TABLE I

PIPERAZINIUM SALTS OF PERHALO-ORGANIC ACIDS

			Data Concerning Piperazinium Salts							
			Calcd.				Found			
Fluoro Acid	Formula	M.P. °C.	C	H	F	Cl	C	H	F	Cl
Perfluoroacetic	CF_3COOH	229–231	30.6	3.85	36.3	...	30.08	3.79	36.64	...
Perfluoropropionic	CF_3CF_2COOH	241–242.5	29.0	2.92	45.9	...	29.54	3.11	45.58	...
Perfluorobutyric	$CF_3(CF_2)_2COOH$	240.8–241.8	28.0	2.35	51.8	...	28.25	2.52	51.64	...
Perfluorohexanoic	$CF_3(CF_2)_4COOH$	240.5–241.5	26.9	1.69	58.6	...	26.63	1.76	58.41	...
Perfluorooctanoic	$CF_3(CF_2)_6COOH$	240–241	26.3	1.54	62.36	...	26.48	1.41	62.19	...
Kel F 683	$Cl(CF_2\text{-}CFCl)_2CF_2COOH$	Above 250	23.64	1.49	...	26.16	23.85	1.65	...	26.42
Kel F 8114	$Cl(CF_2\text{-}CFCl)_3CF_2COOH$	Above 250	22.96	1.16	...	27.11	22.81	1.49	...	27.05
Perfluoroglutaric	$HOOC(CF_2)_3COOH$	269–270	33.15	3.71	34.96	...	33.24	3.62	34.68	...
Perfluoromethoxyacetic[a]	CF_3OCF_2COOH	191–191.5	26.9	2.76	42.6	...	27.11	2.70	42.83	...

[a] The preparation and structure determination of this acid will be the subject of a forthcoming publication.

TABLE II

N-PHENYLPIPERAZINIUM SALTS OF PERHALO-ORGANIC ACIDS

			Data Concerning N-Phenylpiperazinium Salts							
			Calcd.				Found			
Fluoro acid	Formula	M.P. °C.	C	H	F	Cl	C	H	F	Cl
Perfluoroacetic	CF_3COOH	151–154	52.2	5.48	20.6	...	52.32	5.48	20.82	...
Perfluoropropionic	CF_3CF_2COOH	144–144.5	47.8	4.64	29.1	...	47.72	4.52	29.38	...
Perfluorobutyric	$CF_3(CF_2)_2COOH$	124–126	44.7	4.02	35.4	...	44.33	4.00	35.61	...
Perfluorohexanoic	$CF_3(CF_2)_4COOH$	122–124	40.3	3.18	44.0	...	40.05	3.40	43.75	...
Perfluorooctanoic	$CF_3(CF_2)_6COOH$	125.5–128	37.5	2.62	49.5	...	37.63	2.62	50.10	...
Kel F 683	$Cl(CF_2\text{-}CFCl)_2CF_2COOH$	133–134	36.6	2.88	...	20.2	36.76	3.00	...	20.1
Kel F 8114	$Cl(CF_2\text{-}CFCl)_3CF_2COOH$	141–142	33.7	2.36	...	22.1	33.55	2.71	...	21.88

The melting points and mixed melting points of the piperazinium and *N*-phenylpiperazinium salts, in conjunction with the physical constants of the acids, have been useful in these laboratories for the identification of perfluoro organic acids.

Various attempts to obtain specimens of the 5 and 7 perfluoro acids proved futile.

Data concerning the piperazinium and N-phenylpiperazinium salts of perfluoro acids prepared are shown in Tables I and II.

EXPERIMENTAL

Piperazinium salts. About 1 ml. of the acid and 10 ml. of propanol-2 were placed in a small beaker packed in ice. Anhydrous piperazine was slowly added with stirring until the mixture was basic to litmus paper. Another 10 ml. portion of propanol-2 was added with stirring and the slurry was filtered while cold. Ten milliliters of boiling 95% ethanol were added to the crude product; water was added dropwise to the boiling mixture until the solid dissolved. The solution was cooled in an ice bath until crystallization was complete. Three recrystallizations gave a constant melting product.

