Syntheses of Organic Phosphates. III. Syntheses and Properties of 2-Amino-3-pyridylmethyl and 2-Chloro-3-pyridylmethyl Phosphates[1]

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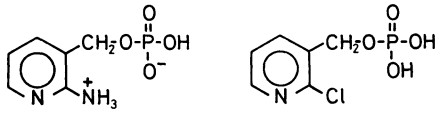
Two substituted pyridylmethyl phosphates, 2-amino-3-pyridylmethyl (I) and 2-chloro-3-pyridylmethyl phosphates (II), were prepared and their properties were discussed. Acid dissociation constants and NMR data suggested that the neutral species of I exists in the zwitterion form consisting of the protonated amino group and the monoanionic phosphate moiety, while that of II in the dihydrogen phosphate form analogous to the simple alkyl phosphates. In addition, physical properties of 2-amino-3-pyridylmethanol and 2-chloro-3-pyridylmethanol, which are respectively precursors of phosphates I and II, as well as 1,2-dihydro-2-oxo-3-hydroxymethylpyridine, were examined by IR and NMR measurements.

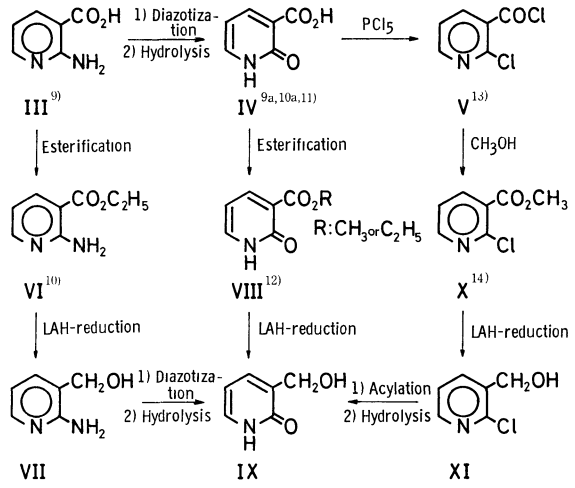
In a series of our studies on the chemistry of organic phosphates, some phosphates, which carry a heteroaromatic moiety, have been prepared.[2-5] Their hydrolytic behaviors have been investigated with particular attention to the intramolecular catalysis brought about by the proximity participation of a functional group.[4-7] In order to search for further evidence of the proximity catalysis in hydrolysis, two phosphates, 2-amino-3-pyridylmethyl (I) and 2-chloro-3-pyridylmethyl phosphates (II), were synthesized in this work.



I II

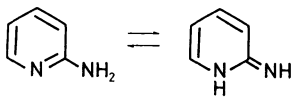
2-Chloro-3-pyridylmethanol (XI) which is the precursor of II was also found to be a new material. On the other hand, Cislak has already prepared 2-amino-3-pyridylmethanol (VII), the precursor of I, by a method different from the present one.[8] Their physical properties were examined in this work.

Pyridylmethanols. Both pyridylmethanols, VII and XI, were prepared from the same starting material, 2-aminonicotinic acid (III),[9] according to the processes shown in Scheme 1. The synthesis of 1,2-dihydro-2-oxo-3-hydroxymethylpyridine (IX) was also carried out.



Scheme 1.

The following tautomerism would be considered for 2-aminopyridines.[15] In the case of 2-amino-3-pyridylmethanol, however, we confirmed the absence of such a tautomerism on the basis that the correlation between the symmetric and asymmetric N–H stretching vibrational modes for this alcohol is in good agreement with the Bellamy-Williams relationship for the aromatic primary amines.[16] The alcoholic hydroxyl proton only



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11) a) F. G. Mann and J. H. Jurnbull, *J. Chem. Soc.*, **1951**, 761; b) S. Carboni, *Gazz. Chim. Ital.*, **83**, 637 (1953); *Chem. Abstr.*, **49**, 1039 (1955).
12) For the methyl ester, A. Kirpal, *Monatsh. Chem.*, **27**, 371 (1906); for the ethyl ester, A. Dornow, *Ber.*, **73**, 153 (1940).
13) Mp 40—41 °C. This compound was converted by hydrolysis to 2-chloronicotinic acid; mp 192—193 °C. The acid has been prepared by Seide; O. Seide, *Ber.*, **57**, 1802 (1924).
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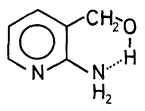
15) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, **1948**, 2240; the ionic strength is not certain.
16) L. J. Bellamy and R. L. Williams, *Spectrochim. Acta*, **9**, 341 (1957).

