 80 °C, the same signals were present, but in a ratio of *ca.* 1:0.4:1:1. A ^1H n.m.r. spectrum of a solution of 3-dichloromethyl-6-methoxypyridine in similar mixtures of methanol and THF (or methan[^2H]ol and THF) showed the same signals in a ratio of 1:1:1:1. The spectrum was not significantly altered by the addition of a trace of dry methanol and/or solid sodium methoxide.

Reactions of 3-*Dichloromethyl*-6-*methoxypyridine* (**24**).—(*a*) *With methoxide*. A solution of 3-dichloromethyl-6-methoxypyridine (0.1 g, 0.52 mmol) and sodium (0.035 g, 1.56 mmol) in dry methanol (5 ml) under nitrogen, was heated under reflux for 4 h. Work-up as described above gave 3-dimethoxymethyl-6-methoxypyridine (**23**) (0.06 g, 60%) with properties identical to those reported above.

(*b*) *With ethoxide*. A solution of 3-dichloromethyl-6-methoxypyridine (0.3 g, 1.56 mmol) and sodium (0.11 g, 4.7 mmol) in dry ethanol (10 ml) under nitrogen, was heated under reflux for 4 h. The mixture was cooled and filtered, and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue oil [silica, diethyl ether–light petroleum (1:12) with 5% triethylamine] gave in the second fraction 3-*diethoxymethyl*-6-*methoxypyridine* (**25**) (0.21 g, 60%), as an oil, δ 1.17 (6 H, t, 2 × CH_3), 3.51 (4 H, m, 2 × CH_2), 3.89 (3 H, s, OCH_3, 5.43 (1 H, s, acetal CH), 6.68 (1 H, d, 5-H), 7.62 (1 H, dd, 4-H), and 8.17 (1 H, d, 2-H); δ_C 15.0 (2 × CH_3), 60.9 (2 × CH_2), 100.0 (acetal C), 110.3 (C-5), 127.7 (C-3), 137.1 (C-4), 145.5 (C-2), and 164.2 (C-6); *m/z* 212 (*M* + 1) (Found: C, 62.8; H, 7.9; N, 6.8. $C_{11}H_{17}NO_3$ requires C, 62.5; H, 8.1; N, 6.6%).

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