3 (R^1 = 4-PhCO) (1.25 g, 0.0025 mol) and methyl propiolate (0.42 g, 0.0050 mol). Elution with a mixture of ether and methylene chloride (1:5 v/v) gave yellow crystals which were recrystallized from a mixture of ether and light petroleum (1:4 v/v) to give 7 (0.454 g, 65%): mp 174–175 °C; ir (KBr) 1700 ($\nu_{C=O}$, ester), 1650 cm^{-1} ($\nu_{C=O}$, benzoyl); NMR ($CDCl_3$) δ 8.60 (s, 1 H, H_9), 8.03 (d, 1 H, $J_{5,6}$ = 7 Hz, H_5), 7.82 (dd, 2 H, J_{AB} = 8, J_{AC} = 2 Hz, H_A, ortho H in benzoyl), 7.60–7.45 (m, 3 H, meta and para H in benzoyl), 7.33 (s, 2 H, H_2 and H_3), 7.27 (d, 1 H, $J_{5,6}$ = 7 Hz, H_6) 3.83 (s, 3 H, CH_3); mass spectrum *m/e* 279 ($M^{\cdot+}$, 100), 249 (15), 248 ($M^{\cdot+}$ – MeO·, 90), 221 ($M^{\cdot+}$ – CO – HCHO, 7), 202 (15), 165 (13).

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.01. Found: C, 72.80; H, 4.78; N, 4.86.

Acknowledgments. This work was supported by grants from the National Science Foundation and from the National Institutes of Health (GM 16626) for which we are grateful, and during the tenure (by V.A.) of a University of Alabama Graduate School Fellowship (1973–1974).

Registry No.—1 (R′ = H), 110-86-1; 1 (R′ = 4-Me), 108-89-4; 1 (R′ = 4-CN), 100-48-1; 1 (R′ = 4-PhCO), 14548-46-0; 1 (R′ = 4-*t*-Bu), 3978-81-2; 1 (R′ = 3,5-Cl_2), 2457-47-8; 1 (R′ = 3,5-Me_2), 591-22-0; **2**, 37891-93-3; **7**, 58747-68-5; *p*-toluenesulfonylmethanol, 2182-69-6; trifluoromethanesulfonic anhydride, 358-23-6.

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Phosphorus Derivatives of Nitrogen Heterocycles. 4. Pyridyl-4-phosphonates

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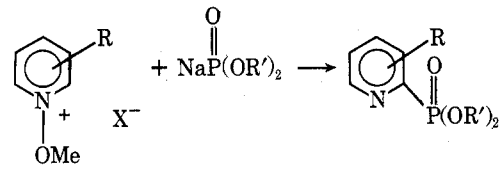
The reaction of 1-triphenylmethylpyridinium salts, e.g., **1**, with sodio diisopropylphosphonate yields diisopropyl pyridyl-4-phosphonates, e.g., **3**. The reaction is applicable to pyridinium salts having no α substituents. The esters are characterized by ^1H, ^{13}C, and ^{31}P NMR spectra. Hydrolysis of the esters yields the corresponding pyridyl-4-phosphonic acids whose dissociation constants are reported.

Previously we have described a general route for the synthesis of pyridyl-2-phosphonates (eq 1) and reported some of



(1)

the properties of these compounds.[1,2] Although numerous attempts were made to induce attack at the 4 position by changes in solvent, reaction temperature, etc., this was completely unsuccessful[3] and only where both positions α to nitrogen are substituted does attack by the phosphonate anion occur at the 4 position. The present paper describes a new approach which yields exclusively pyridyl-4-phosphonates and thus complements the earlier method.