Table 1. NMR data of 2-substituted 3-pyridylmethanols[a)]

Substituted 3-pyridyl-methanol	Solvent	Chemical shift, ppm					Coupling constant, Hz			
		CH_2	H-4	H-5	H-6	Others	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	J_{CH_2-OH}
2-Chloro-	Acetone[b)]	4.70, s	8.00, q	7.40, q	8.30, q	-OH; 4.67, br.s	4.5	2.0	7.5	—
	DMSO[c)]	4.57, d	7.95	7.43	8.19	-OH; 5.49, t	4.5	2.0	7.5	5.5
2-Amino-	Acetone[d)]	4.58, s	7.40, sx	6.55, q	7.90, q	$-NH_2$ / $-OH$); 4.99, br.s	5.0	2.0	7.5	—
	DMSO[c)]	4.34	8.18	6.50	7.81	($-NH_2$; 3.91, br.s / $-OH$; 5.04, br.s	5.0	2.0	7.0	—
1,2-Dihydro-2-oxo-	DMSO[c)]	4.28, s	7.22, m	6.17 t	7.38 m	-OH; 4.91, br.s	6.5	1.5	6.5	—

a) All the spectra were referred to TMS as an internal reference at ordinary temperature. Multiplicity: s=singlet, br. s=broad singlet, d=doublet, t=triplet, q=quartet, sx=sextet, m=multiplet.
b) 12 wt% in acetone.
c) 2.8 mol% in dimethyl sulfoxide.
d) 10 wt% in acetone.

gave a broad singlet NMR signal even in dimethyl sulfoxide. Apparently, the hydrogen bonding of the hydroxyl proton with the solvent must be disturbed by a strong intramolecular hydrogen bonding involving both hydroxyl and amino groups. This interaction may give rise to a slow hydrogen exchange, causing NMR line-broadening. The result is consistent with configuration XII. The appropriate data for NMR chemical shifts are summarized in Table 1.

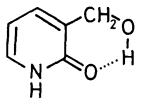


XII

Albert *et al.* reported the pK_a-value of the protonated 2-aminopyridine as 6.86 at 20 °C.[15] The pK_a value of the protonated 2-amino-3-pyridylmethanol was determined in this work to be 6.35 at 25 °C (μ= 0.10 with potassium chloride). Although the hydroxymethyl group is an electron-withdrawing substituent ($\sigma^*=+0.555$),[17] the decrease in pK_a upon substitution with the group ($\Delta pK_a=0.51$) seems to be too large to be attributed wholly to its electronic nature: pK_a, 9.94 for phenol, 9.92 for 2-hydroxymethylphenol, 9.83 for 3-hydroxymethylphenol, and 9.82 for 4-hydroxymethylphenol at 25 °C;[18] 3.99 for benzoic acid and 3.84 for 2-hydroxymethylbenzoic acid at 20 °C.[19] Consequently, the intramolecular hydrogen bonding, XII, may take place and result in the enhanced dissociation of proton from the protonated 2-amino group.

For 2-chloro-3-pyridylmethanol, the NMR hydroxyl proton resonance in dimethyl sulfoxide was well resolved into a triplet through coupling with the α-methylene. The strong hydrogen bonding of the hydroxyl group with dimethyl sulfoxide seems to be responsible for the inhibition of the hydroxyl proton exchange. As a result, pyridylmethanol does not involve an intramolecular hydrogen bonding strong enough to reject the interaction with dimethyl sulfoxide.

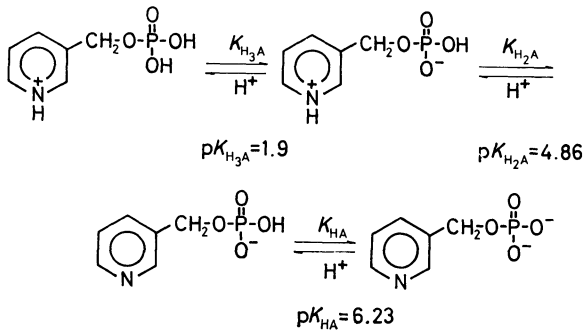
1,2-Dihydro-2-oxo-3-hydroxymethylpyridine (IX) showed a broad hydroxyl proton resonance signal in its NMR spectrum, indicating the existence of an intramolecular hydrogen bonding (XIII).



