[CONTRIBUTION FROM THE RESEARCH LABORATORY, VICTOR CHEMICAL WORKS]

Preparation and Properties of Some Unsymmetrical Tetraalkyl Pyrophosphates[1]

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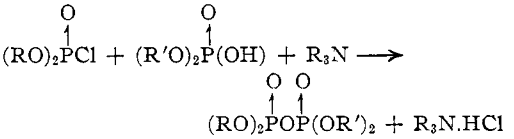
Introduction

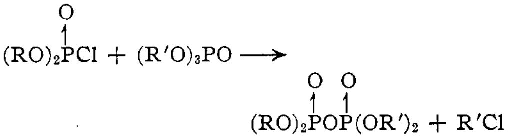
The preparation and properties of some tetraalkyl pyrophosphates, $(RO)_2\overset{O}{\overset{\uparrow}{P}}O\overset{O}{\overset{\uparrow}{P}}(OR')_2$ in which R and R′ are identical have already been described.[2] The toxicity and the rate of hydrolysis of these compounds depend on the nature of the alkyl groups. The ethyl ester is the most toxic, with a decrease in the toxicity as the size of the alkyl groups is increased or decreased. The tetraisopropyl ester was found to be the most resistant to hydrolysis, even more so than the water-insoluble tetra-*n*-butyl ester.

To further extend these research efforts there have been prepared two series of unsymmetrical tetraalkyl pyrophosphates in which R and R′ are different: (a) the diethyl dialkyl pyrophosphates, for the purpose of studying the effect on the toxic properties of the highly toxic tetraethyl ester by the substitution of two of the ethyl groups with two other alkyl groups, and (b) the di-isopropyl dialkyl pyrophosphates to determine the influence of the isopropyl groups on the rate of hydrolysis of the resulting compounds.

Two general methods were studied for the synthesis of the unsymmetrical tetraalkyl pyrophosphates involving, (a) interaction of dialkyl chlorophosphate with a dialkyl phosphoric acid in the presence of a tertiary amine (Equation 1), and (b) the action of dialkyl chlorophosphate on trialkyl phosphate (Equation 2).



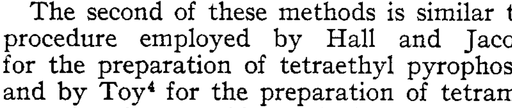
$$(RO)_2\overset{O}{\overset{\uparrow}{P}}Cl + (R'O)_2\overset{O}{\overset{\uparrow}{P}}(OH) + R_3N \longrightarrow (RO)_2\overset{O}{\overset{\uparrow}{P}}O\overset{O}{\overset{\uparrow}{P}}(OR')_2 + R_3N.HCl \quad (1)$$



$$(RO)_2\overset{O}{\overset{\uparrow}{P}}Cl + (R'O)_3PO \longrightarrow (RO)_2\overset{O}{\overset{\uparrow}{P}}O\overset{O}{\overset{\uparrow}{P}}(OR')_2 + R'Cl \quad (2)$$

Method (a) involving the action of dialkyl chlorophosphate [$(RO)_2POCl$] on dialkyl phosphoric acid [$(R'O)_2PO(OH)$] in the presence of a tertiary organic base such as pyridine or triethylamine is similar to the procedure described previously for the preparation of tetraethyl pyrophosphate.[2] This method produces readily, and in good yield, the whole series of unsymmetrical tetraalkyl pyrophosphates. In those cases in which small quantities of acidic contaminants were present in the less water-soluble members of the series they were effectively removed by washing the benzene solution with a 5% suspension of sodium hydrogen carbonate in a saturated sodium chloride solution. The products thus obtained upon distillation are practically devoid of any free acidity as determined by titration of the compound in acetone with a standard ethylene glycol solution of sodium hydroxide.