The approach taken was to attach a bulky substituent to nitrogen, namely triphenylmethyl, to shield the 2 positions of the pyridine from nucleophilic attack, an approach which was partially successful for hydride attack.[4] Thus, triphenylmethylpyridinium tetrafluoroborate (1) upon treatment with the sodio derivative of diisopropyl phosphite yielded diisopropyl pyridyl-4-phosphonate (**3**). The 1,4-dihydropyridine **2** is presumably an intermediate but decomposes to **3** under the reaction conditions. The ^1H NMR spectrum of **3** fully supports the assigned structure showing a multiplet, δ 7.65, for the protons at C_3 and C_5 and a multiplet, δ 8.75, for the protons at C_2 and C_6, in addition to isopropoxy groups.[5] The ^{13}C NMR spectrum further supports the structural as-

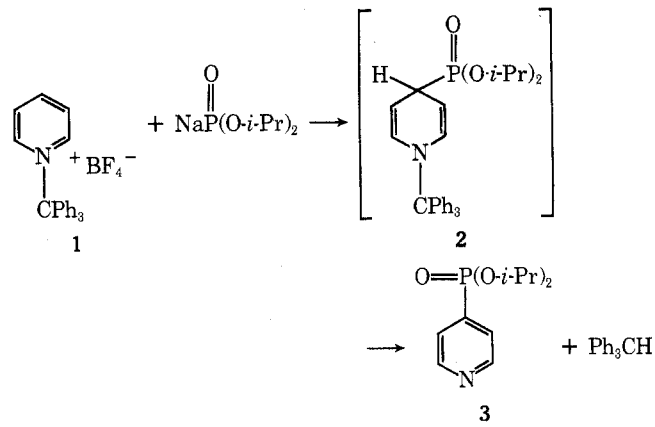


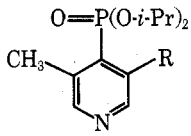
Table I. ^{13}C NMR Spectral Data

Compd	Chemical shifts, δ (J_{P-C}, Hz)					
	C_2	C_3	C_4	C_5	C_6	Other
3	150.0 (12)	125.2 (8)	137.8 (188)	125.2 (8)	150.0 (12)	71.6 (OCH), 24.1 (CH_3)
4	153.0 (12)	136.0 (9)	138.2 (188)	130.5 (9)	148.6 (12)	71.7 (OCH) 24.3 (CH_3) 18.0 ($ArCH_3$)
5	151.3 (13)	137.1 (9)	136.4 (178)	137.1 (9)	151.3 (13)	71.5 (OCH) 24.5 (CH_3) 19.9 ($ArCH_3$)
6	143.9 (11)	130.9 (9)	159.3 (168)	130.9 (9)	143.9 (11)	
7	143.8 (11)	147.1 (9)	161.1 (155)	134.1 (9)	143.8 (11)	22.9 ($ArCH_3$)
8	144.9 (9)	146.2 (11)	160.1 (163)	146.2 (11)	144.9 (9)	25.1 ($ArCH_3$)

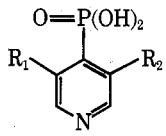
Table II. Dissociation Constants of Pyridyl-4-phosphonic Acids

Phosphonic acid	pK_a^1	pK_a^2	pK_a of parent pyridine
Pyridyl-4-	4.53	6.61	5.17
3-Methylpyridyl-4-	4.85	6.90	5.67
3,5-Dimethylpyridyl-4-	5.50	7.60	6.14
2,6-Dimethylpyridyl-4-[2]	5.12	7.52	6.75
2,3,6-Trimethylpyridyl-4-[2]	5.06	8.04	7.40

signment (Table I).[6] A similar sequence of reactions on 3-methylpyridine and 3,5-dimethylpyridine yielded the corresponding pyridyl-4-phosphonates **4** and **5**.



4, R = H
5, R = CH_3



6, $R_1 = R_2 = H$
7, $R_1 = CH_3$; $R_2 = H$
8, $R_1 = R_2 = CH_3$

Hydrolysis of the esters **3**, **4**, and **5** with aqueous hydrochloric acid yielded the corresponding acids, **6**, **7**, and **8**, as high-melting solids. In light of our previous work on the dissociation constants of pyridylphosphonic acids[2] it was of interest to determine the dissociation constants for **6**, **7**, and **8**. Table II lists the dissociation constants for these acids and the parent pyridines.

