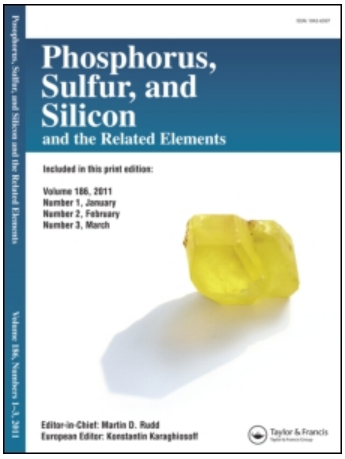

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Maier, Ludwig and Crutchfield, Marvin M.(1978) 'ORGANIC PHOSPHORUS COMPOUNDS 70 PREPARATION AND PROPERTIES OF NEW PHOSPHORUS CONTAINING CHELATING AGENTS FOR CALCIUM AND MAGNESIUM IONS', Phosphorus, Sulfur, and Silicon and the Related Elements, 5: 1, 45 — 51
To link to this Article: DOI: 10.1080/03086647808069861
URL: http://dx.doi.org/10.1080/03086647808069861

Phosphorus and Sulfur
1978, Vol. 5, pp. 45–51

ORGANIC PHOSPHORUS COMPOUNDS 70

PREPARATION AND PROPERTIES OF NEW PHOSPHORUS CONTAINING CHELATING AGENTS FOR CALCIUM AND MAGNESIUM IONS[1]

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(*Received April 21st 1977*)

Dedicated to Professor Martin Schmeisser on the occasion of his 65th birthday.

Several phosphonic acids of the type $H_2O_3PCH_2OCHRCO_2H$, R = H, CH_3, CO_2H; $[H_2O_3P(CH_2)_x]_2Y$, x = 1, 2; Y = O, S; and $[o\text{-}H_2O_3P(CH_2)]_2C_6H_4$; have been synthesized and their capacity to chelate with calcium has been determined.

The chelating power of nitrilotriacetic acid towards calcium ions is increased when the carboxy groups are replaced by phosphonic acid groups. Thus the stability constant of the Ca-complex ($-\log \beta Ca_1$) of nitrilotriacetic acid is 6.41 whereas that of nitrilotri(methylenephosphonic acid), $N(CH_2PO_3H_2)_3$, is 6.68. A further increase to 6.8[2] in the stability constant of the Ca-complex is achieved when in the latter compound PO replaces nitrogen.

It seemed of interest to synthesize chelating agents in which the bridging nitrogen is replaced by other atoms such as oxygen or sulfur and in which part or all of the carboxy-groups are replaced by the phosphonic acid groups.

A SYNTHESIS OF CHELATING COMPOUNDS

Ether formation by the reaction of an alcoholate with an alkyl halide is a well-known reaction in organic chemistry. This procedure was successfully employed for synthesizing the esters II, IV and VI:

$$(EtO)_2\overset{\overset{O}{\|}}{P}CH_2ONa + ClCH_2CO_2Et \rightarrow (EtO)_2\overset{\overset{O}{\|}}{P}CH_2OCH_2CO_2Et$$

II

$$(RO)_2\overset{\overset{O}{\|}}{P}CH_2ONa + BrC(CH_3)(CO_2Et)_2 \rightarrow (RO)_2\overset{\overset{O}{\|}}{P}CH_2OC(CH_3)(CO_2Et)_2$$

R = Et IV
R = *i*-Pr VI

When it was attempted, however, to cause α-bromomalonic ester to react in the same way, a complex reaction occurred and the expected product $(EtO)_2(O)PCH_2OCH(CO_2Et)_2$, could not be isolated. Obviously the acidic hydrogen of the malonic part was metallated by $(EtO)_2(O)PCH_2ONa$ and the product underwent further reaction.

