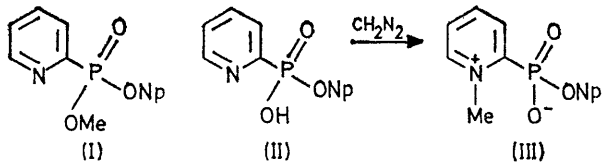
Direct *N*-Methylation of 2-Pyridylphosphonic Acids by Diazomethane

By **John S. Loran, Richard A. Naylor,** and **Andrew Williams,*** University Chemical Laboratories, Canterbury, Kent CT2 7NH

N-Methylation of 2-pyridylphosphonic acids is shown to involve direct attack rather than a route through *O*-methylation followed by rearrangement.

In a recent kinetic study of the hydrolysis of phosphodiesters it was necessary to synthesise *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate (I) [1a] and the initial method using diazomethane and the acid (II) gave a



Np = 4-nitrophenyl

practically quantitative yield of the *N*-methyl isomer (III), another kinetically useful material.

N-Methylation of pyridines and related compounds by diazomethane gives poor yields except when tetrafluoroboric acid is used as catalyst.[1b] It was therefore of interest to investigate the function of the phosphonic acid moiety and whether the path involves direct attack or rearrangement of an *O*-methyl intermediate.

EXPERIMENTAL

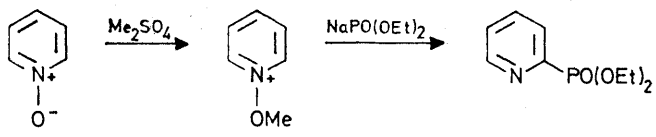
Materials.—Diazomethane was prepared from nitrosomethylurea (4 g) [2] which was added in small portions with agitation to a 50% solution of potassium hydroxide (50 ml) covered with a layer of ether (100 ml) in a conical flask at 5° in an ice-bath. The mixture was maintained at this temperature for 30 min, after which the ether layer was

[1] (*a*) J. S. Loran, Ph.D. Thesis, University of Kent, 1975; (*b*) R. Daniels and C. G. Kormendy, *J. Org. Chem.*, 1962, **27**, 1860.

[2] A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longmans, London, 1967, 3rd edn., p. 969.

decanted and dried over KOH pellets. Diazoethane was prepared from *N*-ethylnitrosourea by a similar method.

Diethyl 2-pyridylphosphonate was prepared by a modification of Redmore's method:[3] dimethyl sulphate (63 g, 0.5 mol) was added to pyridine *N*-oxide (47.6 g, 0.5 mol) slowly at room temperature with stirring. After the initial exothermic reaction had occurred the solution was stirred for 2 h at 60°. The product solution was added with stirring over 3 h to a solution of sodium (11.5 g, 0.5 g atom) in diethyl phosphite (100 g) keeping the temperature below −15°. The mixture was allowed to warm to room temperature and stirred overnight. Water (150 ml) was added and the solution extracted with chloroform (3 × 150 ml); the organic phase was then extracted with 4N-HCl (2 × 75 ml) which was neutralised and extracted with chloroform. The chloroform solution was dried and evaporated *in vacuo* to yield a brown oil which gave a faintly yellow liquid on distillation (39.5 g, 37%), b.p. 134° at 0.1 Torr (lit.,[3] 105—112° at 0.08 Torr).



2-Pyridylphosphonic acid was obtained in practically quantitative yield by refluxing the diethyl ester with HCl solution (20%) for *ca.* 12 h. Evaporation of the solution and trituration of the residue at low temperature with ethanol–ether gave a solid which was recrystallised from aqueous ethanol, m.p. 224—226° (lit.,[3] 224—227°).

O-*Phenyl* 2-*Pyridylphosphonate*.—2-Pyridylphosphonic acid (3.16 g, 20 mmol) was dissolved in pyridine (50 ml; freshly distilled from NaOH pellets). Phenol (1.86 g, 20 mmol) was added to this solution followed by dicyclohexylcarbodi-imide (10 g, excess) and the mixture stirred overnight with protection from moisture. Water (50 ml) was then added and stirring continued for 3 h after which precipitated urea was filtered off and solvents removed *in vacuo* to yield a yellow solid. Recrystallisation from ethanol–ether gave a *solid* (3.5 g, 75%), m.p. 168—170° (Found: C, 56.7; H, 4.5; N, 6.1. $C_{11}H_9NO_3P$ requires C, 56.2; H, 4.3; N, 6.0%); $\nu_{max.}$ (Nujol) 1 300s (P=O), 1 220s (P–O–Ar), 900s, 800s, and 760s cm^{-1} (aromatic CH bend); τ (D_2O) 1.0—2.0 (4 H, m, pyridine H), 2.4—3.1 (5 H, m, phenyl H), and 5.1 (1 H, s, POH); *m/e* 234 (M^+), 218 ($C_{11}H_9NO_2P$), and 94 (C_6H_5OH).

