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SYNTHESIS OF METHYLPYRIDINE DERIVATIVES—XXXIII[1]

PHOSPHONYLATION AND CHLORINATION OF METHYLPYRIDINE AND 3-NITRO-METHYLPYRIDINE DERIVATIVES†

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Abstract—Novel phosphonylation of the active Me group of pyridine derivatives is described.

Reaction of 2 (and 4) -methylpyridine (3 and 5) with PCl_5 in $POCl_3$ gave 2 (and 4) -trichloromethylpyridine (4 and 6). Similarly, reaction of 4 (and 6) -methyl-3-nitropyridine (7 and 9) afforded the corresponding trichloromethyl derivative (8 and 10). However, the similar reaction of 2-methyl-3-nitropyridine (11) gave dichloro-(3-nitro-2-pyridyl)-methylphosphonic dichloride (12).

Mechanisms of the formation of these products are discussed.

There is extensive literature dealing with the chlorination of the active Me group of aromatic N-heterocyclic compounds, but only a few references are available concerning such reaction with PCl_5 and $POCl_3$.[2–4]

Previously, we have reported that 2,6-dimethylpyridine reacted with PCl_5 in $POCl_3$ to give low yields of 2-chloromethyl-6-methylpyridine (3%) and 2,6-bistrichloromethylpyridine (1%). Similar treatment of 2,6-dimethyl-3-nitropyridine (1) gave 6-methyl-3-nitro-2-trichloromethylpyridine (2) in 38% yield.[5] The present paper reports the reaction of methylpyridine and 3-nitro-methylpyridine derivatives to give the chlorinated and phosphonylated products.

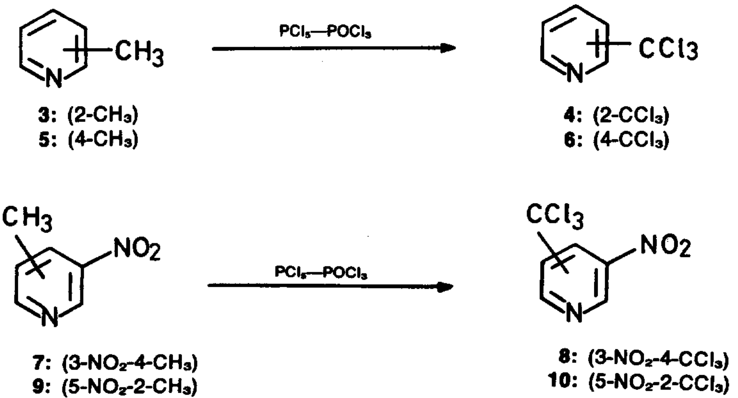
Refluxing of 2-methylpyridine (3) with excess PCl_5 in $POCl_3$ gave 2-trichloromethylpyridine (4) in 15% yield. Similarly, 4-methylpyridine (5) was chlorinated to give 4-trichloromethylpyridine (6) in 10% yield.

Similar reaction of 4-methyl-3-nitropyridine (7) and 2-methyl-5-nitropyridine (9) gave 3-nitro-4-trichloromethylpyridine (8) and 5-nitro-2-trichloromethylpyridine (10) in 4 and 28% yields, respectively.

When 2-methyl-3-nitropyridine (11) was heated with excess PCl_5 in $POCl_3$, a 34% yield of the product, $C_6H_3Cl_4N_2O_3P$ (12), was obtained. On the basis of its chemical behavior and spectroscopy we assigned the structure, dichloro-(3-nitro-2-pyridyl)-methylphosphonic dichloride (12). Namely, heating of compound 12 in water gave the free acid (13) and 2-dichloromethyl-3-nitropyridine (14) in 64 and 5% yields, respectively. Refluxing of 12 in absolute methanol or ethanol afforded the monomethyl (15a) and monoethyl ester (15b) in 43 and 62% yields, respectively. Treatment of 12 with sodium ethoxide in ethanol gave rise to the diethyl ester (16). Structural assignments of these products were made on the basis of their elemental analyses and spectroscopical data detailed in the experimental section.

