Reaction of 2-(2-Hydroxy-5-methoxyphenyl)benzothiazole in PPA.—A mixture of 0.4 g (1.55 mmol) of 2-(2-hydroxy-5-methoxyphenyl)benzothiazole and 60 g of PPA was heated at 170° for 15 hr. Work-up as above in A gave 2-(2,5-dihydroxyphenyl)benzothiazole, 0.12 g (30%), mp 193–196°. An infrared spectrum of the product was identical with that of 2-(2,5-dihydroxyphenyl)benzothiazole prepared from 5-hydroxysalicylic acid and *o*-aminothiophenol in PPA.

Registry No.—**4** (X = O), 835-64-3; **9**, 24978-46-9; 2-(2,5-dihydroxyphenyl)benzothiazole, 24978-47-0.

A Convenient Method of Esterification of Polyphosphonic Acids

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Unlike carboxylic acids, phosphonic acids cannot be esterified by direct reaction with alcohols. Esterification is usually accomplished by converting the phosphonic acid to the corresponding acid chloride which will react with an alcohol in the presence of base to yield the phosphonate ester.[2]

In the course of a recent study it became of interest to synthesize a series of esters from methylenediphosphonic acid (MDP). Siddall and Prohaska[3] have prepared tetra(3-methyl-2-butyl) methylenediphosphonate in 50% yield from methylenediphosphonic tetrachloride and the alcohol in the presence of pyridine. Methylenediphosphonic tetrachloride is also obtained in 50% yield[4] so that the overall conversion from MDP to its tetraalkyl ester proceeds in low yield and involves two rather difficult steps.[3,4]

This note describes a one-step method of esterification of MDP which results in 70–90% yields of the tetraalkyl esters. The method is not limited to MDP but has been shown to be applicable to esterifications of *vic*-tri- and tetraphosphonic acids as well as 1-hydroxy-1,1-diphosphonic acids.

Three literature reports led us to attempt the esterification of polyphosphonic acids with esters of orthoformic acid. Trialkyl orthoformates are known[5] to effect the esterification of carboxylic acids in up to 95% yield. Fitch[6] has prepared alkyl hypophosphites from hypophosphorous acid and trialkyl orthoformates. Finally a 1960 patent[7] describes the esterification of benzenephosphonic acid with triethyl orthoformate.

MDP was found to react at elevated temperatures with trialkyl orthoformates to yield tetraalkyl methylenediphosphonates, along with the corresponding alcohol and alkyl formate (eq 1). It was necessary to continuously remove the lower boiling alcohols and formates (reduced pressure is required when R = $C_{18}H_{37}$) so that higher reaction temperatures could be obtained. Tetramethyl, tetraethyl, tetraallyl, and tetrakis(octadecyl) methylenediphosphonates were successfully prepared *via* this procedure. Their ^{31}P nmr chemical shifts are given in Table I.

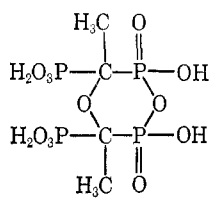
$$H_2O_3PCH_2PO_3H_2 + 4(RO)_3CH \xrightarrow{\Delta} R_2O_3PCH_2PO_3R_2 + 4ROH + 4HC(O)OR \quad (1)$$

To broaden the scope of this esterification method, the recently reported[8] vicinal tri- and tetraphosphonic acids were allowed to react with triethyl orthoformate. Esterification proceeded as described above and hexaethyl propane-1,2,3-triphosphonate and octaethyl butane-1,2,3,4-tetraphosphonate were isolated by distillation. In this case the polyphosphonic acid halides are unknown so that an alternative method of esterification is not available. Phosphorus nmr chemical shifts are given in Table I.

Another class of polyphosphonic acids for which the acid halides are unknown is the alkyl-1-hydroxy-1,1-diphosphonic acids. An attempt was made[9] to esterify ethane-1-hydroxy-1,1-diphosphonic acid with diazomethane. The tetramethyl ester was perhaps prepared initially but completely rearranged to the phosphate-phosphonate.[10a] Under the conditions used,[9] the tetramethyl ester of ethane-1-methoxy-1,1-diphosphonic acid always accompanied the phosphate–phosphonate in the final product.