O-(4-*Nitrophenyl*) 2-*Pyridylphosphonate*.—This was prepared by a method similar to that for the phenyl ester in 88% yield. The solid was recrystallised from water to give a *powder*, m.p. 165—168° (Found: C, 44.6; H, 3.5; N, 9.3. $C_{11}H_8N_2O_5P,H_2O$ requires C, 44.3; H, 3.7; N, 9.4%); $\nu_{max.}$ (Nujol) 3 260m (OH), 1 512s, 1 350s (NO_2), 1 080s, and 995m cm^{-1} (P–O–Ar). The compound was estimated to be 99.1% pure by titration with standard NaOH in a Radiometer (Copenhagen) automatic titrator.

O-(4-*Nitrophenyl*) (N-*Methyl*-2-*pyridinio*)*phosphonate*.—*O*-(4-Nitrophenyl) pyridylphosphonate (1 g) was dissolved in methanol (5 ml), and, after cooling in an ice-bath, an ethereal solution of diazomethane was slowly added until a yellow colour persisted. The solvents were removed *in vacuo* at room temperature and the solid residue recrystallised from ethanol. The *crystals* (*ca.* 100%) had m.p. 199—202° (Found: C, 48.7; H, 4.0; N, 9.2. $C_{12}H_{11}N_2O_5P$ requires C, 48.9; H, 3.7; N, 9.5%); $\nu_{max.}$ (Nujol) 1 280s (P=O), 1 240m (P–O–Ar), 770s, 750s, 740s, 700m cm^{-1} (aromatic CH bend); τ ([$^2H_6$]DMSO) 1.0—3.0 (8 H, m, pyridine and 4-nitrophenyl H) and 5.3(3 H, s, NCH_3); *m/e* 294 (M^+), 263 ($C_{11}H_8N_2O_4P$), and 139 (4-nitrophenol). The compound was estimated to be 98% pure by spectroscopic assay of the 4-nitrophenol released on hydrolysis.

O-*Phenyl* (N-*Methyl*-2-*pyridinio*)*phosphonate*.—This ester was prepared as described for the 4-nitrophenyl ester but the product oil (*ca.* 100%) decomposed on distillation. The n.m.r. spectrum indicated the absence of impurities, τ (neat) 0.7—2.0 (4 H, m, pyridinium H), 2.5—2.9 (5 H, m, phenyl H), and 5.2 (3 H, s, NCH_3), *m/e* 249 (M^+), 234 ($C_{11}H_9NO_3P$), and 218 ($C_{11}H_9NO_2P$).

OO-*Dimethyl* 2-*Pyridylphosphonate*.—This was prepared by a method similar to that described for the diethyl analogue using dimethyl phosphite. The preparation gave OO-*dimethyl* 2-*pyridylphosphonate* in low yield (5.6%), b.p. 115° at 0.6 Torr, together with substantial quantities of *OO*-dimethyl methylphosphonate, b.p. 60° at 0.1 Torr. The material had $\nu_{max.}$ (neat, liquid film) 2 960s, 2 855s (CH stretch), 1 240s (P=O), 1 180w (P–O–CH_3), 790m, and 710m cm^{-1} (pyridine CH bend), τ (neat) 1.2—3.0 (4 H, m, pyridine H), 6.4, 6.6 (6 H, d, $POCH_3$), and 6.7 (d), and 9.0 (d) (*OO*-dimethyl methylphosphonate impurity). Analysis also indicated contamination but ordinary distillation procedures did not render the material pure.