The piperazinium salts of Kel F 683, Kel F 8114 and perfluoroglutaric acids were recrystallized from boiling water.

The piperazinium salt of perfluorooctanoic acid was crystallized from boiling 1-butanol.

N-Phenylpiperazinium salts. About 4 ml. of the acid and 20 ml. of propanol-2 were placed in a small beaker packed in ice. *N*-Phenylpiperazine was slowly added with stirring until the mixture was basic to litmus paper. The mixture was heated until the solid dissolved. The crystals which formed on cooling were recrystallized three times to give a constant melting product.

The *N*-phenylpiperazinium salts of Kel F 683 and Kel F 8114 acids were recrystallized from hot absolute ethanol.

The melting points were determined in sealed tubes by means of a brass block preheated to within 5 degrees of the respective melting point.

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Instability of Certain Organophosphorus Compounds Containing Pentavalent Phosphorus[1]

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In connection with the preparation of a variety of potentially toxic organophosphorus compounds,

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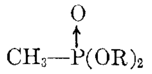
(1) This work was done on a subcontract with the University of Chicago in fulfillment of a contract with the Chemical Corps.

(2) Member of the Armed Forces assigned to the Army Chemical Corps.

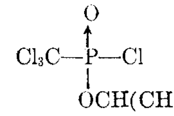
several unstable structures have been encountered. The present report is concerned with the preparation and properties of certain of these compounds.

Of three derivatives (I–III) of methylphosphonic acid whose preparation has been attempted, only the bistetrahydrofurfuryl methylphosphonate, I, was sufficiently stable to permit isolation in a pure condition, and this compound suffered some polymerization during distillation. The analogous furfuryl ester (II) decomposed violently when distillation was attempted at 100°. In view of the activity of sarin (isopropyl methylphosphonofluoridate) as an anticholinesterase, the analogous isopropyl trichloromethylphosphonochloridate, III, was prepared, but it proved to be too unstable to permit satisfactory purification. Replacement of the chlorine on phosphorus by fluorine, using sodium fluoride in benzene,[3] was unsuccessful. In view of the fact that boiling water hydrolyzes only one chlorine[4] in trichloromethylphosphonic dichloride, it is of interest that hydrolysis of the ester acid chloride, III, yields the trichloromethylphosphonic acid.



$CH_3—\overset{O\atop\uparrow}{P}(OR)_2$

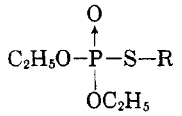
I. R = tetrahydrofurfuryl
[II. R = furfuryl]



$Cl_3C—\overset{O\atop\uparrow}{\underset{OCH(CH_3)_2}{P}}—Cl$

III

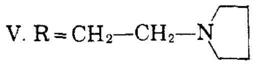
Attempts to prepare two S-substituted derivatives (IV, V) of diethyl phosphorothioate, by reaction of the appropriate halide with diethyl potassium phosphorothioate, yielded highly unstable materials. Although a compound distillable with decomposition was obtained in the attempted preparation of IV, its analysis was in poor agreement with that calculated, and it altered rapidly on standing at room temperature.



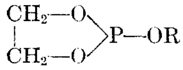
$C_2H_5O—\overset{O\atop\uparrow}{\underset{OC_2H_5}{P}}—S—R$

IV. R = $CH_2—CN$

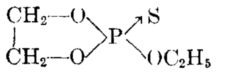
V.



A simple derivative, VI, and a polyfunctional derivative, VII, of ethylene phosphite were prepared from ethylene phosphorochloridite. Although these compounds are stable to distillation and to storage in absence of moisture and air, they are highly reactive compounds as has been previously reported.[5] Ethyl ethylene phosphite (VI) reacts relatively slowly with dry air, and the product is a polymer, not ethyl ethylene phosphate. In contrast, reaction of VI with sulfur yields the ethyl ethylene phosphorothioate, VIII. The latter compound, obtained in poor yield by distillation, decomposes slowly at room temperature, rapidly at 160°. The trimethylene compound analogous to VII was also prepared, and was found to be less reactive toward water than is VII. Reaction of either VII or the trimethylene analog with sulfur yields unstable products which rapidly polymerize.



