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Phosphorus Derivatives of Nitrogen Heterocycles. 2. Pyridinephosphonic Acid Derivatives[1]

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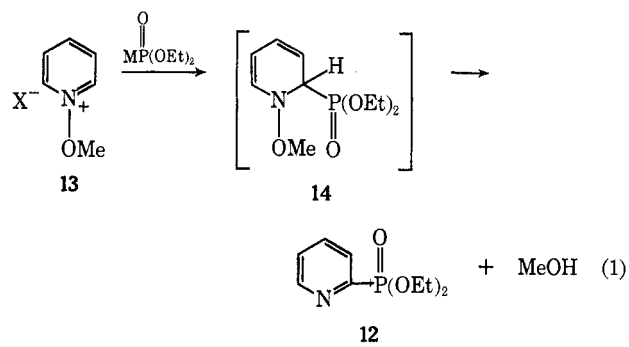
The reaction of *N*-alkoxypyridinium salts with alkali metal derivatives of dialkyl phosphonates provides a general synthesis of dialkyl pyridine-2-phosphonates in yields of 35–65%. 3-Methyl-*N*-methoxypyridinium methosulfate yields a mixture of diethyl 3-methylpyridine-2-phosphonate (**17**) and diethyl 5-methylpyridine-2-phosphonate (**18**) upon reaction with diethyl sodiophosphonate in a ratio of 6:1. The pyridinephosphonate esters are hydrolyzed in 18% HCl to the corresponding pyridinephosphonic acids. 4 substitution was obtained in one case only, the reaction of 2,6-dimethyl-*N*-methoxypyridinium methosulfate with diethyl sodiophosphonate. Nmr and uv spectra of the pyridinephosphonates gave no evidence for d_π–p_π bonding.

The number of examples of nitrogen heterocyclic systems in which phosphorus is attached as a ring substituent has grown recently.[1-7] One of the synthetic methods employed is the 1,3-dipolar addition of diazoalkanes to alkynylphosphonates illustrated in the preparation of the pyrazole (**2**) from diethyl ethynylphosphonate (**1**) and diazomethane.[2] Alternatively, the dipolar addition of α-diazophosphonates to olefins provides a synthesis of dihydropyrazoles exemplified in the addition of diazophosphonate (**3**) to methylvinyl ketone yielding dihydropyrazolephosphonate (**4**).[3] Nucleophilic displacement on diethyl phosphorochloridate by pyrrolyl Grignard reagent (**5**) yields diethyl pyrrole-2-phosphonate (**6**).[4] Other methods include the nucleophilic attack of trialkyl phosphites (Arbusov reaction) or salts of dialkyl phosphonates (Michaelis–Becker–Nylen reaction) on heterocyclic chlorides or bromides.[5] These procedures require reactive halides, so that while 2-chloropyrimidine (**7**) is converted into diisopropyl pyrimidine-2-phosphonate (**8**) by reaction with triisopropyl phosphite[5a] 2-bromopyridine is unreactive to trialkyl phosphites or dialkyl metal phosphonates.[5b] Although no general method for the preparation of pyridine phosphonates has been described, pyridine-3-phosphonic acid (**10**) has been prepared from 3-pyridyl diazonium tetrafluoroborate (**9**) by reaction with phosphorus trichloride followed by hydrolysis,[6] and diethyl pyridine-2-phosphonate (**12**) has been obtained by reaction of triethyl phosphite on 2-nitropyridine *N*-oxide (**11**).[7] The present paper describes a general method for the preparation of dialkyl pyridine-2-phosphonates.

Activation of the pyridine ring to nucleophilic attack by conversion into an *N*-alkoxypyridinium salt (*via* the *N*-oxide) has allowed the preparation of many substituted pyridines.[8] The preparation of cyanopyridines is a particularly elegant illustration of this principle.[9]