On hydrolysis of the ester II with concentrated HCl mainly the acid III was formed. The ^{31}P-NMR spectrum indicated that the crude product contained some hydroxymethylphosphonic acid, $H_2O_3PCH_2OH$,

$$(EtO)_2\overset{\overset{O}{\|}}{P}CH_2OCH_2CO_2Et + 3HCl \rightarrow (HO)_2\overset{\overset{O}{\|}}{P}CH_2OCH_2CO_2H + [(HO)_2\overset{\overset{O}{\|}}{P}CH_2OH]$$

III

which was most probably the result of an ether cleavage reaction of II or III. Hydrolysis of the ester IV with

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concentrated HCl caused a decarboxylation at the same time and gave the acid V.

$$(EtO)_2P(O)CH_2OC(CH_3)(CO_2Et)_2 + 4HCl \rightarrow$$

IV

$$(HO)_2P(O)CH_2OCH(CH_3)CO_2H$$

V

Basic hydrolysis of VI with three equivalents of NaOH in alcoholic solution gave the half-ester VII:

$$(i\text{-PrO})_2P(O)CH_2OC(CH_3)(CO_2Et)_2 + 3NaOH \rightarrow$$

VI

$$NaO(i\text{-PrO})P(O)CH_2OC(CH_3)(CO_2Na)_2$$

VII

The free acid of VII could not be prepared by pyrolysis of VII. A thermographic analysis showed that on heating to 125°C VII loses 8.72% water and is then stable up to 250°C; by further heating to 340°C the weight loss is 21.84% where another inflection point occurs. By loss of propene only the weight loss would have been 12.48%. Above 360°C the compound decomposes completely.

The most commonly used methods for synthesizing phosphonates are the Michaelis–Arbuzov rearrangement and the Michaelis–Becker–Nylen reaction.[3] These two procedures were also successfully used for preparing compounds of the following types:

$$(EtO)_3P + ClCH_2CO_2Et \rightarrow (EtO)_2P(O)CH_2CO_2Et + EtCl$$

VIII

$$2(EtO)_3P + ClCH_2YCH_2Cl \rightarrow (EtO)_2P(O)CH_2YCH_2P(O)(OEt)_2 + 2EtCl$$

X, Y = O
XVI, Y = S

Interaction of $(EtO)_3P$ and $ClCH_2CO_2Et$ gave a high yield of the ester VIII.[4] The reaction with bis-(chloromethyl) ether had to be run under pressure at 170–180° in order to achieve a good conversion, while the reaction with bis(chloromethyl) thioether proceeded well under ordinary pressure at 170°.[5] For preparing ester X, bis-(bromomethyl) ether was previously employed.[6] A modified Arbuzov reaction was also successfully used for synthesizing bis-(2-phosphonylethyl) ether XII, while the corresponding thioether could not be made by this procedure. It was observed that bis-(2-chloroethyl) ether did not react with triethylphosphite, when the two compounds were re-

$$2(EtO)_3P + ClCH_2CH_2OCH_2CH_2Cl \rightarrow$$

$$(EtO)_2P(O)CH_2CH_2OCH_2CH_2P(O)(OEt)_2 + 2EtCl$$

XII

$$2(EtO)_3P + ClCH_2CH_2SCH_2CH_2Cl \not\rightarrow$$

$$(EtO)_2P(O)CH_2CH_2SCH_2CH_2P(O)(OEt)_2 + 2EtCl$$

fluxed for 22 hr; however, when 1 g of $NiCl_2$ was added as a catalyst and the reaction carried out in an autoclave at 170–220°, XII was formed in 33.8% yield. At the same time 2-phosphonylethyl-2-chloroethyl ether, $(EtO)_2(O)PCH_2CH_2OCH_2CH_2Cl$ XIII, was also isolated in 14.7% yield.