VI. R = C_2H_5
VII. R = $CH_2—CH_2—N(C_2H_5)_2$



VIII

It was noted that the phosphorus esters containing the five- or six-membered rings may be recognized by characteristic bands in the infrared, regardless of whether the phosphorus is tri- or pentavalent. For compounds containing the five-atom ring, $\overline{OCH_2CH_2OP}$, there occurs a very sharp, intense band at 10.82–10.84μ, while compounds containing the similar six-atom ring display absorption at 10.69–10.71μ. Such bands have been observed in no other phosphorus compounds.

EXPERIMENTAL[6]

Bistetrahydrofurfuryl methylphosphonate (I). A mixture of 18 g. (0.18 mole) of tetrahydrofurfuryl alcohol and 18 g. (0.18 mole) of triethylamine was added dropwise with stirring to a solution of 11 g. (0.083 mole) of methylphosphonic dichloride in 100 ml. of dry benzene. The reaction was exothermic, and the temperature was allowed to rise to reflux. The mixture was stirred for 30 min. after completion of addition, the amine salt was removed by filtration, and the filtrate was concentrated at reduced pressure. Distillation of the residue yielded 17.8 g. (45%) of the di-ester, b.p. 138°/0.5 mm., n_D^{25} 1.4700–1.4703. A sample redistilled for analysis left a residue of about one third its weight and had b.p. 150°/0.8 mm., n_D^{25} 1.4699.

Anal. Calcd. for $C_{11}H_{21}O_5P$: C, 49.99; H, 8.01; P, 11.72. Found: C, 50.02; H, 8.15; P, 11.59.

Isopropyl trichloromethylphosphonochloridate (III). To a solution of 2.0 g. (8.5 mmole) of sublimed trichloromethylphosphonic dichloride[7] in 20 ml. of anhydrous ether, stirred at 0°, there was added in one portion 0.85 g. (8.5 mmole) of triethylamine. To the slightly cloudy solution there was next added during about 15 min. a solution of 0.51 g. of dry isopropyl alcohol in 20 ml. of anhydrous ether. After addition was complete, stirring with cooling in an ice bath was continued for 30 min., then the amine salt was removed by suction filtration and washed with dry ether. Removal of solvent from the filtrate at reduced pressure left a colorless oily residue weighing 1.95 g. (98% yield). This material crystallized on cooling in an ice bath and remelted at room

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[3] B. C. Saunders and G. J. Stacey, *J. Chem. Soc.*, 695 (1948).

[4] A. Ya. Yakubovich and V. A. Ginsburg, *Doklady Akad. Nauk S.S.S.R.*, **82**, 273 (1952); *Chem. Abstr.*, **47**, 2685 (1953). This behavior has been verified during the present investigation.

[5] A. E. Arbuzov, V. M. Zoroastrova, and N. I. Rizpolozhenskii, *Izvest. Akad. Nauk S.S.S.R., Odtel. Khim. Nauk*, **1948**, 208; *Chem. Abstr.*, **42**, 4932 (1948).

[6] Analyses are by the Microanalytical Division, Department of Chemistry, University of California. Boiling points are uncorrected; unless otherwise specified, distillations were through a half-meter simple Podbielniak column of the type which has been described in detail (J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, pp. 237–243). Melting points were determined on a Fisher micro hot stage.

[7] K. C. Kennard and C. S. Hamilton, *Org. Syntheses*, **37**, 82 (1957).

temperature. The analytical sample was evaporatively distilled at 0.1 mm. pressure.

Anal. Calcd. for $C_4H_7O_2PCl_4$: Cl, 54.6. Found: Cl, 52.0.