It has been found that *N*-methoxypyridinium salts (**13**) react with alkali metal derivatives of diethylphosphonate[10] to form diethyl pyridine-2-phosphonate (**12**) (eq 1). This reaction is a strongly exothermic process



whose efficiency is highly dependent upon the reaction conditions. Although the preparation of diethyl sodiophosphonate has been carried out by reaction of diethyl phosphonate with metallic sodium[13] or sodium hydride[14] in a hydrocarbon or ether solvent, it is more convenient for reaction with *N*-alkoxypyridinium salts to use diethyl phosphonate as solvent for the sodiophosphonate and the quaternary salt. It is important to carry out the addition of the *N*-alkoxypyridinium salt to the dialkyl sodiophosphonate at −15 to 0° in order to obtain good yields of pyridine phosphonate. No direct evidence has been obtained to support the intermediacy of dihydropyridine (**14**), but spectral evidence for dihydropyridines has been obtained in the addition of other nu-

(1) Part 1: D. Redmore, *J. Org. Chem.*, **34**, 1420 (1969).
(2) B. C. Saunders and P. Simpson, *J. Chem. Soc.*, 3351 (1963).
(3) D. Seyferth and J. D. H. Paetsch, *J. Org. Chem.*, **34**, 1481 (1969); M. Regitz, W. Anschutz, and A. Liedhegener, *Chem. Ber.*, **101**, 3734 (1969).
(4) C. E. Griffin, R. P. Peller, and J. A. Peters, *J. Org. Chem.*, **30**, 91 (1965).
(5) (a) G. M. Kosolapoff and C. H. Roy, *ibid.*, **26**, 1895 (1961); (b) A. Burger, J. B. Clements, N. D. Dawson, and R. B. Henderson, *ibid.*, **20**, 1383 (1955).
(6) R. D. Bennett, A. Burger, and W. A. Volk, *ibid.*, **23**, 940 (1958).
(7) J. I. G. Cadogan, D. J. Sears, and D. M. Smith, *J. Chem. Soc. C*, 1314 (1969).
(8) A. R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
(9) W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.*, **81**, 4004 (1959).
(10) Although for convenience the structure of the alkali metal dialkyl phosphonates is represented through this paper as MP(=O)(OR)$_2$, spectroscopic evidence favors the form MOP(OR)$_2$.[11,12]
(11) Infrared spectra of the alkali metal dialkyl phosphonates: L. W. Daasch, *J. Amer. Chem. Soc.*, **80**, 5301 (1958).
(12) ^{31}P nmr spectra of alkali metal dialkyl phosphonates: K. Moedritzer, *J. Inorg. Nucl. Chem.*, **22**, 19 (1961).
(13) G. M. Kosolapoff, "Organosphosphorus Compounds," Wiley, New York, N. Y., 1950, pp 123–124; G. M. Kosolapoff and A. D. Brown, *Chem. Commun.*, 1266 (1969).
(14) R. G. Harvey, H. I. Jacobson, and E. V. Jensen, *J. Amer. Chem. Soc.*, **85**, 1623 (1967).

cleophiles to alkoxypyridinium salts.[15] The higher yields at the low temperature are readily explained in terms of the dihydropyridine intermediate **14**. At temperatures of the order of 20–30° the formation of **14** and its conversion to **12**, with methanol elimination, are both rapid. If methanol increases in concentration, it competes with pyridinium compound (**13**) for the diethyl sodiophosphonate (eq 2) and hence lowers the yield of pyridine phosphonate.[16] At lower temperatures the formation of **12** from **14** is slow relative to formation of

$$NaP(=O)(OEt)_2 + MeOH \rightleftharpoons HP(=O)(OEt)_2 + NaOMe \quad (2)$$

14 and hence the diethyl sodiophosphonate is used efficiently. No difference was noted when diethyl lithiophosphonate replaced the sodium salt in this reaction, and dibutyl pyridine-2-phosphonate was obtained by the reaction of dibutyl sodiophosphonate on pyridinium salt (**13**) in 20% yield.

