5 cc. of methylene chloride was added over a period of 45 min. The mixture was stirred for 10 min., 6 cc. of glacial acetic acid and 0.58 cc. of water added, and then warmed to 20°. Chromic acid (0.66 g.) dissolved in 0.4 cc. of water and 0.75 cc. of glacial acetic acid was added subsequently over a period of 10 min., and the resulting mixture stirred for 15 hr. The dark solution was then poured into 50 cc. of water and 10 cc. of methylene chloride, the organic phase separated, and the water layer extracted three more times with 10 cc. of methylene chloride each. To the combined extracts was added 3.5 cc. of methanol and 0.46 g. of zinc dust and the mixture refluxed for 45 min. An additional 0.5 cc. of glacial acetic acid and 0.40 g. of zinc dust was added and reflux continued for another 30 min.

The zinc dust was filtered, washed with methylene chloride, and the filtrate stirred at room temperature for 2 hr. after addition of 2 cc. of concd. hydrochloric acid. The solution was then poured into water, the methylene chloride layer separated, and the water phase extracted with more methylene chloride. Evaporation of the solvent yielded 1.05 g. of a residue, which was chromatographed on a column of Florisil (280 × 20 mm.). Ether eluted pure VII (0.120 g.), fraction I, followed by a mixture of VI and VII, fraction II and pure VI (0.384 g.), m.p. 171–175°, fraction III. Subsequent elution with ether–ethyl acetate resulted in a mixture of VI and VII.

Fraction I was recrystallized from methanol yielding 0.08 g. material of m.p. 248–250.5°, $[\alpha]^{23}D$ −95°, infrared absorption at 1764 cm.$^{-1}$ (5-membered lactone).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.77; H, 9.36.

Fraction III, m.p. 171–175° (0.384 g.) was recrystallized from acetone-water: yield, 0.154 g., m.p. 186–187°, $[\alpha]^{23}D$ +49°, infrared absorption at 1672 cm.$^{-1}$ (α,β-unsaturated ketone), 1773 cm.$^{-1}$ (5-membered lactone), λ_{max} 240 mμ (ϵ 16,100).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.05; H, 8.80.

Oxidation of VII. To 0.2 g. of VII in 40 cc. of acetone at 10° was added 0.2 cc. of chromic acid reagent[5] and the mixture stirred for 4 min. It was then poured into ice water, the precipitated material filtered, dissolved in 6 cc. of methylene chloride, and, after addition of 1 cc. of methanol and 0.3 cc. of conc. hydrochloric acid, stirred at room temperature for 2 hr. Water was then added, the methylene chloride layer separated, and the water phase extracted with methylene chloride. The extract was dried with sodium sulfate and the solvent evaporated yielding 0.180 g. residue. This was filtered in benzene through a column of 15 g. of Florisil, furnishing 0.143 g. of material, which, after recrystallization from methanol, gave 0.070 g. product identical with VI by infrared and ultraviolet spectra, mixed m.p., and rotation.

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MEDICAL RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC.
GROTON, CONN.

Derivatives of Phosphonic Acids

D. C. SCHROEDER, P. O. CORCORAN, C. L. HOLDEN, AND M. A. MULLIGAN

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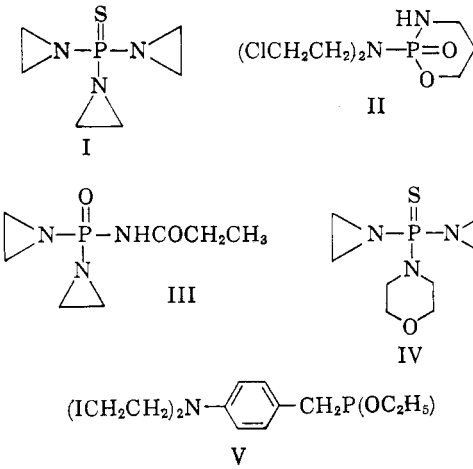
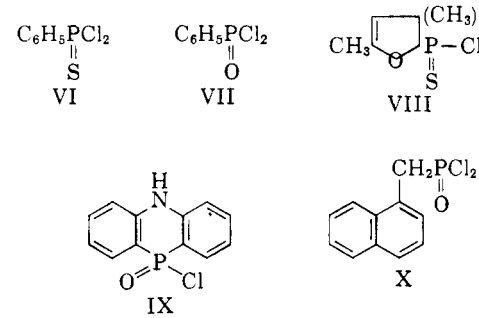
A number of organophosphorus compounds—*e.g.*, I, II, III, IV, and V—have shown varying degrees



of effectiveness in the treatment of cancer.[1] As most of these compounds are derivatives of phosphoric acid, it seemed of interest to prepare certain derivatives of phosphonic acids and have them screened for antitumor activity. We concentrated mostly on phosphonamides, but also included a few esters and salts. In some cases the phosphorus atom was incorporated into a heterocyclic ring as in II. The phosphonamides were prepared by treating phenylphosphonothionic dichloride (VI), phenylphosphonic dichloride (VII), 2-chloro-2-thiono-3,3,5-trimethyl-1,2-oxaphosphol-4-ine (VIII), dibenzophosphazinyl chloride (IX), and 1-naphthylmethylphosphonic dichloride (X) with primary or secondary amines.[2] In some cases the reaction was