In order to prove that the compounds thus prepared are truly the unsymmetrical tetraalkyl pyrophosphates and that no migration of the alkoxy groups had occurred during the process of preparation or purification, the structure of a representative member of the series, the diethyl dibutyl pyrophosphate, was determined. A sample of the distilled diethyl dibutyl pyrophosphate was hydrolyzed in a sodium hydroxide solution in accordance with equation 3. Acidification of the resulting solution resulted in the separation of the water insoluble dibutyl phosphoric acid from the water soluble diethyl phosphoric acid. An 89% recovery of dibutyl phosphoric acid was achieved, thus establishing the truly unsymmetrical structure of the compound.



$$(C_2H_5O)_2\overset{O}{\overset{\uparrow}{P}}O\overset{O}{\overset{\uparrow}{P}}(OC_4H_9\text{-}n)_2 + 2NaOH \longrightarrow (C_2H_5O)_2\overset{O}{\overset{\uparrow}{P}}ONa + (n\text{-}C_4H_9O)_2\overset{O}{\overset{\uparrow}{P}}ONa \quad (3)$$

The second of these methods is similar to the procedure employed by Hall and Jacobson[3] for the preparation of tetraethyl pyrophosphate and by Toy[4] for the preparation of tetramethyl pyrophosphate. This method was found to be less practicable than method (a). The dimethyl diethyl pyrophosphate prepared by this method is identical in physical and chemical properties with the corresponding compound prepared by method (a), but the dimethyl di-*n*-propyl and the diethyl di-*n*-propyl pyrophosphate prepared are somewhat different from the corresponding compounds with respect to the specific gravity and the rate of hydrolysis. These slight differences in the properties indicate contamination by small quantities of by-products due to the complexity of the reaction. The yields are in general lower than those obtained by method (a). Several attempts to prepare the dimethyl di-isopropyl ester from di-isopropyl chlorophosphate and trimethyl phosphate were unsuccessful. In each case the loss in weight exceeded by at least 100% that required for methyl chloride, had the latter been the only

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[1] Presented before the Division of Organic Chemistry at the 116th meeting of the American Chemical Society, Atlantic City, N. J., September 18-23, 1949.

[2] Toy, THIS JOURNAL, **70**, 3882 (1948).

[3] Hall and Jacobson, *Ind. Eng. Chem.*, **40**, 694 (1948).

[4] Toy, THIS JOURNAL, **71**, 2268 (1949).

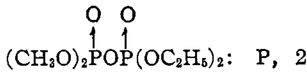
volatile product. The resultant product was a viscous acidic material which decomposed further upon attempted distillation even under reduced pressure. Phosphorus trichloride, hydrogen chloride and copper bronze were tried as catalyst but without success.

Experimental

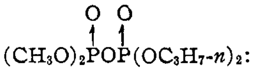
Method (a).—Preparation by the action of $(RO)_2POCl$ on $(R'O)_2PO(OH)$ in the presence of a tertiary amine.

The dialkyl chlorophosphates were obtained by the interaction of phosphorus trichloride and the alcohol followed by chlorination of the intermediate.[5] Since the dialkyl chlorophosphates, especially the dimethyl and the di-isopropyl compounds, have a tendency to decompose upon storage, only the freshly redistilled materials were used. The dialkyl phosphoric acids were obtained by the hydrolysis of the tetraalkyl pyrophosphates,[2] or of the dialkyl chlorophosphates.[6]

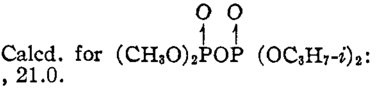
Dimethyl Diethyl Pyrophosphate.—A mixture consisting of 46.5 g. of 97.5% diethyl phosphoric acid (0.295 mole) and 42.5 g. (0.294 mole) of dimethyl chlorophosphate dissolved in 150 cc. of absolute ether was placed in a 500-cc. 3-necked flask equipped with a stirrer, a thermometer and a dropping funnel. To this mixture was added 24 g. (0.304 mole) of pyridine dissolved in 50 cc. of ether. The heat of reaction caused the temperature to rise above 25°, but the temperature of the reaction was maintained at 28–30° by periodic cooling with a water-bath. Some pyridine hydrochloride precipitated. After the completion of the addition (forty minutes) the stirring was allowed to continue until no more heat of reaction was observed (about one hour). The mixture was filtered and the residue washed with ether. The ether filtrate and washings were heated under reduced pressure finally to 55° (liquid temperature) at 2 mm. in order to remove the solvent and lower boiling materials, A 32-g. portion of the residue thus obtained was distilled in a Hickman pot still (bath temperature 100–105°; *p*, 0.003 mm.; distillation rate, one drop/1–2 seconds). The distillate weighed 27 g. which corresponds to a yield of 83.2%; $n^{25}D$ 1.4156, d^{25}_4 1.259, free acidity 1.4 cc. 0.1 *N* of NaOH/g. *Hydrolysis*, per cent. hydrolyzed: 57% in 2 hours; 79% in 4 hours; 87% in 6 hours.