Reaction of ethane-1-hydroxy-1,1-diphosphonic acid with trimethyl orthoformate was found to produce the corresponding tetramethyl ester which was isolated in about 70% yield by crystallization. This ester proved to be identical with authentic tetramethyl ethane-1-hydroxy-1,1-diphosphonate prepared by a combination of the methods of Fitch and Moedritzer[10a] and Pudovik, *et al.*[10b]

It is known[11] that ethane-1-hydroxy-1,1-diphosphonic acid can dimerize to a very stable cyclic condensate containing C–O–C and P–O–P linkages (compound I). This condensate was easily converted to the hexamethyl ester by reaction with trimethyl orthoformate. As reported elsewhere,[11] the ester was utilized in establishing the structure of I.



I

An attempt to esterify ethane-1-hydroxy-1,1,2-triphosphonic acid with trimethyl orthoformate resulted in partial esterification with concomitant rearrangement to the phosphate–diphosphonate as shown by ^{31}P nmr. To further characterize the course of the re-

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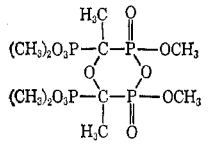
TABLE I

Compd	Registry no.	Bp/mm, (mp)	δ (^{31}P nmr)[a]	Calcd, % C	H	P	mol wt	Found, % C	H	P	mol wt[b]	% yield
$[(CH_3)_2O_3P]_2CH_2$	16001-93-7	87–90°/0.05	−23.0	25.9	6.1	26.7	232	25.9	6.2	26.7	235	70–90[c]
$[(C_2H_5)_2O_3P]_2CH_2$	1660-94-2	90–94°/0.1	−19.0	37.5	7.7	21.5	288	37.4	7.8	21.8	280	70–90[c]
$[(CH_2{=}CHCH_2)_2O_3P]_2CH_2$	25091-05-8	...[d]	−20.0	46.4	6.6	18.4	336	46.5	6.6	17.6	355	99[e]
$[(C_{18}H_{37})_2O_3P]_2CH_2$	25091-06-9	(60–62°)[f]	−19.5	73.9	12.8	5.2	1156	73.1	12.7	5.0	1110	86[e]
$(C_2H_5)_2O_3P{-}CH_2$ | $(C_2H_5)_2O_3P{-}CH$ | $(C_2H_5)_2O_3P{-}CH_2$	25091-07-0	170°/0.1	−28.5[g]	39.8	7.8	20.5	452	39.2	8.1	20.6	425	72
$(C_2H_5)_2O_3P{-}CH_2$ | $(C_2H_5)_2O_3P{-}CH$ | $(C_2H_5)_2O_3P{-}CH$ | $(C_2H_5)_2O_3P{-}CH_2$	25091-08-1	...[h]	−30.3[g]	39.9	7.7	20.6	603	39.8	7.6	20.6	580	79
$[(CH_3)_2O_3P]_3C(OH)CH_3$	15207-88-2	(67–70°)[i]	−22.0	27.4	6.1	23.7	262	27.3	6.1	24.9	265	70
	16218-84-1	(141–144°)[j]	−15.8[k] −6.5[k]	26.1	5.3	26.9	460	26.4	5.5	26.0	458	62

[a] Chemical shifts are reported in ppm shift from 85% H_3PO_4. [b] Average of three determinations. [c] Range of yields from several experiments. [d] CAUTION!! Attempted vacuum distillation of this material resulted in violent decomposition. Purification was accomplished by chromatography on acid-washed alumina. [e] Based on crude yield of alcohol and formate. [f] Recrystallized from hexane–petroleum ether. [g] ^{31}P nmr resonances for "end" and "middle" phosphonate groups have been shown to be degenerate. See ref 8. [h] It was necessary to molecularly distill the crude ester. [i] Recrystallized from acetone–hexane. [j] Recrystallized from ethyl acetate–ethyl ether. [k] The resonance at −15.8 ppm has been shown to arise from the dangling phosphonate groups, and that at −6.5 ppm from phosphorus atoms in the ring. See ref 11.

arrangement, this esterification was driven to completion and the resulting product hydrolyzed to the acid. After neutralization with base, the tetrasodium salt of ethane-1-hydroxy-1,2-diphosphonic acid was isolated by crystallization. Structure elucidation was accomplished *via* ^{31}P and ^{1}H nmr decoupling experiments. The probable reaction pathway is shown in Scheme I.