Diethyl pyridine-2-phosphonate (**12**) was characterized by analytical and spectral data. The uv spectrum of **12** is virtually identical with that of pyridine showing maxima at 254 nm (ϵ 2660), 259 (2790) and 266 (1970). This, together with the nmr spectrum of **12** which is compared with the spectra of pyridine and ethyl 2-picolonate in Table I, indicates little or no d_π–p_π bonding to be present in the phosphonate.[17–19]

TABLE I

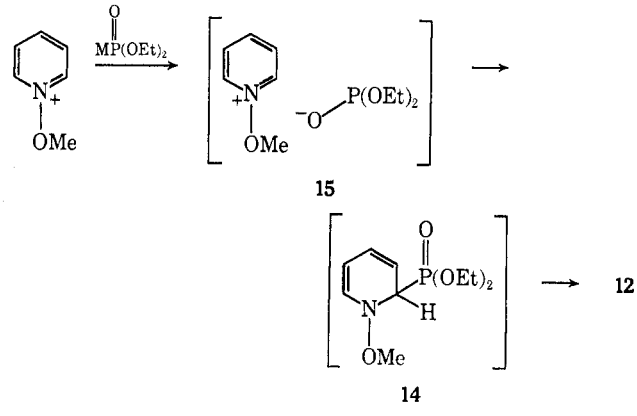
NMR CHEMICAL SHIFTS OF PYRIDINES[a]

	δ, H (3)	δ, H (4)	δ, H (5)	δ, H (6)
Pyridine	7.06	7.36	7.06	8.50
Ethyl 2-picolonate	8.12	7.87	7.50	8.75
12	8.10	8.02	7.65	8.88

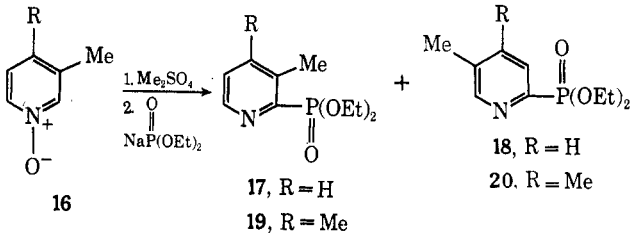
[a] 20% solutions in CCl_4.

The ester was readily hydrolyzed (18% HCl) to the corresponding pyridinephosphonic acid which was obtained as a high melting solid. The diethyl ester readily formed a methiodide and a low melting picrate. Various alternate routes to diethyl pyridine-2-phosphonate were examined with little success. 2-Bromopyridine heated with triethyl phosphite in presence of copper gave a 1% conversion to phosphonate **12**.[20] Attempted direct 1,2-nucleophilic addition of diethyl sodiophosphonate to pyridine gave no pyridine phosphonate as determined by glc analysis.

The reaction of cyanide ion on *N*-alkoxypyridinium salts yields both 2-cyano-and 4-cyanopyridine in ratios varying from 17 to 0.35 depending on factors such as reaction temperature, solvent, and pH.[15] In the reaction of the phosphonate anion, however, exclusive 2 substitution has been observed under all conditions as determined by gas chromatography and nmr spectra. The exclusive 2 substitution suggests that a dipolar complex such as depicted in **15** precedes the dihydropyridine intermediate (**14**). In this respect this reaction resembles the reaction of aryl- and alkyllithiums with pyridines.[21] Resemblance is found too for alkyl substituted alkoxypyridinium salts; thus, 3-methylpyridine *N*-oxide



is converted into a mixture of diethyl 3-methylpyridine-2-phosphonate (**17**) and diethyl 5-methylpyridine-2-phosphonate (**18**) in a ratio of 6:1 and 3,4-dimethylpyridine *N*-oxide yields a mixture of diethyl 3,4-dimethylpyridine-2-phosphonate (**19**) and diethyl 4,5-dimethylpyridine-2-phosphonate (**20**) in a ratio of 3:1.[22] These ratios are readily determined from the nmr spectrum in which the 3-methyl (δ 2.70) is readily distinguished from the 5-methyl (δ 2.42) and confirmed by glc analysis. 2-Picoline, 4-picoline, and 4-*tert*-butylpyridine *N*-oxides all are converted into phosphonates by substitution at the 2 position.



The only example in which 4 substitution has been observed is in the attack of diethyl sodiophosphonate on *N*-methoxy-2,6-dimethylpyridinium methosulfate (**21**). This reaction was found to be considerably slower than the examples in which the pyridinium salt had an unsubstituted 2 position. The products from the reaction of **21** were 2,6-lutidine (**22**) (47%), 2,6-lutidine *N*-oxide (**23**) (6%), and diethyl 2,6-dimethylpyridine-4-phosphonate (**24**) (24%). Products **22** and **23** arise from attack of the nucleophile on hydrogen and carbon of the *N*-methoxy group, respectively, modes of attack previously observed for other nucleophiles such as mercaptide ions.[8,23] The nmr spectrum of **24** showed the expected resonances for the ethoxy and methyl groups while the C_3 and C_5 protons appeared as a doublet, δ 7.44, J_{PCH} = 13.5 Hz. Although splitting of the ortho

(15) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, pp 303–305.