Anal. Calcd. for $(CH_3O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2$: P, 23.7. Found: P, 23.6.

Dimethyl Di-*n*-propyl Pyrophosphate.—Thirty-two and three-tenths grams of 97.5% di-*n*-propyl phosphoric acid (0.173 mole) and 25 g. (0.173 mole) of dimethyl chlorophosphate dissolved in 100 cc. of absolute ether were allowed to react with 14 g. (0.177 mole) of pyridine dissolved in 50 cc. of ether at 29–31°. Upon completion of the reaction the pyridine hydrochloride was removed by filtration and the solvent then eliminated by distillation under reduced pressure. A 27.6-g. portion of the residue (weighing 50.2 g.) was distilled in the Hickman still (bath temperature, 105–110°; *p*, 0.002 mm.; distillation rate, one drop/5–10 seconds). The distillate weighed 23.3 g. which corresponds to a yield of 84.5%; $n^{25}D$ 1.4210, d^{25}_4 1.192, free acidity 2.1 cc. 0.1 *N* NaOH/g. *Hydrolysis*, 49% in 2 hours; 66% in 4 hours; 77% in 6 hours.


Anal. Calcd. for $(CH_3O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}n)_2$: P, 21.3. Found: P, 21.1.

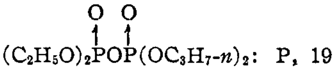
Dimethyl Di-isopropyl Pyrophosphate.—Thirty grams (0.165 mole) of di-isopropyl phosphoric acid (99.6%) and 24 g. (0.166 mole) dimethyl chlorophosphate dissolved in 200 cc. of absolute ether were allowed to react with 13.5 g. (0.171 mole) of pyridine dissolved in 25 cc. of ether. The crude product obtained after the removal of the solvent was purified by distillation in the Hickman still (bath temperature, 95–100°; p, 0.006–0.008 mm.; distillation rate, one drop/3–4 sec.). A 65% yield of the distilled product was obtained; $n^{25}D$ 1.4165, d^{25}_4 1.178, free acidity 1.35 cc. of 0.1 *N* NaOH/g.


Anal. Calcd. for $(CH_3O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}i)_2$: P, 21.3. Found: P, 21.0.

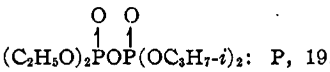
The same compound was also prepared by the action of dimethyl phosphoric acid on di-isopropyl chlorophosphate in the presence of pyridine. No ether solvent was used since dimethylphosphoric acid was found to be insoluble in ether. Upon completion of the reaction, ether was added to effect the separation of the pyridine hydrochloride. The distilled product obtained by this procedure was found to be less pure and to have a higher free acidity contamination than that obtained using reagents specified above.

Diethyl Di-*n*-propyl Pyrophosphate.—Thirty-four and eight-tenths grams of 99% diethyl phosphoric acid (0.224 mole) and 45.5 g. (0.227 mole) of di-*n*-propyl chlorophosphate were dissolved in 200 cc. of absolute ether. The temperature of the reaction was maintained at 35–38°. When no more heat of reaction was observed the mixture was heated to reflux for one hour and then cooled and filtered. The crude residue obtained after the removal of the solvent weighed 70 g. A 35-g. portion of this residue was distilled in a Hickman pot still (bath temperature 118–120°; *p*, 0.005–0.007 mm.; distillation rate, one drop/1–2 seconds). The distillate weighed 31 g. which corresponds to a yield of 86.2%; $n^{25}D$ 1.4210, free acidity 2 cc. 0.1 *N* NaOH/g.

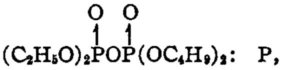
For the removal of the acidic contaminant the following procedure was used. Thirty-four grams of the original residue dissolved in 75 cc. of benzene, was washed with 2.5 g. of sodium hydrogen carbonate suspended in 47.5 cc. of a saturated sodium chloride solution cooled to 15°. The benzene layer, after drying with anhydrous magnesium sulfate, was heated to 100° at 3 mm. to remove the solvent; the residue thus obtained was distilled in the Hickman still. The distillate weighed 24 g. corresponding to a 68.8% yield; $n^{25}D$ 1.4212, d^{25}_4 1.141, free acidity 0.3 cc. 0.1 *N* NaOH/g. *Hydrolysis*, 78% in 24 hours; 93% in 48 hours; 97% in 72 hours.