Experimental Section

Melting points and boiling points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratories and Petrolite Corp., Analytical Section. ^1H NMR spectra were obtained with a Varian A-60 spectrometer, and ^{31}P and ^{13}C spectra with a JEOL FX-60 spectrometer operating at 24.15 and 15.04 MHz, respectively.

Diisopropyl Pyridyl-4-phosphonate (3). Pyridine (10 ml) was added to a solution of triphenylcarbenium tetrafluoroborate (19 g, 0.058 mol) in methylene chloride (250 ml) with cooling. After standing at 5 °C overnight the resulting crystals, triphenylmethylpyridinium tetrafluoroborate (1), 13.6 g, were filtered. To a suspension of these crystals in benzene (130 ml) was added a solution of sodio diisopropyl phosphonate (0.035 mol) in diisopropyl phosphonate (14 ml) during 45 min at 5–10 °C. The mixture was heated at reflux for 2 h and allowed to cool and water (50 ml) added. The organic phase was separated and extracted with 3 N HCl to recover the basic portion. Distillation of the crude base yielded pyridine and 2.5 g (30%) of diisopropyl pyridyl-4-phosphonate, bp 104–105 °C (0.4 mm), which solidified upon standing. Recrystallization from hexane gave pure **3**: mp 45–46 °C; NMR ($CDCl_3$) δ 1.27 (d, 6, J = 6.5 Hz), 1.39 (d, 6, J = 6.5 Hz), 4.78 (m, 2), 7.65 (m, 2), 8.75 (m, 2).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.58; H, 7.54; N, 5.84; P, 12.85.

Diethyl Pyridyl-4-phosphonate. Using the method described above treatment of tritylpyridinium tetrafluoroborate with sodio diethyl phosphonate yielded diethyl pyridyl-4-phosphonate (39%), bp 101–103 °C (0.5 mm), ^{31}P NMR δ −14.96.

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23; H, 6.51; N, 6.51. Found:[7] C, 48.51; H, 6.68; N, 6.12.

Warming the above ester in ethanol with picric acid gave a crystalline picrate which was recrystallized from ethanol to give needles, mp 152–153 °C.

Anal. Calcd for $C_{15}H_{17}N_4O_{10}P$: C, 40.54; H, 3.83; N, 12.61. Found: C, 40.58; H, 3.69; N, 12.20.

Pyridyl-4-phosphonic Acid (6). Ester **3** (2.5 g) was heated at reflux with 18% HCl (30 ml) for 4 h. The gum obtained by evaporation of the aqueous acid yielded white crystals upon treatment with ethanol. Recrystallization from water/ethanol gave 1.2 g (75%) of pure pyridyl-4-phosphonic acid: mp 318 °C; NMR (D_2O) δ 8.43 (m, 2, H at C_3, C_5), 9.00 (m, 2, H at C_2, C_6).

Anal. Calcd for $C_5H_6NO_3P$: C, 37.74; H, 3.77; N, 8.80; P, 19.50. Found: C, 37.86; H, 4.00; N, 8.47; P, 19.83.

Diisopropyl 3-Methylpyridyl-4-phosphonate (4). Crude triphenylmethyl-β-picolinium tetrafluoroborate prepared from triphenylcarbenium tetrafluoroborate (50 g, 0.15 mol) and β-picoline (30 ml) in methylene chloride (400 ml) was isolated by evaporation of the solvent and dispersed in benzene (350 ml). Sodio diisopropyl phosphonate (0.15 mol) in diisopropyl phosphonate (40 ml) was added over a period of 30 min at 5–10 °C. After heating at reflux for 2 h the reaction mixture was worked up in the manner described for **3**. Distillation yielded excess β-picoline and diisopropyl 3-methylpyridyl-4-phosphonate (**4**): 20.6 g (53%); bp 103–105 °C (0.1 mm); NMR ($CDCl_3$) δ 1.25 (d, 6, J = 6 Hz), 1.38 (d, 6, J = 6 Hz), 2.57 (d, 3, J = 1.5 Hz), 4.75 (m, 2), 7.79 (d of d, 1, J_{P-CH} = 14, $J_{H,H}$ = 5 Hz, H at C_5), 8.60 (m, 2, H at C_2, C_6); ^{31}P NMR δ − 12.9.