Similar reaction of 2-methyl-3-nitropyridine 1-oxide (17) gave the phosphonic dichloride (12) and the dichloromethyl derivative (14) in 8 and 6% yields, respectively.

Reaction of 4-chloro-2-methyl-3-nitropyridine (18) under the same condition gave the product,



Scheme 1.

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$C_6H_2Cl_6NOP$ (**19**), to which we assigned the structure, dichloro-(3,4-dichloro-2-pyridyl)methylphosphonic dichloride.

Lastly, reaction of methyl 6-methyl-5-nitropyridine-2-carboxylate (**20**) was carried out. The products obtained were not phosphonylated derivatives but trichloromethyl derivatives, **21** and **22**.

As mentioned above, the Me group at 2 and 4-position of pyridine is usually chlorinated giving the trichloromethylpyridine derivatives, while 2-methyl-3-nitropyridine derivatives such as **11** and **18** are transformed into the phosphonylated products such as **12** and **19**. This is the first instance of direct phosphonylation of methylpyridines with PCl_5 and $POCl_3$. If the 6-position is blocked with Me or methoxycarbonyl group (**1** or **20**), products obtained are not the phosphonates but the trichloromethyl derivatives (**2** or **21**).

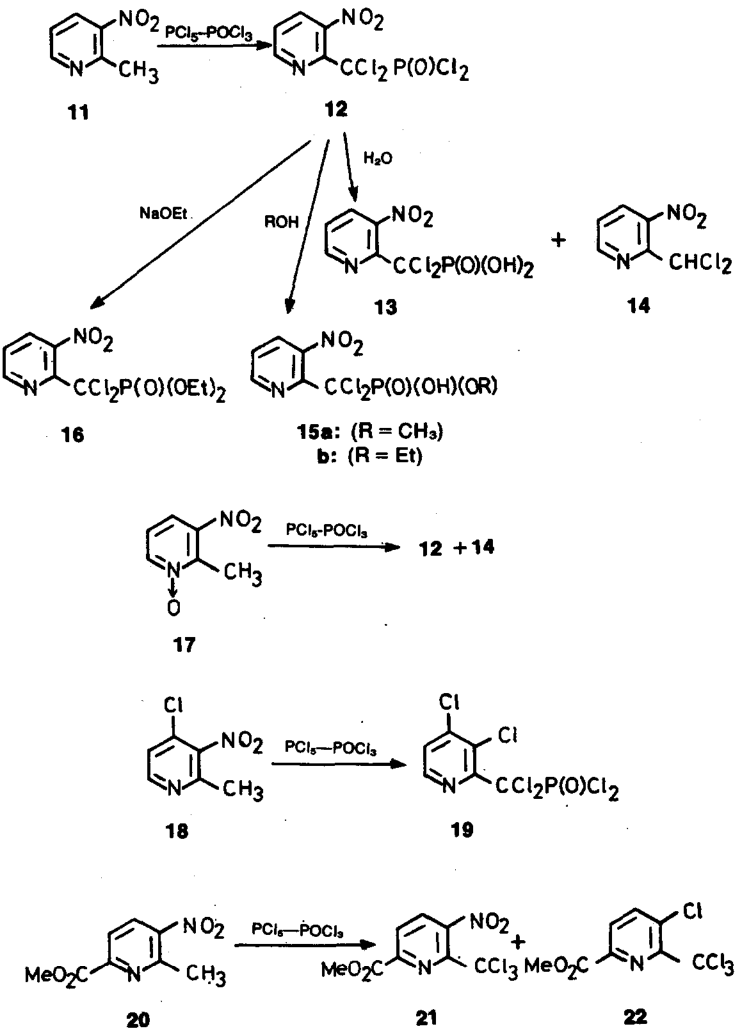
Although the details of the mechanism of the formations of these products still remain obscure at present, likely hypothesis will be suggested as follows. The behavior of the methylpyridine series toward $POCl_3 + PCl_5$ depends on the following factors: (1) The substituent effect of the 3-nitro group to the nucleophilic activity of the methyl group. (2) The ability of the ring nitrogen to form a complex with the strongest available electrophile, i.e. $PCl_4^+Cl^-$ if sterically possible. (3) The fact that chlorination by $PCl_4^+Cl^-$ has a lower enthalpy of activation (ΔH^+) but much higher steric requirement than the phosphonylation by $POCl_3$ because oxygen is much smaller than chlorine.