Anal. Calcd. for $(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}n)_2$: P, 19.5. Found: P, 19.4.

Diethyl Di-isopropyl Pyrophosphate.—Forty grams (0.26 mole) of pure diethyl phosphoric acid and 52 g. (0.26 mole) of di-isopropyl chlorophosphate dissolved in 100 cc. of absolute ether were allowed to react with 21.6 g. (0.274 mole) of pyridine dissolved in 50 cc. of absolute ether. A 54-g. portion of the crude product obtained was distilled in the Hickman pot still (bath temperature 105°; *p*, 0.01 to 0.006 mm.; distillation rate, one drop/sec.). The distillate weighed 52.6 g. which corresponds to a 91% yield; $n^{25}D$ 1.4175, d^{25}_4 1.132, free acidity 1.7 cc. 0.1 *N* NaOH/g.


Anal. Calcd. for $(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}i)_2$: P, 19.5, Found: P, 19.2.

Diethyl Di-*n*-butyl Pyrophosphate.—Using absolute ether as solvent thirty-five grams (0.22 mole) of diethyl phosphoric acid and 51 g. (0.223 mole) of dibutyl chlorophosphate were allowed to react with 18 g. (0.228 mole) of pyridine. The crude product obtained from the reaction mixture was distilled in a Hickman pot still (bath temperature 115–118°; *p*, 0.007 mm.; distillation rate one drop/2–4 sec.). A 95.4% yield of the distilled product was obtained; $n^{25}D$ 1.4245, d^{25}_4 1.107, free acidity 1.4 cc. 0.1 *N* NaOH/g.


Anal. Calcd. for $(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_4H_9)_2$: P, 17.9. Found: P, 18.1.

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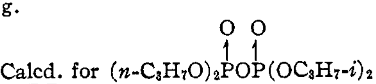
[5] McCombie, Saunders and Stacey, *J. Chem. Soc.*, 380 (1945).

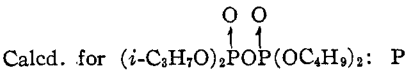
[6] Toy, to be published later.

Di-*n*-propyl Di-isopropyl Pyrophosphate.—Twenty and eight-tenths grams of 98.5% di-isopropyl phosphoric acid (0.113 mole) and 23 g. (0.115 mole) of di-*n*-propyl chlorophosphate were allowed to react with 9.5 g. (0.12 mole) of pyridine in the presence of ether as solvent. The crude product obtained from the reaction mixture was distilled in the Hickman still (bath temperature, 110–114°; *p*, 0.003–0.009 mm.; distillation rate, one drop/2–4 sec.). The distillate weighed 32.6 g. (82.7%). It had an initial acidity of 3.8 cc. 0.1 *N* NaOH/g. It was further purified by washing with sodium hydrogen carbonate in brine and then redistilled. This purification step resulted in a 4% loss of the product. The distillate had the following properties: $n^{25}\text{D}$ 1.4210, d^{25}_4 1.095, free acidity 0.1 cc. 0.1 *N* NaOH/g.



Anal. Calcd. for $(n\text{-}C_3H_7O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}i)_2$: P, 17.9. Found: P, 17.7.

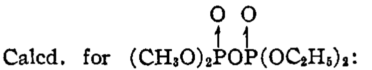
Di-isopropyl Di-*n*-butyl Pyrophosphate.—To 26.4 g. of 98.5% di-isopropyl phosphoric acid (0.143 mole) and 33.2 g. (0.145 mole) of di-*n*-butyl chlorophosphate in 200 cc. of absolute ether, were added 15.5 g. (0.153 mole) of triethylamine[7] in 25 cc. of absolute ether at 35–37°. The crude residue was distilled in a Hickman still (bath temperature, 118–120°; *p*, 0.002 mm.; distillation rate, one drop/1–2 sec.). The distilled yield amounted to 87.0%; $n^{25}\text{D}$ 1.4235, d^{25}_4 1.068, free acidity 10.5 cc. of 0.1*N* NaOH/g.



Anal. Calcd. for $(i\text{-}C_3H_7O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_4H_9)_2$: P, 16.6. Found: P, 16.3.