Anal. Calcd for $C_{12}H_{20}NO_3P$: C, 56.03; H, 7.78; N, 5.45; P, 12.06. Found:[7] C, 54.35; H, 7.83; N, 5.18; P, 12.09.

Warming **4** with picric acid in ethanol yielded a crystalline picrate which was recrystallized from ethanol to yield an analytically pure salt, mp 72–74 °C.

Anal. Calcd for $C_{18}H_{23}N_4O_{10}P$: C, 44.44; H, 4.73; N, 11.52. Found: C, 44.55; H, 4.91; N, 11.45.

3-Methylpyridyl-4-phosphonic Acid (7). Hydrolysis of **4** with 18% HCl yielded after crystallization from water/ethanol 3-methylpyridyl-4-phosphonic acid (**7**), mp 296 °C, in 95% yield: NMR (D_2O) δ 2.87 (s, 3), 8.42 (m, 1, H at C_5), 8.80 (m, 2, H at C_2, C_6).

Anal. Calcd for $C_6H_8NO_3P$: C, 41.62; H, 4.62; N, 8.09; P, 17.92. Found: C, 41.85; H, 4.60; N, 7.85; P, 17.69.

Diisopropyl 3,5-Dimethylpyridyl-4-phosphonate (5). The method used for **4** gave diisopropyl 3,5-dimethylpyridyl-4-phosphonate (28%): bp 97–99 °C (0.1 mm); NMR ($CDCl_3$) δ 1.18 (d, 6, J = 6 Hz), 1.37 (d, 6, J = 6 Hz), 2.56 (d, 6, J = 1.5 Hz), 4.70 (m, 2), 8.25 (d, 2, J = 6 Hz); ^{31}P NMR δ − 13.6.

Anal. Calcd for $C_{13}H_{22}NO_3P$: C, 57.56; H, 8.12; N, 5.17; P, 11.44. Found: [7]C, 56.45; H, 8.24; N, 5.10; P, 11.15.

Warming **5** in ethanol with picric acid yielded a picrate purified by recrystallization from ethanol, mp 139–140 °C.

Anal. Calcd for $C_{19}H_{25}N_4O_{10}P$: C, 45.60; H, 5.00; N, 11.20. Found: C, 45.51; H, 5.19; N, 11.03.

3,5-Dimethylpyridyl-4-phosphonic Acid (8). Hydrolysis of ester **5** in the normal manner gave after crystallization from water/ethanol the phosphonic acid **8**, mp 333 °C, in 70% yield: NMR (D_2O) δ 2.87 (s, 6), 8.62 (d, 2, J = 3 Hz).

Anal. Calcd for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49; P, 16.58. Found: C, 44.89; H, 5.43; N, 7.46; P, 16.81.

Registry No.—**1**, 26156-84-3; **3**, 58815-96-6; **4**, 58815-97-7; **4** picrate, 58815-98-8; **5**, 58815-99-9; **5** picrate, 58816-00-5; **6**, 58816-01-6; **7**, 58816-02-7; **8**, 58816-03-8; sodio diisopropyl phosphonate, 58816-04-9; diethyl pyridyl-4-phosphonate, 37175-34-1; diethyl pyridyl-4-phosphonate picrate, 58816-05-0; triphenylmethyl-β-picolinium tetrafluoroborate, 58816-07-2; triphenylmethyl-3,5-dimethylpyridinium tetrafluoroborate, 58816-09-4.