Previously ester XII as well as the corresponding thioether had been prepared by the Michaelis–Becker reaction.[5]

Hydrolysis of the esters XII and XIII with concentrated HCl under reflux gave the corresponding acids XIV and XV in high yield:

$$(EtO)_2P(O)CH_2CH_2OCH_2CH_2P(O)(OEt)_2 + 4HCl \rightarrow$$

XII

$$(HO)_2P(O)CH_2CH_2OCH_2CH_2P(O)(OH)_2$$

XIV

$$(EtO)_2P(O)CH_2CH_2OCH_2CH_2Cl + 2HCl \rightarrow$$

XIII

$$(HO)_2P(O)CH_2CH_2OCH_2CH_2Cl$$

XV

TABLE I
Ca-sequestering capacities of ligands at pH 10

Compound	mg $CaCO_3$/g ligand	mg P/g ligand	mg $CaCO_3$/100 mg P
1. $Na_2O_3PCH_2OCH_2PO_3Na_2$ (XI)	236.3	210.7	112.1
2. $Na_2O_3PCH_2CH_2OCH_2CH_2PO_3Na_2$ (XIV)	30.0	192.4	15.6
3. $Na_2O_3PCH_2SCH_2PO_3Na_2$ (XVII)	6.2	200.0	3.1
4. *o*-$(Na_2O_3PCH_2)_2C_6H_4$ (XIX)	110.0	175.0	62.0
5. $Na_2O_3PCH_2CO_2Na$ (IX)	165.0	150.4	109.7
6. $Na_2O_3PCH_2OCH_2CO_2Na$ (III)	207.0	131.2	158.1
7. $Na_5P_3O_{10}$	190–250	252.7	75.1–98.9
8. $[Na_2O_3PCH_2CH_2]_3P{=}O$	69.5	245.0	28.3
9. $[Na_2O_3PCH_2][Na_2O_3PCH_2CH_2]_2P{=}O$	75.0	252.0	29.7

The disphosphonate *o*-$(Et_2O_3PCH_2)_2C_6H_4$ XVIII was obtained in high yield from α,α'-dibromo-*o*-xylene and $(EtO)_3P$. Hydrolysis of this ester with concentrated HCl produced the corresponding acid in high yield. Other phosphonic acids such as $(H_2O_3PCH_2CH_2)_2PO_2H$,[7] $(H_2O_3PCH_2CH_2)_2(H_2O_3PCH_2)PO$ and $(H_2O_3PCH_2CH_2)_3PO$[8] were prepared by published procedures.

B PHOSPHORUS-31 AND HYDROGEN-1 NMR SPECTRA OF THE COMPOUNDS PREPARED

The ^{31}P- and ^{1}H-NMR chemical shifts are summarized in Table II. Since the signals of the ester IV, $(Et_2O_3PCH_2OC(CH_3)(CO_2Et)_2$ were partially overlapping, $Eu(DPM)_3$ was added to the solution. The observation that the signals for $POCH_2$ and PCH_2 were moved by far the most downfield indicates that it is the P = O group which forms a complex with $Eu(DPM)_3$ in preference to the C = O group.

C COMPLEXING CAPACITY OF SOME PHOSPHONIC ACIDS TOWARDS Ca-IONS

The sequestering capacity of the ligands was determined by dissolving 1 g of the complexing agent in water (0.1 M solution), adjusting the pH to 10 and adding 10 ml of a 2% solution of Na_2CO_3. Then the solution was titrated with a calcium acetate monohydrate solution of known titer to a distinct and permanent turbidity. The results, summarized in Table I, indicate that, on a weight basis of the ligands, bis-(phosphonylmethyl) ether (No. 1) is the best complexing agent for $CaCO_3$. However, if one calculates the mg $CaCO_3$ sequestered per 100 mg of phosphorus, present as the ligand, then carboxymethylphosphonylmethyl ether (No. 6) gives for the $CaCO_3$ sequestered a value which is nearly 50% higher than that obtained with bis-(phosphonylmethyl)-ether.

EXPERIMENTAL PART

(with Miss H. Benz, Miss S. Herrmann and Mr. H. P. Dettling)

The ^{1}H- and ^{31}P-NMR chemical shifts are summarized in Table II. All operations were carried out under an atmosphere of nitrogen.