Method (b).—Preparation by interaction of $(RO)_2POCl$ with $(R'O)_3PO$.

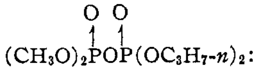
Dimethyl Diethyl Pyrophosphate.—One hundred and forty grams (1 mole) of trimethyl phosphate was heated with 86.3 g. (0.5 mole) of diethyl chlorophosphate. Gaseous methyl chloride evolved steadily at 110–112°. After three and one-half hours at 111–112° evolution of gas slowed down whereupon the temperature was raised to 115–120° for two more hours until no further reaction was noticeable. Upon cooling, the reaction mixture was found to have lost 25.6 g. as compared with a theoretical loss of 25.3 g. due to methyl chloride. The mixture was distilled under reduced pressure, first to remove the excess trimethyl phosphate; the fraction boiling at 100–106° at 0.01 to 0.015 mm. was collected. This product fraction weighed 87 g. (66.5%). Upon redistillation a product with the following properties was obtained: $n^{25}\text{D}$ 1.4152; d^{25}_4 1.259; free acidity 0.53 cc. 0.1 *N* NaOH/g. *Hydrolysis:* 56% in 2 hours; 80% in 4 hours; 89% in 6 hours.



Anal. Calcd. for $(CH_3O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_2H_5)_2$: P, 23.7. Found: P, 23.5.

Dimethyl Di-*n*-propyl Pyrophosphate.—Employing the above procedure 66.8 g. (0.333 mole) of di-*n*-propyl chlorophosphate and 93.5 g. (0.666 mole or 100% excess) of trimethyl phosphate were heated at 120–125° until gaseous evolution had slowed down (4.5 hours): loss in weight 16.4 g.; theoretical loss due to methyl chloride, 16.8 g.

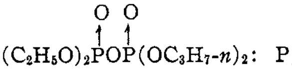
A 34.6-g. portion of the residue (weighing 86.4 g.), obtained by heating the reaction mixture to 100° (liquid temperature) at 1 mm. was distilled carefully under reduced pressure. The main fraction boiled at 113–115° at 0.02 to 0.05 mm. when the liquid temperature was maintained at 120–125° to a maximum of 135°. Some decomposition had occurred as indicated by the difficulty in maintaining the low pressure when the liquid temperature was increased to above 130°. The yield of the distilled product was 27.3 g. which corresponds to a 70.3% yield. Thus purified, the product was found to redistill readily without decomposition and to possess the following properties: b. p. 103–106° at 0.005 to 0.008 mm.; $n^{25}\text{D}$ 1.4199; d^{25}_4 1.190, free acidity 1.7 cc. 0.1 *N* NaOH/g. *Hydrolysis:* 54% in 2 hours; 71% in 4 hours; 80% in 6 hours.



Anal. Calcd. for $(CH_3O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}n)_2$: P, 21.3. Found: P, 21.0.

Diethyl Di-*n*-propyl Pyrophosphate.—A mixture of 144.6 g. (0.8 mole or 300% excess) of triethyl phosphate and 40.1 g. (0.2 mole) of di-*n*-propyl chlorophosphate was heated at 138–142° for two hours. The excess triethyl phosphate was removed by distillation under reduced pressure (< 2 mm.) until no more distillate came over at a liquid temperature of 100°. The crude residue weighed 57.6 g. A 28.8-g. portion of the residue was distilled in a Hickman pot still (bath temperature 100°; *p*, 0.002 mm.; distillation rate, one drop/3–4 seconds). The distillate weighed 22.6 g. which corresponds to a yield of 71%; $n^{25}\text{D}$ 1.4219, free acidity 1.5 cc. 0.1 *N* NaOH/g.

A 27-g. portion of the original residue was purified by solution in benzene, washed with sodium hydrogen carbonate in brine at 12–14°. After removal of the solvent the crude product was distilled in the Hickman still. The distillate weighed 24 g. (64% of theory); $n^{25}\text{D}$ 1.4219, d^{25}_4 1.139, free acidity 0.1 cc. 0.1 *N* NaOH/g. *Hydrolysis:* 76% in 24 hours; 91% in 48 hours; 94% in 72 hours.



Anal. Calcd. for $(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OC_3H_7\text{-}n)_2$: P, 19.5. Found: P, 19.4.

