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HETEROCYCLIC PHOSPHONIC ACIDS. II

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As part of a program designed to make available for biological testing phosphonic acids containing heterocyclic systems (1) we turned our attention to derivatives bearing formal relations to thiamine and niacin type structures. Since 2-(4-methyl-5-thiazolyl)ethyl pyrophosphoric acid can inhibit cocarboxylase activity, 2-(4-methyl-5-thiazolyl)ethylphosphonic acid was prepared *via* its butyl ester by the Nylen reaction (2). This reaction could not be effected with the other moiety of thiamine, 2-methyl-4-aminopyrimidyl-5-methyl bromide. However, condensation of diethyl phosphite with 2-ethylmercapto-4-formyl-6-hydroxypyrimidine (3) in the presence of triethylamine gave diethyl α-hydroxy-α-[4-(2-ethylmercapto-6-hydroxy)pyrimidyl]-methylphosphonate which suffered cleavage of the thio ether group on acid hydrolysis and furnished α-hydroxy-α-[4-(2,6-dihydroxy)-pyrimidyl]-methylphosphonic acid.

Another pyrimidine derivative was obtained by hydrolyzing 4-hydroxy-6-diethoxymethylpyrimidine (4) with dilute acetic acid to 4-hydroxy-6-formylpyrimidine and condensing this compound with diethyl phosphite. The resulting ester was hydrolyzed readily to α-hydroxy-α-[4-(6-hydroxy)-pyrimidyl]-methylphosphonic acid. In a similar way, pyridine-2- and -4-aldehyde, and isoquinoline-3-aldehyde were converted to the respective α-hydroxyphosphonate esters (Table I). Hydrolysis of these esters furnished the corresponding water-soluble α-hydroxyphosphonic acids, of which α-(4-pyridyl)- and α-(3-isoquinolyl)-α-hydroxymethylphosphonic acids could be isolated and characterized.

Kosolapoff (5) has described diethyl acridine-9-phosphonate, and the corresponding free acid, as the only recorded compounds in which a phosphonate group, directly attached to a nitrogen heterocycle, had been built onto a preexisting ring from a heterocyclic halide by the Michaelis-Arbuzov reaction. The Nylen reaction did not work with 9-chloroacridine (5). In an effort to prepare a pyridinephosphonic acid from a reactive halogenopyridine, both the Michaelis-Arbuzov and the Nylen reactions were tried with 2-chloro- and 2-bromo-pyridine but no conversion seemed to take place. By contrast, 2-chloroquinoline and 2-chlorolepidine reacted with sodium dibutyl phosphite, and the resulting oily esters were hydrolyzed readily to 2-quinolyl- and 2-lepidyl-phosphonic acid, respectively. 2-Chloro-4,8-dimethylquinoline could not be induced to undergo the Nylen reaction.

None of the phosphonate esters described in this article exhibited noteworthy pharmacological properties. Weak antifungal activity was found for some of the α-hydroxyphosphonate esters.

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TABLE I

HETEROCYCLIC DIETHYL α-HYDROXYPHOSPHONATES AND α-HYDROXYPHOSPHONIC ACIDS

RCHOHPO(OR')$_2$		Appearance	M.p., °C	Yield, %	Solvent of Crystallization	Molecular Composition	Calc'd		Found	
R	R'						C	H	C	H
4-Pyridyl	C_2H_5	Oil								
•HCl		Flakes	160–161		EtOAc–EtOH	$C_{10}H_{17}ClNO_4P$	42.64	6.08	42.57	6.03
•Picrate		Yellow needles	160–162[a]		EtOH	$C_{16}H_{19}N_4O_{11}P$	40.51	4.04	40.28	4.22
	H	Flakes[b]	226–227[a]	47		$C_6H_{10}NO_6P$	34.79	4.85	34.52	4.61
		Flakes[c]	229–230[a]		H_2O	$C_6H_{12}NO_6P$	32.01	5.37	31.77	5.09
2-Pyridyl	C_2H_5	Oil								
•Picrate		Yellow plates	142.5–143.5[a]			$C_{16}H_{19}N_4O_{11}P$	40.51	4.04	40.17	4.11
3-Isoquinolyl	C_2H_5	Oil								
•HBr		Flakes	139–139.5[a]		EtOH–Et_2O	$C_{14}H_{19}BrNO_4P$	44.61	5.09	44.40	4.99
	H	Colorless	238–239[a]	41.5	H_2O	$C_{10}H_{10}NO_4P$	50.21	4.22	50.12	4.41
4-(2-Ethylmercapto-6-hydroxy)pyrimidyl	C_2H_5	*Prisms*	145–147	82.5	EtOAc–EtOH	$C_{11}H_{19}N_2O_4PS$	40.86	5.93	41.01	5.84
4-(2,6-dihydroxy)-pyrimidyl	H	Colorless	204–205.5[a,e]	59	H_2O[e]	$C_5H_7N_2O_6P$	27.04	3.18	26.65	3.34
4-(6-Hydroxy)pyrimidyl	C_2H_5	Flakes	183–183.5	94	EtOH	$C_9H_{15}N_2O_5P$	41.22	5.77	41.16	5.77
	H	Flakes	226[a]	84	H_2O	$C_5H_7N_2O_5P$	29.14	3.42	29.07	3.50