1. $(EtO)_2PCH_2ONa$ (I)

To a sodium suspension (2.3 g = 0.1 g.atom) in 50 ml of toluene is added 14 g (0.10 mol) of $(EtO)_2P(O)H$, and then the mixture let stand over night. All sodium is consumed. Toluene is distilled under high vacuum, 50 ml Et_2O added to the residue and then slowly 3 g (0.1 mol) paraformaldehyde. A clear solution is obtained.

2. $(EtO)_2PCH_2OCH_2CO_2Et$ (II)

To 19 g (0.1 mol) of I in 50 ml Et_2O is slowly added 16.7 g (0.1 mol) of $BrCH_2CO_2Et$ and then the mixture is refluxed for 3 hr. The precipitated NaBr is filtered and the filtrate washed with ether. The ether layers are combined and distilled to give 9.3 g (36.5%) II, a clear liquid, b.p. 92–98%/0.2 torr, n_D^{20} 1.4360 (lit.[10] b.p. 147– 9°/1.5 torr. n_D^{20} 1.4348).

3. $(HO)_2PCH_2OCH_2CO_2H$ (III)

A mixture of 6.3 g of II and 25 ml HCl conc. is refluxed for 17 hr. Evaporation to dryness yields III as a slightly colored oil which does not crystallize, but it gives a crystalline cyclohexylamine salt of m.p. 155–164°. III titrates as a tribasic acid with inflection points at pH 5.3 (2 eq. found 100.4, calc. 85.04) and pH 9.4 (1 eq. found 167.1, calc. 170.8) the ^{1}H- and ^{31}P-NMR spectra also indicate that III is not pure. The ^{31}P-NMR spectrum shows peaks at (in H_2O): −22.5 ppm, probably $H_2O_3PCH_2OH$ (lit.[9] reports −22.6 ppm): −19 ppm (~80% III); −16 ppm (unknown).