XIII

Pyridylmethyl Phosphates. Both phosphates, I and II, were prepared from the corresponding pyridylmethanols according to the established procedures.[2-5]

For simple alkyl phosphate monoesters, three species have to be considered, in general, where pK_{H_2A}=1—2 and pK_{HA}=5—7. Meanwhile, an additional ionic species must be considered for pyridylalkyl phosphates as shown typically for 3-pyridylmethyl phosphate in Scheme 2.[2] The second acid dissociation constant



Scheme 2.

found for 2-chloro-3-pyridylmethyl phosphate (pK_{H_2A}= 2, Table 2) is considerably smaller than those for the other pyridylalkyl phosphates (pK_{H_2A}=4—5).[2-5] Brown and McDaniel obtained the pK_a value of 0.72 for 2-chloropyridine in an aqueous media at 25 °C.[20] The phosphorylated hydroxymethyl group acts as an electron-withdrawing group to some extent.[2] Consequently, the pK_a-value for dissociation of a pyridinium proton in 2-chloro-3-pyridylmethyl phosphate should

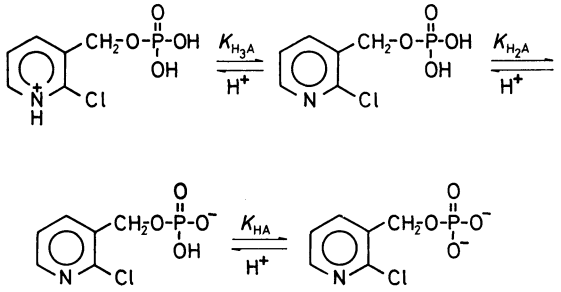
17) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Wiley & Sons, Inc., New York, N.Y. (1956), Chapt. 13.
18) G. R. Sprengling and C. W. Lewis, *J. Amer. Chem. Soc.*, **71**, 2624 (1949).
19) M. M. Delépine and M. J. Tironflet, *C. R. Acad. Sci. Paris*, **236**, 1426 (1953).
20) H. C. Brown and D. H. McDaniel, *J. Amer. Chem. Soc.*, **77**, 3753 (1955).

Table 2. Acid dissociation constants for the phosphates at μ=0.10 (KCl or KNO_3)

Phosphate	pK_{H_2A}		pK_{HA}	
	25 °C	80 °C	25 °C	80 °C
2-Chloro-3-pyridylmethyl	2.17	1.8[a]	5.97	6.3[a]
2-Amino-3-pyridylmethyl	5.42	5.11[b]	7.03	7.40[b]
3-Pyridylmethyl	4.86[c]	4.43[d]	6.23[c]	6.48[d]

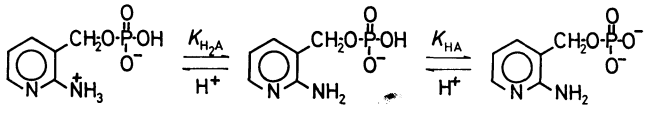
a) Quoted from Ref. 21.
b) At 70.0 °C.
c) Quoted from Ref. 2.
d) Quoted from Ref. 6.

be less than that for 2-chloropyridine. If the pK_{H_2A} refers to the dissociation of the first phosphate proton, a little larger value (2.2), relative to that of 3-pyridylmethyl phosphate (1.9), can be attributed to trapping of the phosphate proton by the chlorine atom through an intramolecular hydrogen bonding.[21] Therefore, the plausible acid dissociation processes for the phosphate are reasonably presented in Scheme 3. The neutral species of 2-chloro-3-pyridylmethyl phosphate does not exist in the zwitterion form but in the dihydrogen phosphate. This characteristic structural feature was closely reflected on its hydrolytic behavior.[21]



Scheme 3.

Since 2-amino-3-pyridylmethyl phosphate is tetrabasic, the acid dissociation processes become somewhat complex. The pK_a value of the protonated 2-amino group can be reduced by the phosphorylated 3-hydroxymethyl group playing as an electron-withdrawing substituent, while the acid dissociation of the last-dissociating proton on the phosphate moiety is somewhat depressed by the substitution of an electron-donating 2-amino group. The most plausible acid dissociation processes for the phosphate are reasonably given in Scheme 4.