(16) The pK_a of diethyl phosphonate has been estimated as 15 [P. R. Hammond, *J. Chem. Soc.*, 1365 (1962)]. This estimate may not be accurate since Moedritzer[12] found that the equilibrium mixture formed by addition of equimolar amounts of sodium ethoxide and dibutyl phosphonate contained 30% $NaP(=O)(OBu)_2$ and 70% $HP(=O)(OBu)_2$ (pK_a of EtOH is 15.9).

(17) For a discussion of d_π–p_π bonding in organosphosphorus compounds, see R. F. Hudson, "Structure and Mechanism in Organophorus Chemistry," Academic Press, New York, N. Y., 1965, pp 67–85.

(18) A contribution from d_π–p_π bonding would be reflected in a bathochromic shift in the uv spectrum: see, for example, C. E. Griffin, R. P. Peller, K. R. Martin, and J. A. Peters, *J. Org. Chem.*, **30**, 97 (1965).

(19) Deshielding of the ring protons and significant coupling between ring protons and phosphorus nucleus in the nmr would be an indication of d_π–p_π bonding. For a study of this type, see R. H. Kemp, W. A. Thomas, M. Gordon, and C. E. Griffin, *J. Chem. Soc. B*, 527 (1969).

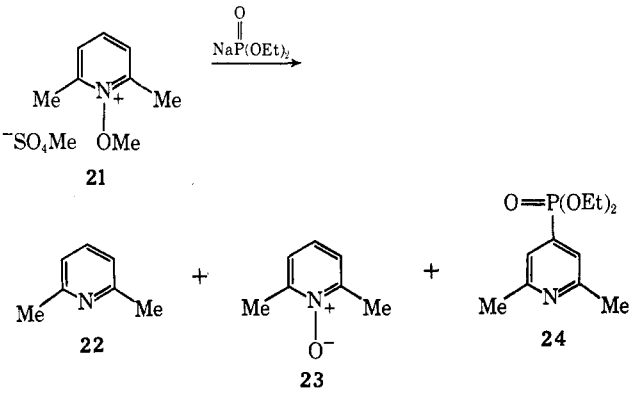
(20) *Cf.* P. Tavs and F. Korte, *Tetrahedron*, **23**, 4677 (1967).

(21) R. A. Abramovitch and J. G. Saha, in "Advances in Heterocylic Chemistry," Vol. 6, Academic Press, New York, N. Y., 1966, pp 274–292.

(22) The ratios are for distilled material.

(23) L. Bauer and L. A. Gardella, *J. Org. Chem.*, **28**, 1320, 1323 (1963); N. A. Coats and A. R. Katritzky, *ibid.*, **24**, 1836 (1959).

protons by phosphorus in this manner has been observed in aryl phosphine oxides (J = 10.5–11.5 Hz)[24a] and in aryl phosphonates (J = 12.2–12.9 Hz),[24b] the 4-phosphonate (**24**) is the only compound in the present study in which this coupling is clearly resolved.



Experimental Section

Melting points and boiling points are uncorrected. The elemental analyses were performed by Clark Analytical Laboratories and the staff of Dr. F. J. Ludwig, Petrolite Corporation, Physical Analytical Section. Nmr spectra were obtained with a Varian Associates A-60 spectrometer, using tetramethylsilane as an internal standard. Infrared spectra were determined on a Beckman IR-4 spectrometer.

The pyridine N-oxides used in this study were from Aldrich Chemical Co. or prepared from the corresponding pyridines by oxidation with hydrogen peroxide under standard conditions.[25] The N-oxides showed properties in agreement with literature reports with the following two exceptions.

3,5-Dimethylpyridine N-Oxide.—Oxidation of 3,5-dimethylpyridine gave the N-oxide, mp 103–105°, from benzene [lit.[26] bp 116–118° (0.1 mm)] which yielded a picrate, mp 139–140°, from ethanol (lit.[26] 138–139°).