TABLE II
Phosphorus-31 and Hydrogen-1-NMR spectra of the compound prepared

	Compound	Solvent	a	b	c	d	^{31}P- chem shifts in ppm ref. 85% H_3PO_4
II	$(CH_3CH_2O)_2P(O)CH_2OCH_2CO_2CH_2CH_3$ (a c b d c a′)	CCl_4	1.27 (*t*) } 9.15H; a′: 1.32 (*t*) }	3.79 (*d*, J_{PCH} 8)	4.09 (*qu*) b + c + d = 9.85H	4.13 (*s*)	−20.2 (in CCl_4)
III	$H_2O_3PCH_2OCH_2CO_2H$ (c a b c)	D_2O	4.41 (*d*, J_{PCH} 9, 2H)	4.8 (*s*, 2H)	6.23 (*s*, 4.5H)		−19.0 (D_2O)
IV	$(CH_3CH_2O)_2P(O)CH_2OC(CH_3)(CO_2CH_2CH_3)_2$[a] (a d c b; e a)	CCl_4	1.28 (*t*) } 12H; a′: 1.32 (*t*) }	1.57 (*s*, 2.85H)	3.87 (*d*, J_{PCH} 10.8) c + d + e = 10.1H	4.07 (2 *qu*)	−19.0 (subst.)
		Eu $(DPM)_3$[b]	1.5 (*t*, 6.1H); a′: 2.68 (*t*, 6.02H)	2.40 (*s*, 3.24H)	8.13 (*d*, J_{PCH} 11, 1.85H)	7.70 (2 *qu*, 3.79H)	
V	$H_2O_3PCH_2OCH(CH_3)CO_2H$ (d b c a d)	D_2O	1.92 (*d*, J_{HH} 6.5, 2.5H)	4.38 (*d*, J_{PCH} 8.5)	4.66 (*qu*, J_{HH} 6.5) (b + c = 3.2H)	5.35 (*s*, 3.3H)	−18.2 ($_2O$)
VI	$[(CH_3)_2CHO]_2P(O)CH_2OC(CH_3)(CO_2CH_2CH_3)_2$[c] (a e c b; d a)	CCl_4	1.3 (*m*, 18.7H)	1.55 (*s*, 2.7H)	3.78 (*d*, J_{PCH} 10.6)	4.2 (*qu*)	−17 (neat)
VII	$NaO(O)P(CH_3)_2CHO)(CH_2-O-C(CH_3))(CO_2Na)_2$ (a d c b)	D_2O	1.25 (*d*, J_{HH} 6, 6.08H)	1.47 (*s*, 2.95H)	3.47 (*d*, J_{PCH} 11 2.08H)	4.5 (*m*, 0.86H)	−17.5 (H_2O)
VIII	$(CH_3CH_2O)_2P(O)CH_2CO_2CH_2CH_3$ (a′ d b c a)	$CDCl_3$	1.26 (*t*) } 9.02H; a′: 1.31 (*t*) }	2.92 (*d*, J_{PCH} 21.3, 2.03H)	4.08 (*qu*)	4.2 (2*q*, c + d = 5.9H)	−19.5 (subst.)
IX	$H_2O_3PCH_2CO_2H$ (c b c)	CD_3OD		2.87 (*d*, J_{PCH} 21.5, 2H)	5.8 (*s*, 3.4H)		−17.6 (H_2O)
X	$[(CH_3CH_2O)_2P(O)CH_2]_2O$ (a c b)	CCl_4	1.32 (*t*, 12H)	3.86 (*d*, J_{PCH} 7)	4.1 (2 *qu*, b + c = 12H)		−19.5 (CCl_4)
XI	$[H_2O_3PCH_2]_2O$ (c b)	D_2O		4.42 (*d*, J_{PCH} 8.3, 4H)	5.83 (*s*, 4H)		−19 (H_2O)

TABLE II–*continued*

	Compound	Solvent	a	b	c	d	^{31}P- chem. shifts in ppm ref. 85% H_3PO_4
XII	$[(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}CH_2CH_2]_2O$ (a d b c)	CCl_4	1.28 (*t*, 12.1H)	1.95 (2*t*, J_{HH} 7.5, J_{PCH} 18.5, 3.91H)	3.61 (2*t*, J_{HH} 7.5, J_{PCCH} 11.2, 4.05H)	4.0 (2 *qu*, 7.95H)	−28 (neat)
XIII	$(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}CH_2CH_2OCH_2CH_2Cl$ (a d b c c c)	CCl_4	1.28 (*t*, 6.2H)	1.95 (2*t*, J_{HH} 7.25, J_{PCH} 18.5, 2H)	3.6 (*m*, 5.4H)	4.0 (2 *qu*, 4.1H)	−28 (subst.)
XIV	$[H_2O_3PCH_2CH_2]_2O$ (c a b)	D_2O	2.65 (broad J_{PCH} 18, 2H)	4.25 (broad, J_{PCCH} 11, 2.07H)	5.7 (*s*, 3.93H)		−15 (Na_2-Salt in H_2O)
XV	$H_2O_3PCH_2CH_2OCH_2CH_2Cl \cdot H_2O$ (c a b b b c)	D_2O	2.62 (broad, J_{PCH} 20, 2H)	4.21 (broad, 6H)	5.45 (*s*, 4H)		−26.5 (in H_2O)
XVI	$[(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}CH_2]_2S$ (a c b)	CCl_4	1.33 (*t*, 12.1H)	2.95 (*d*, J_{PCH} 11.3, 3.8H)	4.1 (2 *qu*, 8.1H)		−24 (subst.)
XVII	$[H_2O_3PCH_2]_2S \cdot H_2O$ (c b c)	D_2O		3.46 (*d*, J_{PCH} 13, 4H)	5.52 (*s*, 7H)		−23.5 (H_2O)
XVIII	1,2-$[(CH_3CH_2O)_2P(O)CH_2]_2C_6H_4$ (a c b d)	CCl_4	1.18 (*t*, 12H)	3.32 (*d*, J_{PCH} 20.5, 4H)	3.88 (2*q*, 8H)	7.12 (*m*, 4H)	−26.5 (subst.)
XIX	1,2$[H_2O_3PCH_2]_2C_6H_4$ (c b d)	D_2O		3.78 (*d*, J_{PCH} 20, 4H)	5.35 (*s*, 4.6H)	7.73 (broad 4H)	−18 (Na-Salt in H_2O)