Hydrolysis of Diethyl Di-*n*-butyl Pyrophosphate.—Approximately 10% of a 26-g. quantity (0.075 mole) of distilled diethyl di-*n*-butyl pyrophosphate was added to 6.3 g. (0.157 mole) of sodium hydroxide dissolved in 56.6 cc. of water (10% solution) at 95–100°. After an induction period of about five to ten minutes, vigorous reaction occurred. The remainder of the pyrophosphate could then be added slowly, the reaction then occurring immediately. The temperature was maintained at 98–100° by the heat of reaction. Upon completion of the addition (10–15 minutes) the mixture was heated at 96–100° for three to four minutes and then cooled to room temperature. To this solution was added 17 g. of concentrated (37%) hydrochloric acid. An oily layer was found to separate and was washed carefully three times with 20-cc. portions of water. It was then dehydrated by heating to 75° at less than 0.5 mm. for five to ten minutes. The residue thus obtained weighed 14 g. (88.6%): neutral equivalent, calculated for $(n\text{-}C_4H_9O)_2PO(OH)$: 210. Found: 208–210; $n^{25}\text{D}$ 1.4255.

Anal. Calcd. for $(n\text{-}C_4H_9O)_2PO(OH)$: P, 14.8. Found: P, 15.1.

Toxicity

The toxicity of the unsymmetrical tetraalkyl pyrophosphates was determined by intraperitoneal injection on male white mice. Only those mice which died within one hour after the injection were counted. The toxicity data are summarized in Table I. The results indicate that the tetraalkyl pyrophosphates containing two ethyl groups are still highly toxic. The substitution of two of the ethyl groups in tetraethyl pyrophosphate with two other alkyl groups does, however, result in a slight decrease in toxicity as the size of the substituent group increases. The diethyl diisopropyl ester is an exception in that it is somewhat less toxic than the diethyl di-*n*-butyl ester.

It had been reported previously[2] that the LD_{50} mg./kg. for the tetra-*n*-propyl ester is 9.5 while that for the corresponding isopropyl ester is

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[7] Similar results were obtained when the above reaction was carried out using pyridine in place of triethylamine.