3,4-Dimethylpyridine N-Oxide.—Oxidation of 3,4-dimethylpyridine gave the N-oxide, mp 137–138°, from benzene (lit.[27] 85°) which yielded a picrate, mp 145–147°, from ethanol (lit. 149°).

Diethyl Pyridine-2-phosphonate (12).—n-Butyllithium (23% in hexane) (63 ml, 0.15 mol) was added dropwise to diethyl phosphonate (25 g, 0.18 mol) at −20 to −30° during 2 hr. To the resulting diethyl lithiophosphonate was added N-methoxypyridinium methosulfate[3] [from pyridine N-oxide (14.3 g, 0.15 mol) and dimethyl sulfate (18.9 g, 0.15 mol)] in diethyl phosphonate (40 ml) in 1 hr at −15°. The reaction mixture was stirred at room temperature overnight and water (100 ml) was added. The mixture was extracted with chloroform (three 75-ml portions) and the organic extract separated into neutral and basic fractions in the conventional manner by extraction (4 N HCl), basification, and reextraction with chloroform. The basic portion was distilled yielding diethyl pyridine-2-phosphonate,[7] 22.9 g (67%), bp 105–112° (0.08 mm). Redistillation gave an analytically pure sample, bp 96–97° (0.03 mm): nmr (neat) δ 1.33 (t, 6, J = 7 Hz, CH_3CH_2O), 4.32 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.66–8.95 (m, 4, ArH); ir (liquid film) 1260 (P=O), 1030 and 970 cm^{-1} (POC); uv max (EtOH) 210 nm (ε 6000), 254 (2660), 259 (2790), and 266 (1970).

Anal. Calcd for $C_9H_{14}NO_3P$: C, 50.23, H, 6.51; N, 6.51; P, 14.42. Found: C, 50.20; H, 6.98; N, 5.90; P, 14.70.

Upon warming in ethanol with picric acid **12** formed a picrate on cooling. Recrystallization from ethanol gave the pure picrate, mp 86–87°.

Anal. Calcd for $C_{15}H_{17}N_4O_{10}P$: C, 40.54; H, 3.83; N, 12.61; P, 6.98. Found: N, 11.99; P, 6.97.

Pyridine-2-phosphonic Acid.—Diethyl pyridine-2-phosphonate (**12**) (5 g) was heated under reflux for 7 hr with 18% HCl (50 ml). Upon evaporation of the solution under reduced pressure, a colorless oil was obtained. Trituration with ethanol yielded a white solid which after recrystallization from aqueous ethanol gave pyridine-2-phosphonic acid, 3.1 g (75%), mp 224–227°.

Anal. Calcd for $C_5H_6NO_3P$: C, 37.74; H, 3.77; N, 8.80; P, 19.50. Found: C, 38.05, 38.09; H, 3.82, 3.92; N, 8.97; P, 17.57.

Diethyl 6-Methylpyridine-2-phosphonate.—Sodium (11.5 g, 0.5 g-atom) was dissolved in diethyl phosphonate (100 g) at 20–40°. To this solution was added a solution of N-methoxypyridinium methosulfate (0.5 mol) [from 2-picoline N-oxide (54.5 g, 0.5 mol) and dimethyl sulfate (63 g, 0.5 mol)] in diethyl phosphonate (30 ml) at 10–20° during 70 min. After stirring overnight at room temperature, the work-up procedure described for **12** was carried out. Distillation gave diethyl 6-methylpyridine-2-phosphonate, 33.7 g (30%), bp 125–127° (0.1 mm). Redistillation gave an analytically pure sample, bp 140° (1.5 mm): nmr (neat) δ 1.33 (t, 6, J = 7 Hz, CH_3CH_2O), 2.60 (s, 3, CH_3Ar), 4.30 (quintet, 4 J = 7 Hz, CH_3CH_2O), 7.5–8.0 (m, 3, ArH); uv max (EtOH) 264 nm (ε 3975) and 272 (2920).

Anal.[28] Calcd for $C_{10}H_{16}NO_3P \cdot H_2O$: C, 48.58; H, 7.29; N, 5.69; P, 12.55. Found: C, 48.99; H, 7.18; N, 5.80; P, 12.95.