[a] e: 4.21 (*qu*).
[b] e: 4.50 (*qu*, 4.05H).
[c] e: 4.7 (*m*), c + d + e = 7.6H.

A purer sample of III was obtained from the cyclohexylamine salt of III by passing it through an acidic ion exchange column and vaporizing the eluate. III was obtained as a colorless oil.

$C_3H_7O_6P \cdot 4H_2O$ (242.1) Calculated: C, 14.88; H, 6.24%
Found: C, 14.42; H, 6.19%

4. $(EtO)_2P(O)CH_2OC(CH_3)(CO_2Et)_2$ (IV)

To 38 g (0.2 mol) of I (prepared from 0.2 mol of diethylphosphite, 0.2 g.atom of Na and 0.2 mol of $(CH_2O)_x$ in 150 ml diglyme) in diglyme is added 50.9 g (0.2 mol) of $BrC(CH_3)(CO_2Et)_2$ over a period of 25 min. An exothermic reaction ensues. By cooling the temperature is kept at 25–30°. Then the mixture is refluxed for 1 hr. let stand over night, filtered and the filtrate distilled. There is obtained after a large forerun [32.3 g, b.p. 23–104°/0.05 torr, containing diethylphosphite and $BrC(CH_3)(CO_2Et)_2$] also 17.8 g (=26.2%) IV, a colorless liquid, b.p. 114–121.5°/0.05 torr, n_D^{20} 1.4381.

5. $(HO)_2P(O)CH_2OCH(CH_3)CO_2H$ (V)

A mixture of 5 g of IV and 60 ml of concentrated HCl is refluxed for 10 hr, carbon black added, filtered and the filtrate evaporated. There is obtained 2.52 g (=93%) V, a clear, slightly yellow, highly viscous mass which does not crystallize.

6. $[(CH_3)_2CHO]_2P(O)CH_2OC(CH_3)(CO_2CH_2CH_2CH_3)_2$ (VI)

To 48.4 g (0.2 mol) of $(i\text{-PrO})_2P(O)CH_2ONa$ (prepared from 0.2 mol of diisopropylphosphite, 0.2 g.atom of Na, and 0.2 mol of paraformaldehyde in 150 ml diglyme) in diglyme is added tropwise 50.6 g (0.2 mol) of $BrC(CH_3)(CO_2Et)_2$ over a period of 20 min. An exothermic reaction ensues. By cooling with ice-water the temperature is kept at 35°C. Then the mixture is refluxed for 2 hr, and, after standing over night, the thick, white-yellowish suspension is filtered and the residue washed with diglyme. The solvent is distilled from the clear, slightly yellow filtrate under reduced pressure. Thereby a small amount of white solid precipitates. This is filtered and the filtrate, a clear, slightly yellow, oily liquid, is heated under vacuum to 140°C at 10^{-3} mm Hg to remove all volatile material. As a residue is obtained 43.05 g (=58.5%) VI, a clear, odorless, yellow liquid.

7. $NaO(CH_3)_2CHO)P(O)CH_2OC(CH_3)(CO_2Na)_2$ (VII)

To 3 g (0.075 mol) of NaOH in 110 ml of ethanol is added 9.21 g (0.025 mol) of VI and the mixture is refluxed for 10 hr. Then the alcohol is distilled and the residue dissolved in H_2O and dimethylformamide added. After 2 days standing, white crystals precipitate. These are filtered and dried in the high vacuum for 3 hr at 200° (this is necessary, since the material retains tenaciously DMF) to give 6 g (=71.4%) pure VII, white crystals which do not melt up to 240°C.