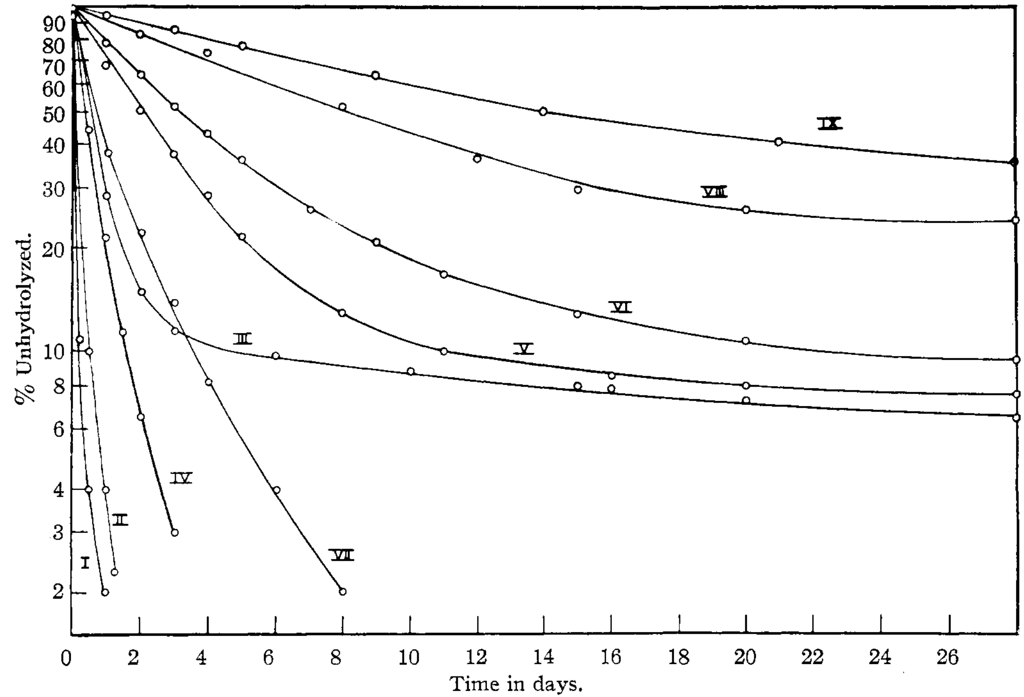

Fig. 1.—Rate of hydrolysis of unsymmetrical tetraalkyl pyrophosphates $(RO)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OR')_2$ at 25°; 0.02 *M* solution: I, R = CH_3, R' = C_2H_5; II, R = CH_3, R' = n-C_3H_7; III, R = CH_3, R' = i-C_3H_7; IV, R = C_2H_5, R' = n-C_3H_7; V, R = C_2H_5, R' = i-C_3H_7; VI, R = n-C_3H_7, R' = i-C_3H_7. 0.02 *M* in contact with water: VII, R = C_2H_5, R' = n-C_4H_9; VIII, R = i-C_3H_7, R' = n-C_4H_9. IX, R = i-C_3H_7, R' = i-C_3H_7 (tetra-isopropyl compound).

Table I

$(RO)_2\overset{\overset{O}{\uparrow}}{P}O\overset{\overset{O}{\uparrow}}{P}(OR')_2$

R	R'	LD_{50} mg./kg.
CH_3	C_2H_5	1.4
CH_3	n-C_3H_7	1.9
CH_3	i-C_3H_7	3.0
C_2H_5	C_2H_5	0.82[2]
C_2H_5	n-C_3H_7	1.6
C_2H_5	i-C_3H_7	2.8
C_2H_5	n-C_4H_9	2.1
n-C_3H_7	i-C_3H_7	11.0
i-C_3H_7	n-C_4H_9	8.4[a]

[a] The tests carried out on this compound did not give a sharp value. The value reported was obtained from an average of six determinations from two separate preparations of the compound on different batches of mice.

13.3. The value of 11 obtained for the mixed di-*n*-propyl di-isopropyl pyrophosphate might therefore have been anticipated. However, the value of 8.4 obtained for the di-isopropyl di-*n*-butyl pyrophosphate was rather unexpected, since it is more toxic than the tetra-isopropyl ester or the tetra-*n*-butyl ester (14.2 mg./kg.).

Hydrolysis

Experimental results for the rates of hydrolysis studies of the various esters are depicted in Fig. 1. Data for the hydrolysis of tetra-isopropyl pyrophosphate, reported previously[2] are also depicted graphically on Fig. 1 for purposes of comparison.

Rates of hydrolysis of the dimethyl and diethyl dialkyl pyrophosphates decrease in a regular fashion as the R groups become larger, except that the compounds containing two isopropyl groups are markedly more resistant than might have been anticipated. This effect of isopropyl groups on hydrolysis rate was first noted in the case of tetra-isopropyl pyrophosphate[2] which was found to be more resistant to attack than the tetra-*n*-butyl ester. It may be assumed that this decrease in reactivity is occasioned by steric effects.

Experimentally, the degree of hydrolysis was determined by the titration of an aliquot of a 0.02 *M* solution at the indicated time interval with a 0.1 *N* sodium hydroxide solution. In the case of the diethyl dibutyl ester and the di-isopropyl dibutyl ester which are only slightly soluble in water, the determinations were carried out by shaking continuously the individual samples of the compound at 0.02 *M* concentration in contact with water for the indicated length of time after which the whole sample was titrated.

Acknowledgment.—The author desires to express his thanks to Mr. A. R. Wreath for determining the physical constants, the analyses, and the rates of hydrolysis; to Mr. W. B. Coleman

for carrying out the toxicity tests, to Dr. Howard Adler for his helpful advice, and to Dr. L. F. Audrieth for his criticisms in the preparation of the manuscript.

Summary

1. A series of unsymmetrical tetraalkyl pyrophosphates $(RO)_2\overset{O}{\overset{\uparrow}{P}}O\overset{O}{\overset{\uparrow}{P}}(OR')_2$ were prepared, (a) by the action of dialkyl chlorophosphate on dialkyl phosphoric acid in the presence of a tertiary base and, (b) by the interaction of dialkyl chlorophosphate and trialkyl phosphate. Compounds whose preparation and properties are described are the dimethyl diethyl-, dimethyl di-*n*-propyl-, dimethyl di-isopropyl-, diethyl di-*n*-propyl-, diethyl di-isopropyl-, diethyl di-*n*-butyl-, di-*n*-propyl di-isopropyl-, and the di-isopropyl di-*n*-butyl pyrophosphates.