6-Methylpyridine-2-phosphonic Acid.—Diethyl 6-methylpyridine-2-phosphonate (4 g) was heated under reflux with 18% HCl (40 ml) for 6 hr. Evaporation of the aqueous acid and trituration of the resulting oil gave a solid 1.1 g (37%), Recrystallization from aqueous ethanol gave 6-methylpyridine-2-phosphonic acid, mp 277–280° dec.

Anal. Calcd for $C_6H_8NO_3P$: C, 41.62; H, 4.62; N, 8.09; P, 17.92; mol wt, 173. Found: C, 41.38; H, 4.72; N, 7.30; P, 17.91; mol wt, 174 (KOH titration).

Diethyl 4-Methylpyridine-2-phosphonate.—This phosphonate was prepared in 55% yield by the procedure described for diethyl 6-methylpyridine-2-phosphonate: bp 109–112° (0.05 mm); nmr (neat) δ 1.26 (t, 6, J = 7 Hz, CH_3CH_2O), 2.42 (s, 3, CH_3Ar), 4.28 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.45 (m, 1, ArH at C_5), 7.90 (m, 1, ArH at C_3), 8.73 (m, 1, ArH at C_6).

Anal.[28] Calcd for $C_{10}H_{16}NO_3P \cdot H_2O$: C, 48.58; H, 7.29; N, 5.69; P, 12.55. Found: C, 48.53, 48.42; H, 7.34, 7.17; N, 6.0; P, 13.16.

4-Methylpyridine-2-phosphonic Acid.—Hydrolysis of diethyl 4-methylpyridine-2-phosphonate (11 g) with 18% HCl (120 ml) yielded after crystallization from aqueous ethanol 4-methylpyridine-2-phosphonic acid (7.2 g) (86%), mp 272–276° dec.

Anal. Calcd for $C_6H_8NO_3P$: C, 41.62; H, 4.62; N, 8.09; P, 17.92; mol wt, 173. Found: C, 41.65; H, 4.63; N, 8.09; P, 16.95; mol wt, 172.6 (KOH titration).

Reaction of N-Methoxy-3-methylpyridinium Methosulfate with Diethyl Sodiophosphonate.—The procedure described for diethyl 6-methylpyridine-2-phosphonate was used. Distillation gave a mixture of diethyl 3-methylpyridine-2-phosphonate (**17**) and diethyl 5-methylpyridine-2-phosphonate (**18**) in 48% yield: bp 100–111° (0.1 mm); nmr (neat) δ 1.36 (t, 6, J = 7 Hz, CH_3CH_2O) 2.42 (s, 3/7, CH_3Ar), 2.70 (s, 18/7, CH_3Ar at C_3), 4.32 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.4–7.95 (m, 2, ArH at C_4, C_5, and C_3), 8.68 (m, 1, ArH at C_6). From the peaks at δ 2.42 and 2.70 the ratio of **17** to **18** is 6:1. Glc confirmed this ratio with the 3-methyl isomer eluting before the 5-methyl isomer. Redistillation gave pure diethyl 3-methylpyridine-2-phosphonate, bp 109–110° (0.07 mm).

Anal.[28] Calcd for $C_{10}H_{16}NO_3P \cdot H_2O$: C, 48.58; H, 7.29; N, 5.69; P, 12.55. Found: C, 48.20, 48.03, 48.17; H, 7.06, 7.24, 7.07; N, 5.85; P, 13.54.

3-Methylpyridine-2-phosphonic Acid.—Diethyl 3-methylpyridine-2-phosphonate (5 g) was heated under reflux with 18% HCl (60 ml) for 6 hr. Evaporation of the aqueous acid and trituration of the resulting oil with ethanol–ether gave a solid which after recrystallization from aqueous ethanol gave 3-methylpyridine-2-phosphonic acid: 2.7 g (65%); mp 279–282°; nmr (D_2O) δ 2.73 (s, 3, CH_3Ar), 7.8–8.8 (m, 3, ArH).

Anal. Calcd for $C_6H_8NO_3P$–H_2O: C, 37.70; H, 5.24; N, 7.33; P, 16.23; mol wt, 191. Found: C, 37.16; H, 4.77; N, 7.20; P, 16.10; mol wt 186 (KOH titration).