8. $(EtO)_2P(O)CH_2CO_2Et$ (VIII)

From 20 g (0.163 mol) of $ClCH_2CO_2Et$, 54.2 g (0.326 mol) of $(EtO)_3P$ according to the literature.[4] After 2 hr reflux fractional distillation yields 35 g (=95.9%) of VIII, b.p. 69–71°/0.01 torr, n_D^{20} 1.4320 (lit.[4] b.p. 140–143°/10 torr).

9. $(HO)_2P(O)CH_2CO_2H$ (IX)

A mixture of 33 g of VIII and 250 ml of concentrated HCl is refluxed for 5 hr, then evaporated and the residue dried in the vacuum. There is obtained 21 g (=100%) IX, m.p. 127–131° (lit.[4] m.p. 142–143°). The acid titrates as a tribasic acid with inflection points at pH 3.8 (1 eq. found 141.9, calculated 140), pH 6.7 (1 eq. found 147, calculated 140), and pH 10 (1 eq. found 150.6, calculated 140).

10. $(EtO)_2P(O)CH_2OCH_2P(O)(OEt)_2$ (X)

A mixture of 32.6 g (0.2835 mol) of $ClCH_2OCH_2Cl$ and 95 g (0.572 mol) of $(EtO)_3P$ is heated in a bomb tube at 170–180° for 6 hr. Fractional distillation of the slightly yellow oil yields, after a forerun (20.3 g, b.p. 40–140°/0.02 torr), also 58.7 g (=65.2%) X, a colorless liquid, b.p. 145–153°/0.005 torr, n_D^{20} 1.4450 (lit.[6] b.p. 193–419°/7.5 torr, n_D^{20} 1.4470).

11. $(HO)_2P(O)CH_2OCH_2P(O)(OH)_2$ (XI)

A mixture of 18 g of X and 150 ml of concentrated HCl is refluxed for 12 hr, evaporated and the residue dried under vacuum. There is obtained 11.6 g (=100%) XI, a viscous mass which crystallizes after standing for some time, m.p. 94° (lit.[6] m.p. 96–98°). XI titrates as a dibasic acid with inflection points at pH 4.8 (2 eq. found 106, calculated 103) and pH 9.4 (2 eq. found 105, calculated 103). Cyclohexylamine salt m.p. 197–200°.

12. $(EtO)_2P(O)CH_2CH_2OCH_2CH_2P(O)(OEt)_2$ (XII)

and

$(EtO)_2P(O)CH_2OCH_2CH_2Cl$ (XIII)

Since no reaction has been observed when a mixture of triethylphosphite and 2,2'-dichloroethyl ether is refluxed for 22 hr, 50 g (0.35 mol) of $(ClCH_2CH_2)_2O$ and 232.5 g (1.4 mol) of $(EtO)_3P$ with 1 g of $NiCl_2$ (violet solution) are heated in an autoclave to 175–220° for 6.5 hr. After cooling only slight pressure increase is noted. EtCl is vented and from the residue excess $(EtO)_3P$ distilled under reduced pressure. The residue, a dark green liquid, is filtered, put through an acidic ion exchanger in alcoholic solution to remove the nickel salt, the eluate treated with carbon black, filtered over celite and distilled. After a forerun there is obtained 12.5 g (=14.7%) XIII, a colorless liquid, b.p. 73–90°/0.001 torr, n_D^{20} 1.4445 (which on redistillation gives b.p. 80–88°/0.001 torr) and

40.9 g (=33.8%) XII, a colourless liquid, b.p. 150–161°/0.002 torr, n_D^{20} 1.4458.