Scheme 4.

For both phosphates of the present study, the dissociation of the pyridinium proton seems to be much enhanced by the presence of an electron-withdrawing group, protonated amino group or chlorine, and the reliable pK_a value for such dissociation was not evaluated under present experimental conditions.

21) Y. Murakami, J. Sunamoto, and N. Kanamoto, This Bulletin, **46**, 1730 (1973).

Experimental

2-Amino-3-pyridylmethanol (VII). A mixture of 16.3 g of lithium aluminum hydride (LAH) and 1 l of dry ether was stirred for 20 min at room temperature. The reaction flask was assembled with a Soxhlet extraction apparatus equipped with an extraction thimble in which 30.0 g of ethyl 2-aminonicotinate was placed. With care for vigorous reaction, the ether–LAH mixture was gently refluxed. After most of the ester was dissolved in ether, an additional 29.3 g sample of the ester was placed in the thimble. Upon refluxing for about 60 hr, the reaction mixture was cooled down to room temperature. After decomposing the excess hydride with water, the ether layer was separated and concentrated to crystallize the crude alcohol (22.9 g). From the residue containing metal hydroxide, 10.5 g of the alcohol was recovered. Both crops of the crude alcohol were combined and recrystallized from ether: colorless leaflet, mp 70 °C. Found: C, 58.11; H, 6.44; N, 22.54%. Calcd for $C_6H_8N_2O$: C, 58.04; H, 6.50; N, 22.57%. UV (methanol): 235.5 (log ε 3.97) and 295.5 nm (log ε 3.66). IR (KBr disk): ν_{NH}, 3410, 3335; δ_{NH}, 1650; ν_{ring}, 1605, 1575; ν_{C-O}, 1036, 1006; δ_{CH}, 791 and 756 cm^{-1}. NMR data are given in Table 1.

2-Chloro-3-pyridylmethanol (XI). A 27.1 g sample of methyl 2-chloronicotinate was treated with LAH in an established manner; yield 11 g (48%), bp 105—112 °C/0.20 mmHg. After being left overnight at room temperature, the distillate was solidified and recrystallized from chloroform: white needles, mp 63—64 °C. Found: C, 50.46; H, 4.24; N, 9.86%. Calcd for C_6H_6NOCl: C, 50.20; H, 4.21; N, 9.76%. UV (methanol): 265.5 nm (log ε 3.62). IR (KBr disk): ν_{OH}, 3280; ν_{ring}, 1588, 1571; ν_{C-O}, 1054, 1044; δ_{CH}, 817, 796, 734, and 718 cm^{-1}. NMR data are given in Table 1.

1,2-Dihydro-2-oxo-3-hydroxymethylpyridine (IX). (i) By the LAH reduction of ethyl 1,2-dihydro-2-oxonicotinate (1.0 g) according to the general procedure, the corresponding alcohol was obtained in poor yield (63 mg); mp 134 °C.

(ii) A solution containing 28.4 g of 2-amino-3-pyridylmethanol in 253 ml of 10% sulfuric acid was poured onto 950 ml of water warmed at 60—70 °C. At the same temperature, 230 ml aqueous solution of sodium nitrite (22.15 g) was added dropwise in 1 hr. After addition of aqueous nitrite was completed, the mixture was continuously stirred at the same temperature for additional 1 hr. The acidic solution was neutralized with anhydrous sodium carbonate and concentrated to 200 ml, to which double volume of ethyl acetate was added. The precipitated inorganic salt was removed. This procedure was repeated until inorganic salt was not detected any longer. Needle-like crystals were recovered from the cooled ethyl acetate solution, and recrystallized from ethanol: yield 19.9 g (70%), mp 137.5—138.4 °C. Found: C, 57.63; H, 5.78; N, 11.11%. Calcd for $C_6H_7O_2N$: C, 57.59; H, 5.64; N, 11.19%. UV (methanol): 230 (log ε 3.79) and 299 nm (log ε 3.77). IR (KBr disk): ν_{NH}, 3400; $\nu_{C=O}$, 1647; ν_{ring}, 1620, 1567; ν_{C-O}, 1040; δ_{CH}, 765 cm^{-1}. NMR data are listed in Table 1.