quite exothermic and reached completion with no further heating. In other instances a reflux period was required. These reactions were encouraged either by using an excess of the amine or by adding a tertiary amine such as trimethylamine or pyridine to remove the hydrogen chloride which was formed. When equivalent quantities of a *tert*-aminoalkylamine and phosphonyl chloride were used, the hydrochloride of the *tert*-aminoalkylamide of the phosphonic acid resulted. Cyclic compounds were prepared by treating phosphonyl dichlorides with certain amino alcohols.

In general these reactions were carried out in an

(1) "Cancer," *Chemical and Engineering News*, American Chemical Society, Vol. **37**, October 12, 1959, p. 60.

(2) G. M. Kosolapoff, *Organophosphorus Compounds*, Wiley, New York, 1950, p. 279.

inert solvent, such as benzene or toluene. However, in certain instances, pyridine (XX), benzene-water (XIX), and no solvent (XXXIV and XXXX) were found to be more advantageous. The mixed ester amide (XI) was formed when XI and 4-aminoacetophenone were permitted to react in ethanol.

IX was prepared by treating dibenzophosphazinic acid[3] with thionyl chloride. By heating diethyl 1-naphthylmethylphosphonate with phosphorus pentachloride in benzene solution for two hours X was obtained.[4] VI, VII, and VIII are commercially available.

Salts of chloromethylphosphonic acid were prepared by mixing cautiously one mole of the acid with one mole of amine and recrystallizing from ethanol-water. Negative tests for ionic chloride and infrared spectra confirmed their structures. Phosphonate esters were synthesized from the appropriate alkyl or aralkyl halide and triethyl phosphite via the Michaelis-Arbuzov reaction.

All of the compounds listed in Table I were subjected to biological screening.[5] XV, XXXII, XXXIII, and XXXVIII showed slight activity against EO 771 (established) tumor in mice.

EXPERIMENTAL

Preparation of phosphonamides. General procedure. Well known methods[2] were used to prepare the phosphonamides listed in Table I. However, because of the varying properties of the starting materials and final products, different conditions for carrying out the reactions, and (or) special techniques in working up the products were often necessary.

Two equivalents—*i.e.*, two moles of monoamine per active chlorine atom in the acid chloride of a primary or secondary amine or one equivalent of the amine and one equivalent of triethylamine were dissolved in dry benzene (or toluene). To this solution was added slowly with stirring one equivalent of the phosphonyl chloride. In some cases (XVI, XXV, XXXVII, XXXVIII, and XXXIX)[6] this reaction was quite exothermic and went to completion by merely stirring overnight. In other instances (XII, XV, XVIII, and XXXVI) a 2–3 hr. reflux period was necessary. The amine hydrochloride which formed was removed by filtration and the filtrate washed thoroughly with water. Concentration of the benzene (or toluene) solution yielded the crude amide. When this residue was a solid, it was purified simply by recrystallization from an appropriate solvent such as ethanol, ethanol-water, or benzene. However, XVIII, XXXVI, XXXVII, and XXXVIII were first isolated as viscous oils. Trituration with ether converted XVIII to a solid and XXXVIII crystallized after standing at room temperature for two weeks. XXXVI and XXXVII remained undistillable oils after trituration with ether, petroleum ether, cold ethanol, water, heating in toluene, chilling, and standing several weeks at room temperature. They were then subjected to 0.1 mm. pressure for 48 hr. to remove all volatiles and thus obtained in a reasonably pure state. 1-Naphthylmethylphosphonic dichloride used in preparing XXV was obtained by treating 0.02 mole of diethyl 1-naphthylmethylphosphonate with 4.2 g. phosphorus pentachloride in 50 ml. of dry benzene at reflux for 2 hr.[4] The reaction was then concentrated under reduced pressure and the residue used directly in the preparation of the dipiperidide.

2-Phenylhydrazino-2-thiono-3,3,5-trimethyl-1,2-oxaphosphol-4-ine (XXXIV). Phenylhydrazine (0.1 mole) was added slowly with cooling and stirring to 0.05 mole of VIII. This mixture was allowed to stand 3 days at room temperature and a solid mass resulted. The product was extracted from the phenylhydrazine hydrochloride with ether. Concentration of the ethereal solution under reduced pressure left a yellow oil which crystallized when triturated with hexane. A pure white crystalline product was obtained by recrystallization from ethanol-water.

P-Phenylphosphonothionic diguanidide (XIX). To a solution of 64.4 g. (0.36 mole) of guanidine carbonate and 43.2 g. (1.08 moles) of sodium hydroxide in 400 ml. of water was added with vigorous stirring 38.2 g. (0.18 mole) of VI in 320 ml. of benzene. Stirring was continued and the reaction mixture heated at reflux for 24 hr. After cooling, the white precipitate which had formed was collected by filtering the two phase solution and recrystallized from ethanol.