Diethyl 3,5-Dimethylpyridine-2-phosphonate.—Following the procedure described for **12**, N-methoxy-3,5-dimethylpyridinium

(24) (a) C. E. Griffin, *Tetrahedron*, **20**, 2399 (1964); (b) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).

(25) Reference 15, pp 24–26.

(26) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 4953 (1960).

(27) E. Profft and G. Schultz, *Arch. Pharm.* (*Weinheim*), **294**, 292 (1961).

(28) Several phosphonate esters were hygroscopic and formed hydrates. Before analysis these esters were stored overnight in a desiccator (magnesium perchorate desiccant) under vacuum.

methosulfate was reacted with diethyl lithiophosphonate. Diethyl 3,5-dimethylpyridine-2-phosphonate was obtained in 54% yield by distillation: bp 107° (0.03 mm); nmr (neat) δ 1.33 (t, 6, J = 7 Hz, CH_3CH_2O), 2.32 (s, 3, CH_3Ar at C_5), 2.63 (s, 3, CH_3Ar at C_3), 4.25 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.52 (d, 1, ArH at C_4), 8.45 (s, 1, ArH at C_6).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.17; H, 7.35; N, 5.47; P, 12.88.

3,5-Dimethylpyridine-2-phosphonic Acid.—Hydrolysis of diethyl 3,5-dimethylpyridine-2-phosphonate (3 g) as described in previous examples yielded, after crystallization from aqueous ethanol, 3,5-dimethylpyridine-2-phosphonic acid, 1.2 g (54%), mp >300°.

Anal. Calcd for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49; P, 16.58; mol wt, 187. Found: C, 44.16; H, 5.62; N, 7.60; P, 16.62; mol wt, 186 (KOH titration).

Diethyl 3,4-Dimethylpyridine-2-phosphonate (19) and diethyl 4,5-Dimethylpyridine-2-phosphonate (20).—The procedure described for diethyl pyridine-2-phosphonate (12) was used. Distillation gave a mixture of 19 and 20 (47.5%): bp 125–126° (0.05 mm); nmr (neat) δ 1.33 (t, 6, J = 7 Hz, CH_3CH_2O), 2.30 (s, 15/4, CH_3Ar at C_4 and CH_3Ar at C_4 in 20), 2.59 (s, 9/4, CH_3-Ar at C_3 in 19), 4.27 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.30 (d, 3/4, ArH at C_5 in 19), 7.76 (d, 1/4, ArH at C_3 in 20), 8.50 (d, 1, ArH at C_6). From both ArH and $ArCH_3$ ratio of 19 to 20 is 3:1.

Anal.[28] Calcd for $C_{11}H_{18}NO_3P \cdot 1/2H_2O$ (mixture of 19 and 20): C, 52.38; H, 7.54; N, 5.56; P, 12.30. Found: C, 52.82, 52.75; H, 7.56, 7.86; N, 5.59; P, 12.69.

Diethyl 2,6-Dimethylpyridine-4-phosphonate (24).—*n*-Butyllithium (23% in hexane) (87 ml, 0.2 mol) was added dropwise during 1.25 hr at −5–0° to diethyl phosphonate (60 g, 0.45 mol). To the resulting diethyl lithiophosphonate was added solid *N*-methoxy 2,6-dimethylpyridinium methosulfate [from 2,6-dimethylpyridine *N*-oxide (24.6 g, 0.2 mol) and dimethylsulfate (25.2 g, 0.2 mol)] portionwise during 2 hr at 5–15°. The mixture was stirred at room temperature overnight and heated at 70° for 2 hr. After cooling, water (150 ml) was added and the organic portion extracted into chloroform (three 100-ml portions). The basic portion was obtained by extraction of the chloroform solution with 3 *N* hydrochloric acid, basification, reextraction with chloroform, and evaporation. Distillation of the residue gave 2,6-dimethylpyridine [10 g (47%), bp 59–61° (70 mm)], and two further fractions [(a) bp 70–95° (0.2 mm) (0.7 g), and (b) bp 95–98° (0.2 mm) (13.5 g)]. Glc analysis indicated fraction a to consist of 2,6-dimethylpyridine (0.1 g), 2,6-dimethylpyridine *N*-oxide (0.5 g), and diethyl 2,6-dimethylpyridine-4-phosphonate (0.1 g) and fraction b to consist of 2,6-dimethylpyridine *N*-oxide (0.6 g) and diethyl 2,6-dimethylpyridine-4-phosphonate (12.6 g). The yield of phosphonate is 24% and the yield of *N*-oxide is 6%. Redistillation of fraction b gave pure phosphonate (24): bp 105° (0.2 mm); nmr (neat) δ 1.32 (t, 6, J = 7 Hz, CH_3CH_2O), 2.55 (s, 6, CH_3Ar), 4.20 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.44 (d, 2, J = 13.5 Hz, ArH).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: N, 5.61; P, 12.88.