Mechanism of each reaction can be elucidated on the basis of these three factors.

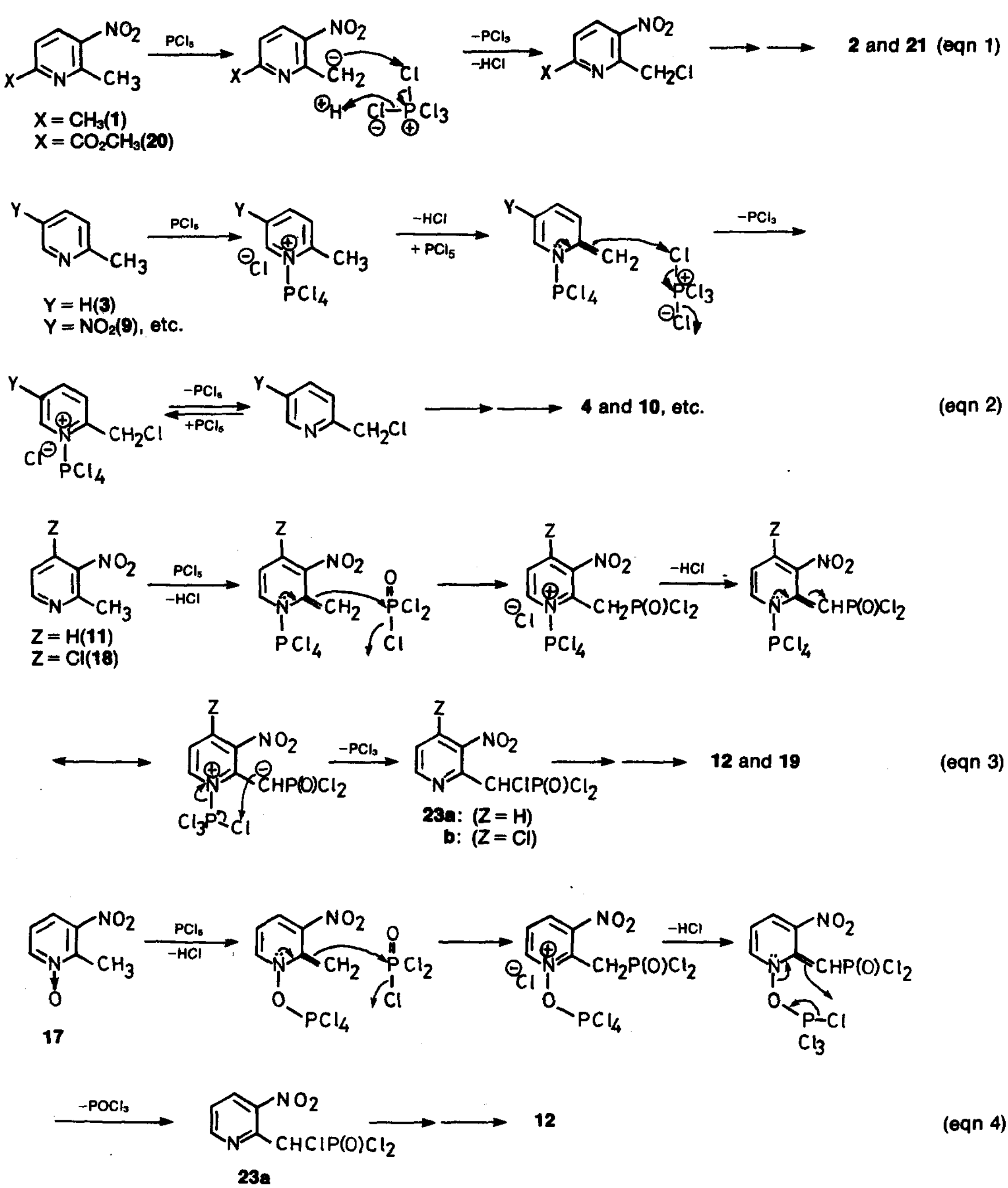
(a) The 6-substituted 2-methyl-3-nitropyridine (**1** and **20**) hardly form a complex with $PCl_4^+Cl^-$, but the 3-nitro group activates the nucleophilicity of the 2-Me group giving the chlorinated products (eqn 1).