Repetition of this preparation on a larger scale yielded similar results and gave material with an identical infrared spectrum. When such material stood 8 days in a closed container at room temperature it became dark red and more viscous, and an altered infrared spectrum was observed.

Hydrolysis of isopropyl trichloromethylphosphonochloridate was carried out by heating on a steam bath for 90 min. a 1.0-g. sample of the oily ester acid chloride with 20 ml. of water. The oil was insoluble in cold water but the mixture became homogeneous as soon as heated. Freeze-drying of the reaction mixture left a semisolid residue weighing 0.74 g. A solution of this residue in 20 ml. of dry ether was treated dropwise with *N*-methylaniline until precipitation was complete. The precipitate was collected by suction filtration, washed with dry ether, and dried. The colorless solid, weight 0.68 g., was recrystallized from absolute alcohol to yield colorless plates, m.p. 220–223° (dec.). The m.p. reported[8] for *N*-methylanilinium trichloromethylphosphonate is 224–225° (dec.).

Anal. Calcd. for $C_8H_{11}O_3NPCl_3$: equiv. wt., 153. Found: equiv. wt., 155.

N-(2-chloroethyl)pyrrolidine was prepared by a published method for preparing amino halides.[9] To a solution of 18 g. (0.16 mole) of *N*-(2-hydroxyethyl)pyrrolidine (b.p. 72–73°/10 mm., n_D^{25} 1.4716) in 75 ml. of benzene, there was added dropwise during 0.5 hr. a solution of 20 g. (0.17 mole) of thionyl chloride in 50 ml. of benzene. The reaction was cooled in ice during the addition and a subsequent 1-hr. period of stirring. The mixture was poured into ice and water containing 25 g. of sodium hydroxide, and the product extracted with ether. Distillation yielded 15.2 g. (72%) of product, b.p. 60–63°/23 mm.

The relatively unstable *N*-(2-chloroethyl)pyrrolidine was characterized by conversion to the *picrate* in anhydrous ether. After crystallization from ethanol, the m.p. was 107.3–107.8°.

Anal. Calcd. for $C_{12}H_{15}N_4O_7Cl$: C, 39.73; H, 4.17; N, 15.45. Found: C, 39.83; H, 4.28; N, 15.67.

Attempts to convert this halide to a phosphorothioate (V) by reaction with diethyl potassium phosphorothioate[10] yielded a resinous undistillable material.

Ethylene phosphorochloridite. Commercial ethylene glycol (150 g.) was added dropwise with stirring to 450 g. of phosphorus trichloride, as the reaction mixture was maintained at 0–5°. After addition was complete, the solution was stirred at room temperature for 1 hr. and at 80–90° for 2 hr. The mixture was then distilled through a Claisen head, and the product collected in the range 60–80°/45 mm. was fractionated through a half-meter Vigreux column with heated jacket and partial reflux head. After a small fore-run, there was collected 121.0 g. (39.5%) of product, b.p. 65–66°/42 mm., n_D^{25} 1.4897; lit.,[11,12] b.p. 66–68°/47 mm., n_D^{20} 1.4894; b.p. 71.3°/50 mm., n_D^{25} 1.4878.

There has been reported[12] a more elaborate method of preparation which gives a better yield.

Ethyl ethylene phosphite (VI). To a stirred solution of 63 g. (0.5 mole) of ethylene phosphorochloridite in 200 ml. of anhydrous ether, there was added during 1 hr. at 10° a solution of 23 g. (0.5 mole) of absolute ethanol and 51 g. (0.5 mole) of triethylamine in 50 ml. of anhydrous ether. After stirring had been continued for an additional 0.5 hr. at room temperature, the mixture was diluted with 200 ml. of ether and the precipitated amine salt removed by filtration. Distillation of the filtrate and washings through a Claisen head yielded 56 g. (83%) of phosphite, b.p. 54–55°/16 mm., n_D^{20} 1.4411; lit.[5,12] b.p. 50.5–51°/15 mm., n_D^{20} 1.4395; b.p. 60–61°/21 mm., n_D^{25} 1.4390.