(iii) The pyridone IX was also obtained through acylation of the alcohol XI, followed by hydrolysis with diluted hydrochloric acid in the presence of sodium acetate; very poor yield.

2-Amino-3-pyridylmethyl Phosphate (I) 2-Amino-3-pyridylmethanol (VII) (1.0 g) was mixed with pyrophosphoric

acid, which was freshly prepared by brief heating of 85% orthophosphoric acid (6.5 g) and phosphorus pentoxide (5.0 g), at 50 °C under protection from moisture. The reaction mixture was heated at 70—80 °C for 20 hr, diluted with 20 ml of water, and heated again in order to hydrolyze any coexisting polyphosphate. The resulting hydrolyzate was poured onto 250 ml of acetone and allowed to stand overnight in a refrigerator. White precipitates were separated and washed sufficiently with acetone; yield 1.18 g. Further recrystallization from water gave white crystals; neutralization equivalence, 102.62 (calcd. 102.06). Found: C, 34.92; H, 4.84; N, 13.42%. Calcd for $C_6H_9O_4N_2P$: C, 35.31; H, 4.44; N, 13.72%. IR (KBr disk): $\nu^{+}_{NH_3}$, 3300, 3130, 2600, 2400, 2020, 1980; $\delta^{+}_{NH_3}$, 1685, 1646; $\nu_{P=O}$, 1247, 1150, 1130; $\nu_{P-O-C(alk)}$, 1020 and 946 cm^{-1}. UV (10^{-4}M, water): 232.5 (ε 8080) and 303.0 nm (ε 6840).

2-Chloro-3-pyridylmethyl Phosphate (II). A 1.44 g sample of 2-chloro-3-pyridylmethanol (XI) was phosphorylated with 12.7 g of pyrophosphoric acid at 80—100 °C for 4 hr according to the method similar to that used for 2-amino-3-pyridylmethanol. The resulting mixture was neutralized with concentrated aqueous ammonia and evaporated to dryness. The residue was extracted twice with a 100 ml portion of hot ethanol. The extracts were evaporated to 10 ml and white crystals (the diammonium salt) were recovered; yield 440 mg. Found: P, 12.1%. Calcd for $C_6H_{13}O_4N_3PCl$: P, 12.02%. The ammonium salt of the phosphate was converted to the free acid form with the use of cation exchange resin, Dowex-50W×8; neutralization equivalence, 108.90 (calcd. 111.77). Found: C, 32.22; H, 3.31; N, 6.12%. Calcd for $C_6H_7NO_4PCl$: C, 32.24; H, 3.16; N, 6.27%. UV (10^{-4}M, water): 266 (ε 3140) and 272 nm (ε 2840). IR (KBr disk): ν_{OH}, ~3400; $\nu_{P=O}$, 1287, 1230—1195 (broad), 1110; $\nu_{P-O-C(alk)}$, 1054 and 1010—970 cm^{-1} (broad). NMR (0.71M, dimethyl sulfoxide-d_6, TMS as an internal reference): δ 5.03 (2H, d, $J_{CH_2-^{31}P}$=8.0 Hz, -C<u>H</u>$_2$-), 6.61 (2H, s, -O<u>H</u>), 7.54 (1H, q, J_{4-5}=7.5 Hz and J_{5-6}=5.0 Hz, H-5), 8.02 (1H, q, J_{4-6}=2.0 Hz, H-4), and 8.46 (1H, q, H-6).

Acid Dissociation Constants. Acid dissociation constants of the pyridylmethyl phosphates and the pyridylmethanols were measured by potentiometric titrations of the corresponding aqueous solutions (2.0×10^{-3}M) with standard base or acid at an ionic strength of 0.10 (KCl or KNO_3). All the measurements were checked by duplicate runs. The procedures for measurements were essentially the same as those adopted in the previous studies.[2-5] A set of electrodes used for pH measurements were glass electrode TOA HG-6005 and reference electrode TOA HC-605, which were connected to the TOA HM-9A expandomatic pH meter. The evaluated acid dissociation constants are listed in Table 2 along with the previous data for comparison.

Thanks are due to Miss Chieko Gondo for her assistance in part of the potentiometric measurements.