(b) The methylpyridines (**3** and **5**) and 4 (and 6)-methyl-3-nitropyridines (**7** and **9**) would form a complex with $PCl_4^+Cl^-$ because there is enough room around the ring nitrogen, but this does not affect the outcome because $PCl_4^+Cl^-$ can approach the nucleophilic site (eqn 2).

(c) The 2-methyl-3-nitropyridine (**11**) and its 4-chloro derivative (**18**) form a complex with $PCl_4^+Cl^-$ because there is also room around the ring nitrogen, but there is no vacancy around the nucleophilic center at the 2-position. Therefore, $PCl_4^+Cl^-$ can not react, instead $POCl_2^+Cl^-$ can get near to react with the nucleophilic carbon giving the phosphonic dichloride intermediate. The next stage might well involve intramolecular



Scheme 2.



Scheme 3.

chlorination to give the monochloro-phosphonic dichloride (**23a**, **b**). Repeating chlorination gives the products (**12** and **19**) (eqn 3).

(d) The 2 - methyl - 3 - nitropyridine 1-oxide (**17**) would form an O-complex with $PCl_4^+Cl^-$. In a similar fashion as above, the nucleophilic carbon at the 2-position reacts with $POCl_2^+Cl^-$ to give the phosphonic dichloride intermediate, which, on S_{Ni} chlorination, is transformed to the same chloro-phosphonic dichloride (**23a**) as an intermediate to **12** (eqn 4).

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were taken by a Nippon-Bunko Model IR-S spectrophotometer. NMR spectra were determined on a Hitachi-Perkin Elmer R-20 spectrophotometer at 60 MHz using TMS (in $CDCl_3$) or sodium 2,2 - dimethyl - 2 - silapentane - 5 - sulfonate (in DMSO-d_6) as internal standards. Mass spectra were measured by a Hitachi RMU-7 mass spectrometer at 80 eV.

2-Trichloromethylpyridine (**4**). A suspension of **3** (7.5 g, 0.08 mol) and PCl_5 (51 g, 0.24 mol) in $POCl_3$ (30 ml, 0.32 mol) was heated at 125–130° for 12 hr. After removal of excess $POCl_3$ *in vacuo*, the residue was poured into ice-water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% $NaHCO_3$ aq, and condensed to give an oily residue, which was distilled to give 2.4 g (15%) of the product as a colorless oil, b.p. 117–120°/20 mm (lit. 112–115°/15 mm[6]). The aqueous layer was neutralized with NaOH, and the mixture was extracted with ether. The ether extract gave 2.1 g (28%) of the starting material **3**.

4-Trichloromethylpyridine (**6**). A suspension of **5** (7.5 g, 0.08 mol) and PCl_5 (51 g) in $POCl_3$ (30 ml) was heated at 125–130°

for 5 hr. After evaporation of excess $POCl_3$, the residue was poured into ice-water. The mixture was neutralized with NaOH, and the soln was extracted with $CHCl_3$. The $CHCl_3$ extract gave 3 g (40%) of the starting material **5** and 1.6 g (10%) of the product **6** as a colorless oil, b.p. 102–104°/13 mm (lit. 105–107°/18 mm[7]).