SCHEME I

$$H_2O_3PCH_2C(OH)(PO_3H_2)_2 \xrightarrow{(CH_3O)_3CH} (CH_3)_2O_3PCH_2C(OH)[PO_3(CH_3)_2]_2 \xrightarrow{\Delta} (CH_3)_2O_3PCH_2CH[OPO_3(CH_3)_2][PO_3(CH_3)_2] \xrightarrow[H_2O]{H^+} H_2O_3PCH_2CH(OH)(PO_3H_2) + H_3PO_4$$

Experimental Section[12]

Methylenediphosphonic acid (MDP) was prepared by pyrolyzing (180°) a sample of tetraisopropyl methylenediphosphonate.[13,14] Propane-1,2,3-triphosphonic acid and butane-1,2,3,4-tetraphosphonic acid were prepared by literature methods[8] as were ethane-1-hydroxy-1,1-diphosphonic acid,[15] its condensate (I),[11] and ethane-1-hydroxy-1,1,2-triphosphonic acid.[16] Trimethyl and triethyl orthoformate were purchased from the Aldrich Chemical Company. Triallyl and tris(octadecyl) orthoformate were purchased from Kay–Fries Chemicals.

All esterifications were performed by combining the polyphosphonic acid with an excess of trialkyl orthoformate, heating, and removing alcohol and alkyl formate by distillation as they were formed. The preparation of tetramethyl methylenediphosphonate is considered typical and is given in detail. Yields, physical measurements, and analytical data for the other esters prepared in this study are collected in Table I.

Tetramethyl Methylenediphosphonate.—MDP (1 equiv) and trimethyl orthoformate (6 equiv) were combined and heated to reflux for 1 hr. The acid was not significantly soluble in trimethyl orthoformate necessitating rapid stirring to assure intimate contact of the two phases. Excess trimethyl orthoformate (100%) was added and the methyl formate and methanol, formed *in situ*, were continuously removed by distillation thereby allowing the reaction temperature to rise. Heating was continued until only one phase remained and trimethyl orthoformate began to distill (bp 99–101°). Removal of excess trimethyl orthoformate left a colorless liquid. This liquid was vacuum distilled to yield pure tetramethyl methylenediphosphonate.

Attempted Preparation of Hexamethyl Ethane-1-hydroxy-1,1,2-triphosphonate.—The reaction temperature was not allowed to exceed 90° in this preparation. Even after extended heating at this temperature esterification was incomplete as evidenced by ^{31}P and ^{1}H nmr. Nevertheless, approximately 18% of the triphosphonate had rearranged to the phosphate–diphosphonate.

Tetrasodium Ethane-1-hydroxy-1,2-diphosphonate.—The above reaction was repeated without temperature control. The maximum reaction temperature (105°) was maintained for 10 hr. After removing volatile products, concentrated HCl was added and the mixture was refluxed 6 hr. Excess HCl was removed and 4 equiv of NaOH (based on starting acid) was added. The title compound was precipitated by addition of methanol and was recrystallized from methanol–water, yield 61%.

Anal. Calcd for $C_2H_4O_7P_2Na_4$ (dihydrate): C, 7.3; P, 18.8; Na, 27.9; H_2O, 10.9. Found: C, 7.6; P, 19.2; Na, 29.0; H_2O, 10.7.

Registry No.—MDP, 1984-15-2.

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(12) All melting and boiling points reported herein are uncorrected. Elemental analyses were carried out in these laboratories. Phosphorus nmr spectra were recorded on a Varian HR-60 spectrometer operating at 24.3 MHz. Chemical shifts are accurate to ±0.5 ppm and are measured from an external 85% H_3PO_4 reference. Molecular weights were determined on a Model 302 Mechrolab osmometer.

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