Dry air was bubbled through a 10-g. sample of this phosphite for 70 hr. while it was heated on a steam bath. A Dry Ice-cooled condenser was necessary to prevent sweeping of the phosphite from the flask in the stream of air. Distillation of the resultant product yielded 5.6 g. of starting material, b.p. 54°/15 mm. n_D^{20} 1.4410, and a nonvolatile residue.

Ethyl ethylene phosphorothioate (VIII). Sulfur (2.1 g., 0.066 mole) was added in small portions with stirring to 10 g. (0.066 mole) of ethyl ethylene phosphite. Addition was at such a rate as to keep the temperature of the exothermic reaction at 35–40°. Stirring was continued for 1 hr. after completion of the addition, then a trace of sulfur was removed by filtration and the product distilled to yield 4.4 g. (36%) of VIII, b.p. 79°/0.5 mm., n_D^{25} 1.4857.

Anal. Calcd. for $C_4H_9O_3PS$: C, 28.57; H, 5.39. Found: C, 28.65; H, 5.23.

A sample which had stood overnight had n_D^{25} 1.4861; after heating for 15 min. at 160° the n_D^{25} was 1.5060, and the viscosity had increased markedly.

2-(Diethylamino)ethyl ethylene phosphite (VII). A solution of 50 g. (0.43 mole) of diethylaminoethanol and 50 g. (0.50 mole) of triethylamine was added dropwise with stirring to a solution of 50 g. (0.40 mole) of ethylene phosphorochloridite in 500 ml. of benzene. The temperature of the reaction mixture was maintained at 5–10° with an ice bath, and the addition required about 1 hr. After the mixture had warmed to room temperature the amine salt was removed by filtration, and the product obtained from the filtrate was distilled to yield 29.1 g. (36%) of phosphite VII, b.p. 95–97°/4 mm., n_D^{25} 1.4618–1.4620. A sample redistilled for analysis had b.p. 97°/4 mm., n_D^{25} 1.4620.

Anal. Calcd. for $C_8H_{18}NO_3P$: C, 46.37; H, 8.76; N, 6.76. Found: C, 46.57; H, 8.54; N, 6.75.

2-(Diethylamino)ethyl trimethylene phosphite was prepared by the same procedure described for VII, utilizing 45 g. (0.38 mole) of diethylaminoethanol, 38 g. (0.38 mole) of triethylamine and 46.8 g. (0.33 mole) of trimethylene phosphorochloridite (b.p. 67–68°/12 mm., prepared as described for ethylene phosphorochloridite; lit.[12] b.p. 77°/25 mm.). There was obtained a yield of 38.2 g. (52%), b.p. 107–110°/3.5–4.0 mm., n_D^{25} 1.4592–1.4609. The analytical sample had b.p. 110°/4.0 mm., n_D^{25} 1.4609.

Anal. Calcd. for $C_9H_{20}NO_3P$: C, 48.86; H, 9.11; N, 6.33. Found: C, 48.75; H, 8.96; N, 6.23.

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[8] I. S. Bengelsdorf and L. B. Barron, *J. Am. Chem. Soc.*, **77**, 2869 (1955).

[9] D. S. Breslow, R. S. Yost, H. G. Walker, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1921 (1944).

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[11] P. A. Rossiiskaya and M. I. Kabachnik, *Izvest. Akad. Nauk S.S.S.R., Odtel. Khim. Nauk*, **1947**, 509; *Chem. Abstr.*, **42**, 2924 (1948).

[12] H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).

Synthesis of 1-Substituted Thymines

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Received July 25, 1958

Gearien and Binkley[1] have recently reported a method for the synthesis of 1-substituted uracils in which ethyl acrylate reacted with a primary

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[1] J. E. Gearien and S. B. Binkley, *J. Org. Chem.*, **23**, 491 (1958).