3 - *Nitro* - 4 - *trichloromethylpyridine* (**8**). A suspension of **7**[8] (2.07 g, 15 mmol) and PCl_5 (17 g, 80 mmol) in $POCl_3$ (7.5 ml, 80 mmol) was heated at 125–130° for 5 hr. After evaporation of excess $POCl_3$, the residue was poured into ice-water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% $NaHCO_3$ aq, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting residue was purified by recrystallization from petroleum ether to give 0.15 g (4%) of the product **8** as colorless needles, m.p. 77–78°; IR ($CHCl_3$) 1550 and 1363 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 8.16 (d, 1, J = 5.5 Hz), 8.90–9.11 (m, 2). (Found: C, 29.74; H, 1.12; Cl, 44.29; N, 11.64. $C_6H_3Cl_3N_2O_2$ requires: C, 29.85; H, 1.25; Cl, 44.05; N, 11.60%).

5 - *Nitro* - 2 - *trichloromethylpyridine* (**10**).[10] Following the procedure described, reaction of **9**[9] (2 g) with PCl_5 (17 g) in $POCl_3$ (7.5 ml) gave 1 g (28%) of the product as colorless needles (from petroleum benzine), m.p. 91–93°; IR ($CHCl_3$) 1538 and 1363 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 8.26 (d, 1, J = 8.5 Hz), 8.67 (dd, 1, J = 8.5 and 2.4 Hz), 9.51 (d, 1, J = 2.4 Hz). (Found: C, 29.85; H, 1.37; Cl, 43.58; N, 12.15. $C_6H_3Cl_3N_2O_2$ requires: C, 29.85; H, 1.25; Cl, 44.05; N, 11.60%).

Dichloro - (3 - *nitro* - 2 - *pyridyl)methylphosphonic dichloride* (**12**). (A) Following the procedure given for compound **8**, **11**[11] (1 g) was allowed to react with PCl_5 (8.5 g) in $POCl_3$ (3.8 ml) for 3 hr to give 0.83 g (34%) of **12**, m.p. 127–128.5° (from ether); IR (KBr) 1535 and 1365 (NO_2), 1290 cm^{-1} (P=O); NMR ($CDCl_3$) δ 7.69 (dd, 1, J = 8.5 and 4.5 Hz), 8.18–8.38 (m, 1), 8.73 (dd, 1, J = 4.5 and 1.3 Hz); MS *m/e* 287 [M^+-35 (Cl), base peak]. (Found: C, 22.27; H, 1.19; Cl, 43.75; N, 8.80. $C_6H_3Cl_4N_2O_3P$ requires: C, 22.25; H, 0.93; Cl, 43.75; N, 8.65%).

(B) Following a similar fashion, **17**[12] (0.46 g) reacted with PCl_5 (3.4 g) in $POCl_3$ (1.5 ml) for 5 hr to give an oily product, which was purified by silica gel (10 g) column chromatography using benzene and $CHCl_3$ as eluants. The benzene elution gave 40 mg (6%) of a crystalline substance, which was identified as **14** by the comparison of its IR spectrum and mixed m.p. with a sample obtained in the next run. The $CHCl_3$ elution gave 80 mg (8%) of **12**, undepressed on admixture with a sample obtained in the above run.

Hydrolysis of compound **12**. A suspension of **12** (0.3 g) in water (15 ml) was heated on a steam bath for 2 hr. The mixture was extracted with ether. The ether soln was condensed to give a crystalline residue, which was recrystallized from petroleum benzine to give 10 mg (5%) of **14** as colorless plates, m.p. 45–46.5°; IR ($CHCl_3$) 1536 and 1351 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.57 (s, 1), 7.58 (dd, 1, J = 8.5 and 5 Hz), 8.38 (dd, 1, J = 8.5 and 1.5 Hz), 8.97 (dd, 1, J = 5 and 1.5 Hz). (Found: C, 34.91; H, 2.19; Cl, 34.19; N, 13.38. $C_6H_4Cl_2N_2O_2$ requires: C, 34.80; H, 1.94; Cl, 34.24; N, 13.53%).