[a] Melted with decomposition. [b] Monohydrate, after drying the dihydrate at 110° (1 mm.) for 48 hours. [c] Dihydrate, after drying at 78° (1 mm.) for 2 hours. [d] Crystallized by slow (1 month) evaporation of the solution of the oily ester in ethanolic picric acid. [e] This sample had been dried at 150° (1 mm.) for 20 hours. The material crystallizing from water melted at 192–194° (dec.).

EXPERIMENTAL[2]

Di-n-butyl 2-(4-methyl-5-thiazolyl)-ethylphosphonate. To a solution of 10.8 g. (0.05 mole) of sodium di-*n*-butyl phosphite (6) in 200 ml. of ligroin was added 11 g. (0.053 mole) of freshly distilled 4-methyl-5-(2-bromoethyl)thiazole (7) and the mixture was stirred and refluxed overnight. It was worked up as usual (6). Fractionation at 0.2–0.3 mm. furnished 3.4 g. of a fore-run, b.p. 60–64°; 9 g. of the desired ester, b.p. 152° (0.3 mm.) and 9.5 g. of a high-boiling residue. The oily ester was characterized as the *picrate*, which melted at 128–129° after crystallization from ethanol.

Anal. Calc'd for $C_{14}H_{26}NO_3PS \cdot C_6H_3N_3O_7$: C, 43.79; H, 5.33.
Found: C, 43.71; H, 5.43.

Hydrolysis of the ester with refluxing concentrated hydrochloric acid overnight, evaporation to dryness, and crystallization of the residue from ethanol-ether gave colorless crystals of *2-(4-methyl-5-thiazolyl)ethylphosphonic acid hydrochloride*, m.p. 155–156° (in a sealed tube in a hydrogen chloride atmosphere).

Anal. Calc'd for $C_6H_{11}ClNO_3PS$: C, 29.64; H, 4.55.
Found: C, 27.85; H, 4.73.

Equivalent weight titrations of this acid were unsuccessful due to its low pk_a.

Aldehydes for the condensation with diethyl phosphite. Pyridine-2- and -4-aldehyde were commercial products. Isoquinoline-3-aldehyde was obtained through the courtesy of Dr. James W. Wilson, III, of Smith, Kline, & French Laboratories. The pyrimidine aldehydes were obtained as follows:

2-Ethylmercapto-4-formyl-6-hydroxypyrimidine. This aldehyde was prepared by the method of Johnson and Schroeder (3). A solution of 15 g. (0.058 mole) of 2-ethylmercapto-4-diethoxymethyl-6-hydroxypyrimidine in 150 ml. of 50% acetic acid was evaporated on a steam-bath to a yellow crystalline residue. Recrystallization from ethyl acetate gave 8.14 g. (76%) of pale yellow needles, m.p. 161–162°. The literature (3) lists m.p. 148–149°.

Anal. Calc'd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38.
Found: C, 45.28; H, 4.06.

The *phenylhydrazone*, prepared in ethanolic-acetic acid solution, crystallized from ethanol as long yellow blades, m.p. 246–248° (dec.).

Anal. Calc'd for $C_{13}H_{14}N_4OS$: C, 56.91; H, 5.14.
Found: C, 56.72; H, 4.90.

4-Hydroxy-6-diethoxymethylpyrimidine. A solution of 57.5 g. (0.25 mole) of 2-mercapto-4-hydroxy-6-diethoxymethylpyrimidine (4) in 900 ml. of water and 60 ml. of 28% ammonium hydroxide was stirred and refluxed with 225 g. of (water-moist) nickel (8) for two hours. The nickel was filtered from the hot solution, washed with 200 ml. of hot ethanol, and the filtrate was concentrated until brown crystals appeared. Recrystallization from ethanol and from ethyl acetate yielded 44.2 g. (89%) of colorless needles, m.p. 123–124°.

Anal. Calc'd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12.
Found: C, 54.45; H, 7.04.

4-Hydroxy-6-formylpyrimidine. A solution of 23 g. (0.12 mole) of 4-hydroxy-6-diethoxymethylpyrimidine in 250 ml. of 50% acetic acid was evaporated on a steam-bath, and the residue recrystallized from acetic acid. The light-brown flakes weighed 10.0 g. (69.5%) and did not melt below 330°.

Anal. Calc'd for $C_5H_4N_2O_2$: C, 48.39; H, 3.25.
Found: C, 48.01; H, 3.42.

The *p-nitrophenylhydrazone* crystallized from ethanol as yellow flakes which did not melt below 275°.

Anal. Calc'd for $C_{11}H_9N_5O_3$: C, 50.96; H, 3.50.
Found: C, 50.89; H, 3.59.