2,6-Dimethylpyridine-4-phosphonic Acid.—Diethyl 2,6-dimethylpyridine-4-phosphonate (24) (4 g) was heated under reflux with 18% HCl (50 ml) for 5 hr. Evaporation of the aqueous acid, trituration with ethanol, and recrystallization from aqueous ethanol yielded pure 2,6-dimethylpyridine-4-phosphonic acid, 2 g (65%), mp >300°.

Anal. Calcd for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49; P, 16.58. Found: C, 44.48; H, 5.42; N, 7.33; P, 16.40.

Registry No.—12, 23081-78-9; 12 (picrate), 26384-80-5; 17, 26384-81-6; 18, 26384-83-8; 19, 26384-82-7; 20, 26384-84-9; 24, 26384-85-0; pyridine-2-phosphonic acid, 26384-86-1; diethyl 6-methylpyridine-2-phosphonate, 26384-87-2; 6-methyl-2-phosphonic acid, 26384-88-3; diethyl 4-methylpyridine-2-phosphonate, 26384-89-4; 4-methylpyridine-2-phosphonic acid, 26384-90-7; 3-methylpyridine-2-phosphonic acid, 26384-91-8; diethyl-3,5-dimethylpyridine-2-phosphonate, 26384-92-9; 3,5-dimethylpyridine-2-phosphonic acid, 26384-93-0; 2,6-dimethylpyridine-4-phosphonic acid, 26394-19-4.

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New Pseudoguaianolides from *Hymenoxys* Species. A New Type of Lactone Closure[1,2]

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Hymenoxys linearifolia Hook. afforded the flavone hymenoxin and two new pseudoguaianolides, linearifolin A and B, whose structure and stereochemistry has been inferred. Linearifolin B contains a δ-lactone ring closed to C-9 of the pseudoguaiane skeleton. *H. acaulis* (Pursh) K. F. Parker yielded 3,3′-dimethoxy-4′,5,7-trihydroxyflavone and the previously known pseudoguaianolide fastigilin C whose stereochemistry is discussed. *H. subintegra* Cockll. gave the modified pseudoguaianolide psilotropin and *H. rusbyi* (Gray) Cockll. psilotropin, the pseudoguaianolide glucoside paucin and the flavone pectolinarigenin.

In an earlier paper[3] we reported the isolation and structure determination of sesquiterpene dilactones and lactone glycosides from several *Hymenoxys* species. We now describe the results of our examinations of *H. linearifolia* Hook., *H. acaulis* (Pursh) K. F. Parker, *H. subintegra* Cockll., and *H. rusbyi* (Gray) Cockll.

Extraction of *H. linearifolia* Hook. yielded the flavone hymenoxin (5,7-dihydroxy-3′,4′,6,8-tetramethoxyflavone) previously isolated[4] from *H. scaposa* DC and two new isomeric sesquiterpene lactones which we have named linearifolin A and B.

Linearifolin A, $C_{20}H_{24}O_6$, mp 187–188°, $[\alpha]D$ −90.0°, exhibited uv absorption at 218 nm (ε 22,500), the high intensity suggesting the presence of at least two chromophores. The ir spectrum indicated the presence of an α,β-unsaturated γ-lactone (1765, 1649 cm^{-1}), a hydroxyl group (3665, 3415 cm^{-1}), an α,β-unsaturated cyclopentenone (1711, 1580 cm^{-1}) of the type found in helenalin[5] and ambrosin,[6] and an unsaturated conju-

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