The aqueous layer was evaporated to dryness *in vacuo*. The residue was recrystallized from acetonitrile to give 0.17 g (64%) of **13** as colorless prisms, m.p. 192–193° dec.; IR (KBr) 3500–2000 (OH), 1555 and 1373 (NO_2), 1225 cm^{-1} (P=O); NMR (DMSO-d_6) δ 7.58 (s, 2), 7.79 (dd, 1, J = 8 and 4.5 Hz), 8.42 (dd, 1, J = 8 and 1.3 Hz), 8.78 (dd, 1, J = 4.5 and 1.3 Hz). (Found: C, 22.87; H, 2.40; Cl,. 22.92; N, 9.16. $C_6H_5Cl_2N_2O_5P \cdot 1.5H_2O$ requires: C, 22.95; H, 2.56; Cl, 22.58; N, 8.92%).

Methyl dichloro - (3 - *nitro* - 2 - *pyridyl)methylphosphonate* (**15a**). .A suspension of **12** (0.3 g) in abs MeOH (30 ml) was refluxed for 1.5 hr. After evaporation of the solvent, the residue was recrystallized from acetonitrile to give 0.12 g (43%) of the product as colorless prisms, m.p. 172–174° dec.; IR (KBr) 3500–2000 (OH), 1535 and 1365 (NO_2), 1260 cm^{-1} (P=O); NMR (DMSO-d_6) δ 2.87 (d, 3, J = 10.7 Hz), 6.87 (s, 1), 7.81 (dd, 1, J = 8.1 and 5 Hz), 8.45 (dd, 1, J = 8.1 and 1.6 Hz), 8.83 (dd, 1, J = 5 and 1.6 Hz). (Found: C, 27.16; H, 2.76; Cl, 23.22; N, 9.54. $C_7H_7Cl_2N_2O_5P \cdot 1/3H_2O$ requires: C, 27.38; H, 2.52; Cl, 23.09; N, 9.12%).

Ethyl dichloro - (3 - *nitro* - 2 - *pyridyl)methylphosphonate* (**15b**). A suspension of **12** (0.2 g) in abs EtOH (30 ml) was refluxed for 2.5 hr. The mixture was condensed, and separated crystals were recrystallized from benzene to give 0.12 g (62%) of **15b** as colorless prisms, m.p. 167–168° dec.; IR (KBr) 3500–2000 (OH), 1542 and 1377 (NO_2), 1240 cm^{-1} (P=O); NMR (DMSO-d_6) δ 1.28 (t, 3, J = 6.7 Hz), 4.28 (dq, 2, J = 6.7 and 8 Hz), 7.03 (s, 1), 7.82 (dd, 1, J = 8.8 and 5 Hz), 8.45 (dd, 1, J = 8.8 and 1.3 Hz), 8.82 (dd, 1, J = 5 and 1.3 Hz). (Found: C, 30.05; H, 3.00; Cl, 22.58; N, 9.06. $C_8H_9Cl_2N_2O_5P$ requires: C, 30.50; H, 2.88; Cl, 22.51; N, 8.89%).

Diethyl dichloro - (3 - *nitro* - 2 - *pyridyl)methylphosphonate* (**16**). To a soln of NaOEt–EtOH prepared from Na (0.09 g) and abs EtOH (10 ml), was added a suspension of **12** (0.65 g) in abs EtOH (5 ml). After refluxing for 15 min, the soln became neutral. The ppt (NaCl) was removed by filtration. The filtrate was condensed, and the residue was recrystallized from petroleum benzine to give 0.19 g (28%) of **16** as colorless pillars, m.p. 112–113°; IR (KBr) 1538 and 1368 (NO_2), 1267 cm^{-1} (P=O); NMR ($CDCl_3$) δ 1.42 (t, 6, J = 7.4 Hz), 4.45 (dq, 4, J = 7.4 and 8 Hz), 7.57 (dd, 1, J = 8.7 and 5 Hz), 7.99–8.17 (m, 1), 8.73 (dd, 1, J = 5 and 1.8 Hz). (Found: C, 34.68; H, 3.86; Cl, 20.80; N, 7.98. $C_{10}H_{13}Cl_2N_2O_5P$ requires: C, 35.01; H, 3.82; Cl, 20.67; N, 8.16%).