2. Alkaline hydrolysis of diethyl dibutyl pyrophosphate yields the diethyl and dibutyl phosphoric acids, thus establishing the structures of the unsymmetrical pyrophosphates prepared by the indicated procedures.

3. Comparative toxicity data for the unsymmetrical tetraalkyl pyrophosphates are presented. Substitution of two of the ethyl groups in tetraethyl pyrophosphate with two other alkyl groups results in only a slight decrease in toxicity.

4. Results of hydrolysis studies covering the dimethyl- and diethyl-dialkyl pyrophosphates show that the rates decrease as the size of the alkyl group becomes larger, except for compounds containing two isopropyl groups which are markedly more resistant. This decrease in reactivity is attributed to steric effects.

CHICAGO HEIGHTS, ILL. RECEIVED NOVEMBER 14, 1949

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, COMMERCIAL SOLVENTS CORPORATION]

Effect of Strain on the Properties of Some 2-Nitroalkylamines

BY MURRAY SENKUS

Earlier work had shown that amines like isopropylamine, morpholine, N-methylaniline and others react with formaldehyde and nitroparaffins or with nitroalcohols derivable from formaldehyde and nitroparaffins to yield 2-nitroalkylamines in good yields; also, that hydrogenation of each of these compounds yields the corresponding polyamine.[1]

Further study of the above reaction has revealed that the yield of a 2-nitroalkylamine under a given set of conditions, for the most part, depends on the structures of the groups attached to the nitrogen in the starting amine. Thus, diisopropylamine (I), N-(1-methylpropyl)-isopropylamine (II), N-(tetrahydrofurfuryl)-isopropylamine (III) and some other amines react with formaldehyde and 2-nitropropane to give the desired 2-nitroalkylamines in much lower conversions than the amines studied earlier; also in contrast to the 2-nitroalkylamines isolated earlier,[1] the 2-nitroalkylamines derived from (I), (II), (III) and others exhibit marked instability. These properties, together with other data, are given in the experimental section of this paper.

It is believed that the low yields of some 2-nitroalkylamines reported herein, as well as the instability of some of the compounds, can be explained on the basis of steric effects. The arguments in support of this theory are advanced in the discussion section.

Experimental

The 2-nitroalkylamines were prepared according to methods described in the earlier work.[1] The yields of some 2-nitroalkylamines prepared by these methods were low, and in order to improve the yields of two of the nitro compounds, the following procedures were developed. **N-(2-Nitroisobutyl)-diisopropylamine** was prepared by distilling a mixture of 650 g. (6.4 moles) of diisopropylamine and 238 g. (2 moles) of 2-nitro-2-methyl-1-propanol through a laboratory column at a 10:1 reflux ratio. Water which formed in the reaction was removed as an azeotrope with the excess diisopropylamine, b. p. 73°. After the formation of water had ceased, the residue was rectified. This rectification gave the desired product in 87% conversion. **N-(2-Nitroisobutyl)-N-(tetrahydrofurfuryl)-isopropylamine** was prepared by refluxing a mixture of 143 g. (1 mole) of (III), 119 g. (1 mole) of 2-nitro-2-methyl-1-propanol and 200 ml. of toluene. Water which formed in the reaction was collected in a moisture trap. The conversion here was 78%.

Hydrogenation of the 2-nitroalkylamines was carried out according to the earlier methods.[1] With the exception of N-(2-nitroisobutyl)-N-(benzyl)-cyclohexylamine and of N-(2-nitroisobutyl)-N-(furfuryl)-cyclohexylamine the 2-nitroalkylamines failed to give the desired polyamines but gave, instead, complex mixtures. For example, N-(2-nitroisobutyl)-diisopropylamine gave the products set forth in Table I.

TABLE I

PRODUCTS FROM THE HYDROGENATION OF N-(2-NITROISOBUTYL)-DIISOPROPYLAMINE (160 G.)

Boiling range, °C.	Weight, g.	Neutralization equivalent	Remarks
35–39	4	60	Isopropylamine
39–50	3		
50–70	4		
70–75	4		
75–82	4		
82–84	42	99	Diisopropylamine
84–112	6		
112–113	7	114	N-(Methyl)-diisopropylamine
113–140	2		
140–200	21		

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[1] (a) Senkus, THIS JOURNAL, **68**, 10 (1946); (b) Johnson, *ibid.*, **68**, 12, 14 (1946).