Analysis XII: $C_{12}H_{28}O_7P_2$ (346.3)

Calculated: C, 41.62; H, 8.15%
Found: C, 41.67; H, 8.19%

Analysis XIII: $C_8H_{18}ClO_4P$ (244.7)

Calculated: C, 39.27; H, 7.42; Cl, 14.49%
Found: C, 39.06; H, 7.58; Cl, 14.36%

13. $(HO)_2PCH_2CH_2OCH_2CH_2P(OH)_2$ (XIV)

A mixture of 20 g of XII and 100 ml of concentrated HCl is refluxed for 16 hr. The clear yellow solution is evaporated. The residue, a clear, slightly yellow oil, crystallized on standing to give 13.75 g (=97.5%) XIV, m.p. 98–105°.

14. $(HO)_2PCH_2CH_2OCH_2CH_2Cl \cdot 0.5H_2O$ (XV)

A mixture of 4 g of XIII and 10 ml of concentrated HCl is refluxed for 6 hr. Evaporation to dryness yields a yellow, viscous oil from which H_2O and HCl is removed by azeotropic distillation with benzene to give 3.02 g (=98%) XV, a clear, slightly yellow oil which would not crystallize. XV titrates as a dibasic acid with inflection points at pH 2.9 (1 eq. found 200.3, calculated 197.5) and pH 5.7 (1 eq. found 194.5, calculated 197.5).

15. $(EtO)_2PCH_2SCH_2P(OEt)_2$ (XVI)

A mixture of 26.2 g (0.2 mol) of $ClCH_2SCH_2Cl$[11] and 99.7 g (0.6 mol) of $(EtO)_3P$ is refluxed at 170° for 7 hr and then fractionally distilled. After a forerun of 41.6 g, b.p. 40–80°/0.01 torr, there is obtained 49.8 g (=74%) XVI, a colorless oil, b.p. 140–155°/0.05–0.1 torr, n_D^{20} 1.4678 (lit.[5] b.p. 179–180°/2 torr, n_D^{20} 1.4696).

$C_{10}H_{24}O_6P_2S$ (334.3) Calculated: C, 35.92; H, 7.23; S, 9.59%
Found: C, 35.39; H, 7.13; S, 9.41%

16. $(HO)_2PCH_2SCH_2P(OH)_2$ (XVII)

A mixture of 20 g (0.06 mol) of XVI and 100 ml of concentrated HCl is refluxed for 20 hr, evaporated and from the residue water removed by azeotropic distillation with benzene. According to the ^{1}H-NMR spectrum an acid was obtained which contained one mol of water. XVII · H_2O titrates as a four basic acid with inflection points at pH 4.5 (2 eq. found 118.7, calculated 120) and pH 9.7 (2 eq. found 119, calculated 120). Cyclohexylamine salt m.p. 215–228°.

$C_2H_8P_2O_6S$ (221.1) Calculated: C, 10.87; H, 3.63; S, 14.44%
(anhydrous Found: C, 10.2; H, 3.50; S, 14.74%

17. *o*-$(Et_2O_3PCH_2)_2C_6H_4$ (XVIII)

A mixture of 26.4 g (0.1 mol) of α,α′-dibromo-*o*-xylene and 66.4 g (0.4 mol) of $(EtO)_3P$ is refluxed for 2 hr. Then all volatile material is removed at reduced pressure. The residue, a clear, slightly yellow oil, 37.7 g (=100%), is pure XVIII.

18. *o*-$(H_2O_3PCH_2)_2C_6H_4$ (XIX)

A mixture of 35.8 g of XVIII and 0.9 mol concentrated HCl is refluxed for 7 hr. Evaporation yields slightly yellow powdery XIX (25.2, g = 100%) m.p. 252° (dec.). XXII titrates as a four basic acid with inflection points at pH 5.3 (2 eq. found 127.3, calculated 133.06) and pH 10.3 (2 eq. found 127, calculated 133.06).

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