Dichloro - (3,4 - *dichloro* - 2 - *pyridyl)methylphosphonic dichloride* (**19**). Following the procedure given for **8**, **18**[13] (0.5 g, 3 mmol) was treated with PCl_5 (3.4 g, 16 mmol) and $POCl_3$ (1.5 ml, 16 mmol) to give 0.2 g (20%) of **19** as colorless prisms, m.p. 202–205°; IR (KBr) 1270 cm^{-1} (P=O); NMR ($CDCl_3$) δ 7.59 (d, 1, J = 5.5 Hz), 8.35 (d, 1, J = 5.5 Hz). (Found: C, 20.32; H, 0.82; Cl, 61.52; N, 4.05. $C_6H_2Cl_6NOP$ requires: C, 20.72; H, 0.58; Cl, 61.16; N, 4.03%).

Methyl 6 - *methyl* - 5 - *nitropyridine* - 2 - *carboxylate* (**20**). To a soln of 6 - methyl - 5 - nitropyridine - 2 - carboxylic acid[11] (3 g) in THF (50 ml), was added a soln of excess diazomethane in ether until evolution of N_2 ceased. The mixture was condensed to give a crystalline substance. Recrystallization from petroleum ether gave 2.33 g (72%) of **20** as needles, m.p. 67–68°; IR ($CHCl_3$) 1728 cm^{-1} (ester CO); NMR ($CDCl_3$) δ 2.91 (s, 3), 4.02 (s, 3), 8.08 (d, 1, J = 8 Hz), 8.36 (d, 1, J = 8 Hz). (Found: C, 49.19; H, 4.10; N, 14.36. $C_8H_8N_2O_4$ requires: C, 48.98; H, 4.11; N, 14.28%).

Methyl 5 - *nitro* - 6 - *trichloromethylpyridine* - 2 - *carboxylate* (**21**) and *methyl* 5 - *chloro* - 6 - *trichloromethylpyridine* - 2 - *carboxylate* (**22**). Applying the procedure given for **8**, **20** (1.76 g) was treated with PCl_5 (10.2 g) and $POCl_3$ (4.5 ml) to give a crystalline substance, which was submitted to silica gel (50 g) column chromatography. The $CHCl_3$–n-hexane (15:85) elution gave 0.22 g (8%) of **21** and 0.54 g (21%) of **22**. Compound **21**: needles (from petroleum benzine), m.p. 131–133°; IR ($CHCl_3$) 1735 (ester CO), 1550 and 1325 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 4.02 (s, 3), 8.09 (d, 1, J = 8 Hz), 8.35 (d, 1, J = 8 Hz). (Found: C, 32.35; H, 1.83; Cl, 35.24; N, 9.22. $C_8H_5Cl_3N_2O_4$ requires: C, 32.08; H, 1.68; Cl, 35.51; N, 9.35%). Compound **22**: prisms (from petroleum benzine), m.p. 102–104°; IR ($CHCl_3$) 1728 cm^{-1} (ester CO); NMR ($CDCl_3$) δ 3.98 (s, 3), 7.97 (d, 1, J = 8 Hz), 8.15 (d, 1, J = 8 Hz). (Found: C, 33.62; H, 2.02; Cl, 48.99; N, 4.91. $C_8H_5Cl_4NO_2$ requires: C, 33.26; H, 1.74; Cl, 49.08; N, 4.84%).

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