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Chemistry of the Dihydrothiazine Ring Moiety of Cephalosporins. 1. Regiospecificity and Stereoselectivity in the Bromine Addition to 2-Cephem Derivatives. A New Route to 2-Methoxy Cephalosporins

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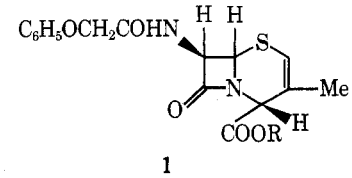
The reactions of Δ^2-deacetoxycephalosporin (**1a**) with Br_2 in aprotic solvents (CCl_4 and CH_2Cl_2) yielded mixtures of the diastereoisomeric 2,3-dibromides **2a** and **3a**. The same reaction in MeOH afforded a mixture of the 2-methoxy-3-bromo derivatives **4a** and **5a**, whereas in 2-PrOH it gave exclusively **2a** and **3a**. **2a** and **3a** were transformed respectively to **4a** and **5a** with practically complete retention of configuration by treatment with MeOH in the presence of $Me_2NC_6H_5$. **4a** and **5a** were dehydrohalogenated to the corresponding 2-methoxy cephalosporin derivatives **6a** and **7a**. Compounds **6b** and **7b** were prepared through a similar sequence. **6** and **7** were transformed into the acids **6** (R = H) and **7** (R = H). The configurations of the substituents at C_2 and C_3 were demonstrated through chemical transformations and from their NMR spectra by NOE experiments. The stereochemical results and the mechanisms of the reactions are discussed.

The 2- or 3-cephem double bond may be a good point of attack for the introduction of new substituents into the dihydrothiazine ring of cephalosporins. Whereas the 3-cephem double bond appears to be very unreactive toward electrophilic reagents,[1] the 2-cephem one appeared to us more susceptible to attack by such agents because of the more favorable electronic effects of the substituents on the double bond. We wish to report the addition of Br_2 to Δ^2-deacetoxycephalosporins **1** and some reactions of the bromine addition products. In addition to the pharmaceutical purpose, this research represents, to our knowledge, the first approach to the study of the stereochemical aspect of the electrophilic addition to the double bond of a vinyl thioether. The mechanism of the bromination reactions of the olefinic double bond,[2] as well as that of the analogous reactions of vinyl ethers,[3] has been extensively studied. It may be stressed, however, that the steric course of this type of reactions is strongly depending on the steric and electronic effects of the double bond substituents and on the reaction conditions[2-4] and, therefore, in several cases not simply predictable.



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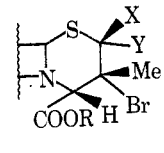
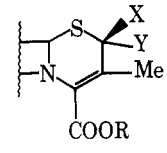


A



B

2, X = Br; Y = H
3, X = H; Y = Br
4, X = OMe; Y = H
5, X = H; Y = OMe

6, X = OMe; Y = H
7, X = H; Y = OMe

a, R = *p*-$MeOC_6H_4CH_2$
b, R = *p*-$NO_2C_6H_4CH_2$

Results

The treatment of a solution of **1a**[5] in CCl_4 or CH_2Cl_2 with a dilute solution of Br_2 in the same solvent afforded mixtures of the two diastereoisomeric dibromides **2a** and **3a**. The ratio between **2a** and **3a** changes with the solvent, the trans dibromide (**2a**) being predominant in CCl_4 and the cis dibromide (**3a**) in CH_2Cl_2 (Table I). The reaction of these mixtures with MeOH in presence of $Me_2NC_6H_5$ yielded in nearly quantitative yield mixtures of the 2-methoxy derivatives **4a** and **5a** with practically complete retention of configuration. A 25:75 mixture of **4a** and **5a** was directly obtained from **1a** by treatment with Br_2 in MeOH. On the contrary, bromination of **1a** in 2-PrOH gave a mixture of **2a** and **3a** (Table I); no trace of alkoxybromo derivatives was revealed. Dehydrohalogenation of **4a** and **5a** with Et_3N in benzene at room temperature gave the corresponding Δ^3 derivatives **6a** and **7a**, which have been separated by preparative TLC. Esters **6b** and **7b** were prepared through a similar sequence. Both **2** and **3**, and **4** and **5** refused to crystallize and separation attempts by chromatography led to extensive decomposition and dehydrobromination to **6** and **7**, respectively; their crude mixtures were, therefore, used directly for subsequent transformations. Compounds **2**, **3**, **4**, and **5** were, however, stable under the reaction conditions. Hydrogenolysis of **6b** and **7b** on Pd/C and cleavage of **6a** with CF_3COOH in benzene in the presence of