Heterocyclic α-hydroxyphosphonate esters. General directions. To an ice-cold manually stirred mixture of 0.1 mole of the heterocyclic aldehyde and one tenth its weight of triethylamine was added 0.1 mole of diethyl phosphite at such a rate that the temperature generally

[2] All melting points are corrected.

did not rise above 30–50°. After completion of the addition, the mixture was heated on a steam bath for 1–2 hours. The oily reaction products were allowed to stand, or were triturated with ether in order to facilitate solidification. Oily esters were converted to their hydrohalides (in ether or acetone) or picrates (in ethanol).

Heterocyclic α-hydroxyphosphonic acids. General directions. The oily or solid α-hydroxyphosphonate esters were refluxed with five volumes of concentrated hydrochloric acid for three hours. In the case of the pyrimidine derivatives, the solutions were concentrated to dryness under reduced pressure, and the residual phosphonic acids were crystallized from water. With the pyridine and isoquinoline compounds, the acidic reaction mixture was neutralized to *p*H 7 with 33% sodium hydroxide solution, and the precipitated phosphonic acid was removed. If no solid precipitated, the neutralized solution was evaporated under reduced pressure, and the residue was crystallized from water.

2-Quinolylphosphonic acid. To a refluxing solution of 25.9 g. (0.12 mole) of sodium dibutyl phosphite in 150 ml. of dry xylene was added dropwise 13 g. (0.078 mole) of 2-chloroquinoline over a period of 45 minutes. After refluxing and stirring for five hours, the reaction mixture was washed with water, the xylene was removed, and the crude oily ester was hydrolyzed with an excess of concentrated hydrochloric acid. The cooled hydrolysate deposited 3.0 g. (28.5%) of colorless crystals which were recrystallized from 80 ml. of boiling water. The compound did not melt below 300°.

Anal. Calc'd for $C_9H_8NO_3P \cdot H_2O$: C, 47.60; H, 4.40; N, 6.16; P, 13.62.
Found: C, 48.18; H, 4.79; N, 6.23; P, 13.85.

2-Lepidylphosphonic acid. Starting with 15 g. (0.08 mole) of 2-chlorolepidine, a reaction was performed as described in the preceding experiment. Dibutyl 2-lepidylphosphonate (b.p. 218°/4.6 mm., yield, 7 g.) was a mobile yellow oil which on acid hydrolysis gave 4.4 g. (25%) of colorless phosphonic acid. Recrystallization from glacial acetic acid gave a material which did not melt below 300°.

Anal. Calc'd for $C_{10}H_{10}NO_3P$: C, 53.82; H, 4.52; N, 6.28; P, 13.88.
Found: C, 53.88; H, 4.59; N, 6.28; P, 13.98.

6-Diethylaminohexylphosphonic acid. A solution of 12.3 g. (0.05 mole) of 1-bromo-6-diethylaminohexane in 100 ml. of ligroin was added to a solution of 2.16 g. (0.1 mole) of sodium di-*n*-butyl phosphite in 300 ml. of ligroin, and the mixture was stirred and refluxed for 22 hours. After washing with water and evaporation of the ligroin, it was fractionated and gave 13.7 g. (39%) of di-*n*-butyl 6-diethylaminohexylphosphonate, b.p. 141–142° (0.08 mm.), 155° (1.0 mm.).

Using a Fisher *Titrimeter*, the equivalent weight was determined; Calc'd, 349; Found, 337, 347; pH_B 5.6 x 10^{-5}.

Two grams of the ester was refluxed with 25 ml. of 37% hydrochloric acid overnight, the mixture was evaporated to dryness, and the residue was recrystallized from ethanol-ether. The colorless needles melted at 142–143.5°.

Anal. Calc'd for $C_{10}H_{25}ClNO_3P$: C, 43.88; H, 9.21; Equiv. weight, 91.2.
Found: C, 44.11; H, 9.05; Equiv. weight, 98.5.

SUMMARY

The synthesis of a number of pyridine, quinoline, isoquinoline, and pyrimidine derivatives containing phosphonic acid groups has been carried out.

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REFERENCES

(1) DAWSON AND BURGER, *J. Am. Chem. Soc.*, **74**, 5312 (1952).
(2) NYLEN, *Ber.*, **57**, 1023 (1924).
(3) JOHNSON AND SCHROEDER, *J. Am. Chem. Soc.*, **53**, 1989 (1931).
(4) JOHNSON AND CRETCHER, *J. Am. Chem. Soc.*, **37**, 2144 (1915).
(5) KOSOLAPOFF, *J. Am. Chem. Soc.*, **69**, 1002 (1947).
(6) KOSOLAPOFF, *J. Am. Chem. Soc.*, **67**, 1180 (1945).
(7) BUCHMAN AND RICHARDSON, *J. Am. Chem. Soc.*, **67**, 395 (1945).
(8) BROWN, *J. Soc. Chem. Ind.*, **69**, 353 (1950).