O-*Methyl* O-(4-*Nitrophenyl*) 2-*Pyridylphosphonate*.—2-Pyridylphosphorodichloridate was prepared by allowing the corresponding acid (10 g, 63 mmol) to react with thionyl chloride (30 g, excess) at room temperature. After the initial reaction had subsided the mixture was heated in an oil-bath under reflux at 85° for 3 h. The excess of thionyl chloride was then evaporated *in vacuo* to leave a viscous liquid (12.3 g, *ca.* 100%), *m/e* 199, 197, and 195 (all M^+) and 160 and 162 (C_5H_4NOPCl). The dichloride (5.35 g, 34 mmol) was dissolved in sodium-dried benzene (50 ml) and a solution of 4-nitrophenol (4.68 g, 34 mmol) in benzene (100 ml) was added with stirring. Potassium chloride (0.3 g) was added as a catalyst and the mixture was refluxed for two weeks. The solution was concentrated by removing most of the benzene under reduced pressure; dry pyridine (2.7 g, 34 mmol) was added after cooling the mixture in ice and protecting from moisture. Excess of methanol (previously distilled from magnesium methoxide)[4] was slowly added dropwise with stirring. The solution was then stirred for a further hour and diluted with benzene, extracted with $NaHCO_3$ solution and with saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo* to yield a straw-coloured oil (vacuum distillation gave rearranged product). The oil had $\nu_{max.}$ (neat) 1 590s, 1 340s (NO_2), 1 260s (P=O), 1 220s (P–O–Ar), 1 160m (P–O–CH_3), 760m, and 790m cm^{-1} (aromatic CH bend); τ ([$^2H_6$]DMSO) 1.0—3.1 (8 H, m, pyridine and 4-nitrophenyl H), 5.8 and 6.0 (3 H, d, P–O–CH_3); *m/e* 294 (M^+), 263 ($C_{11}H_8N_2O_4P$), and 139 (4-nitrophenol). Hydrolysis of the ester and spectroscopic assay of the 4-nitrophenol released showed the product to be 95.6% pure.

Rearrangements.—The *OO*-disubstituted phosphonate esters were subjected to a variety of conditions to induce rearrangement. In all cases the reactions were followed by n.m.r. techniques often using the n.m.r. tube as the reaction

[3] D. Redmore, *J. Org. Chem.*, 1970, **35**, 4114.
[4] Ref. 2, p. 169.

vessel. Heating *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate *in vacuo* to *ca.* 100° gave a black oil which, when triturated with acetone, gave a small yield (*ca.* 5%) of precipitate identical with *O*-(4-nitrophenyl)(*N*-methyl-2-pyridinio)phosphonate (n.m.r., i.r., release of 4-nitrophenol, hydrolysis rate).

General Procedures.—M.p.s were obtained using a Kofler Thermospan instrument and are corrected. Microanalyses were performed by Mr. G. M. Powell and Miss L. Tidy using a Hewlett–Packard model 185 analyser. I.r. spectra were recorded on a Perkin-Elmer 237 instrument and mass spectra by Dr. R. B. Turner with an A.E.I. MS902 machine. N.m.r. spectra were recorded on a Perkin-Elmer R10 machine or by Dr D. O. Smith with a JEOL P.S.100 MHz instrument. U.v. and visible spectra were measured with a Unicam SP 800 spectrophotometer.

RESULTS AND DISCUSSION

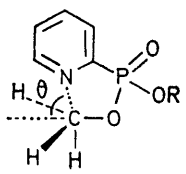
The n.m.r. spectra of the products of reaction of diazomethane with phenyl and 4-nitrophenyl 2-pyridylphosphonates indicates an absorption integrating for three protons (relative to phenyl or 4-nitrophenyl protons) at τ 5.3 close to that expected for an *N*-methylpyridinium group.[5] An *O*-methyl group is not introduced even with excess of diazomethane and only two methyl or ethyl groups (one of which resides on the nitrogen) are introduced when 2-pyridylphosphonic acid is alkylated with diazo-methane or -ethane; the reason for this is that only one labile proton is available in the monoesters and only two in the 2-pyridylphosphonic acid.

Rearrangements.—Refluxing a 50% solution of diethyl 2-pyridylphosphonate in $CDCl_3$ gave no change in the n.m.r. spectrum after 51 h; reaction of diazoethane with the acid under the conditions for the preparation of *O*-(4-nitrophenyl) (*N*-methyl-2-pyridinio)phosphonate gave a product with n.m.r. spectrum consistent with *O*-ethyl (*N*-ethyl-2-pyridinio)phosphinate. Keeping *OO*-dimethyl 2-pyridylphosphonate at 60° in [$^2H_6$]DMSO (with an amount of pyridine equivalent to the ester) over a period of 60 h showed a gradual decrease in intensity of the n.m.r. doublet at τ 6—7 and the appearance of two peaks between τ 5 and 6 due to *N*-methylpyridinium and *N*-methyl-2-pyridiniophosphonate formation.

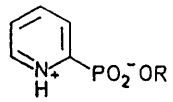
Treating *O*-methyl *O*-(4-nitrophenyl) 2-pyridylphosphonate under the conditions for the preparation of the *N*-methyl isomer (in the absence of diazomethane) gave starting material in quantitative yield.

These experiments demonstrate that alkylation of nitrogen in 2-pyridylphosphonates by diazoalkanes is a direct process although the indirect path with rearrangement of the *O*-alkyl intermediate can occur under different, more vigorous, conditions. The rearrangement is presumably intermolecular and evidence consistent with this is the alkylation of the added pyridine and the low yields of rearranged material.

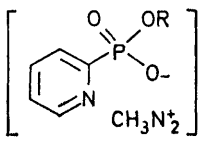
Tenud *et al.*[6] have shown that endocyclic S_N reactions at saturated carbon in certain rearrangements do not occur because the preferred backside attack is not possible in small rings. Indeed, the corresponding endocyclic mechanism for the present rearrangement demands



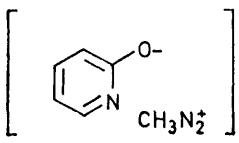
(IV)



(V)



(VI)



(VII)

an angle (θ) of *ca.* 72° with the preferred trajectory suggesting the intramolecular S_N2 mechanism to be of minor importance compared with the intermolecular path which is not so constrained.

Since pyridines are not readily methylated on nitrogen by diazomethane it is of interest to examine the influence of the phosphonic acid group. Many authors have shown that boron trifluoride catalyses the methylation of very weak acids (RNH_2, ROH, *etc.*) [7-13] by diazomethane. The catalyst presumably forms an encounter complex with the weak acid liberating a proton and the reactive $CH_3N_2^+$ system thus produced acts on the most reactive nucleophile. Tetrafluoroboric acid catalyses the methylation of pyridine, quinoline, and isoquinoline by diazomethane [1b] presumably because the tetrafluoroborate counterion is not sufficiently nucleophilic to compete with the nitrogen. In the present case the phosphonic acid provides a labile proton and the substrate is almost completely in its zwitterionic form (V). The phosphonate anion is a much weaker nucleophile than the pyridine nitrogen so that in the reaction complex (VI) the latter competes more efficiently for the methyl group. The site of protonation in the starting material is irrelevant to the product type because the complex (VI) will be formed from either zwitterion (V) or neutral (II) species; however, if proton transfer to the diazo-

[5] W. F. Reynolds and U. R. Priller, *Canad. J. Chem.*, 1968, **46**, 2787.
[6] L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, 1970, **53**, 2059.
[7] E. Müller, M. Bauer, and W. Rundel, *Z. Naturforsch.*, 1959, **14***b*, 209.
[8] E. Müller and W. Rundel, *Angew. Chem.*, 1958, **70**, 105.
[9] E. Müller, R. Meischkeil, and M. Bauer, *Annalen*, 1964, **677**, 55.
[10] E. Müller, W. Rundel, and H. Huber-Emden, *Angew. Chem.*, 1957, **69**, 614.
[11] E. Müller and H. Huber-Emden, *Annalen*, 1961, **649**, 70.
[12] E. Müller, H. Huber-Emden, and W. Rundel, *Annalen*, 1959, **623**, 34.
[13] N. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 1954, **6**, 36; *J. Amer. Chem. Soc.*, 1958, **80**, 2584.

methane is rate limiting the *rate* of methylation will depend on the acid donor [14] and on the equilibrium constants between the various protonic species involved. In cases such as 2-pyridone (VII) [15] and 8-hydroxyquinoline [16] the competing nucleophiles (oxyanions) are sufficiently active to give mixed products.

We thank the Ministry of Defence for support.

[5/2273 *Received*, 20*th November*, 1975]

[14] (*a*) M. M. Kreevoy and D. E. Konasewich, *J. Phys. Chem.*, 1970, **74**, 4464; (*b*) W. J. Albery, A. N. Campbell-Crawford, and K. S. Hobbs, *J.C.S. Perkin II*, 1972, 2180.

[15] N. Kornblum and G. P. Coffey, *J. Org. Chem.*, 1966, **31**, 3447.

[16] (*a*) G. Caronna and B. Sansone, *Gazzetta*, 1939, **69**, 24; (*b*) H. Schenkel-Rudin, *Helv. Chim. Acta*, 1944, **27**, 1456; (*c*) J. P. Phillips and R. W. Keown, *J. Amer. Chem. Soc.*, 1951, **73**, 5483.