N,N'-Di-(4-sulfonamidophenyl)-P-phenylphosphonothionic-diamide (XX). 4-Aminobenzenesulfonamide (0.2 mole) was dissolved in 150 ml. of pyridine. To this was added with stirring 0.1 mole of VI producing a somewhat exothermic reaction. When it had subsided the solution was heated on a steam bath for 2 hr. Upon chilling, the solution became a thick syrup and the addition of water (1 l.) caused an oil to separate. The aqueous phase was removed by decantation and the remaining oil taken up in ethanol. Drop-wise addition of water precipitated a solid product. It was further purified by recrystallization from ethanol-water.

Ethyl N-(4-acetylphenyl)-P-phenyl-phosphonamidothionate (XI). A solution of 10.5 g. (0.05 mole) of VI and 27.0 g. (0.2 mole) of 4-aminoacetophenone in 200 ml. of ethanol was heated 0.5 hr. on a steam bath. Considerable amine hydrochloride precipitated and after chilling was removed by filtration. The filtrate was concentrated under reduced pressure leaving a thick oil. Trituration with water induced crystallization. This product was collected by filtration and recrystallized from ethanol.

Preparation of cyclic compounds from amino alcohols and phosphonyl dichlorides. XXI, XXII, XXIII, and XXIV were prepared in the same manner as described in the general procedure for phosphonamides except that one mole of the amino alcohol and two moles of triethylamine were used for each mole of phosphonyl dichloride (VI or VII). These reactions were quite exothermic and so required no reflux period. XXII and XXIII were first isolated as oils. XXII was converted to a solid by trituration with cold ethanol. XXIII was finally isolated in crystalline form as the monohydrate. Infrared confirmed that it was a hydrate rather than a partially closed ring.

Preparation of tert-aminoalkylphosphonamides. Using one equivalent of *tert*-aminoalkylamine for each equivalent of phosphonyl chloride, XIII, XIV, XVII, and XXXV were precipitated as hydrochlorides after a 2-hr. reflux period in dry benzene. They were collected by filtration and recrystallized from ethanol. XIII and XXXV were stable crystalline products. However, the hydrochlorides of XIV and XVII were extremely hygroscopic and so they were converted to free bases which were easier to handle. This was accomplished by taking them up in water, adding ammonium hydroxide until basic, and extracting with benzene. Concentration of the benzene yielded oils which crystallized when triturated with petroleum ether. The bases were recrystallized from ethanol. Analysis and infrared indicated that XVII was a tetrahydrate.

N-Methylpiperazide of dibenzophosphazinic acid (XXXX).

(3) P. G. Serguv and D. G. Kudryashov, *J. Gen. Chem. U.S.S.R.*, **8**, 266 (1938); *Chem. Abstr.*, **32**, 5403 (1938).

(4) Same as ref. 2, p. 62.

(5) Biological screening was carried out by Dr. S. S. Barkulis and associates of these laboratories.

(6) The evolution of hydrogen sulfide during the preparation of XXXIX gave a clue as to its identity. This was confirmed by elemental analysis and infrared spectrum.

TABLE I

DERIVATIVES OF PHOSPHONIC ACIDS

No.	Compound	Yield, %	M.P.[a]	Empirical Formula
XI	$C_6H_5P(=S)(-OC_2H_5)-NHC_6H_4COCH_{3-4}$	20	140–142	$C_{16}H_{18}NO_2PS$
XII	$C_6H_5P(=S)(-NC_5H_{10})_2$	61[b]	96[c]	$C_{16}H_{25}N_2PS$
XIII	$C_6H_5P(=S)(-N(-CH_2CH_2-)_2NCH_3)_2$	23[b]	202–204	$C_{16}H_{27}N_4PS.2HCl.H_2O$
XIV	$C_6H_5P(=O)[-N(CH_2C_6H_5)C_5H_4N-2]_2$	33[b]	87–90	$C_{30}H_{27}N_4OP$
XV	$C_6H_5P(=S)(-NHNHC_6H_5)_2$	71[d]	198–200	$C_{18}H_{19}N_4PS$
XVI	$C_6H_5P(=S)(-NHC_6H_4Cl-3)_2$	22[d]	C	$C_{18}H_{15}Cl_2N_2PS$
XVII	$C_6H_5P(=S)[-N(CH_2C_6H_5)C_5H_4N-2]_2$	35[b]	66.68	$C_{30}H_{27}N_4PS\cdot4H_2O$
XVIII	$C_6H_5P(=S)(-N(-CH_2CH_2-)_2O)_2$	53[b]	106–108	$C_{14}H_{21}N_2O_2PS$
XIX	$C_6H_5P(=S)[-NHC(=NH)NH_2]_2$	48	210–212	$C_8H_{13}N_6PS$
XX	$C_6H_5P(=S)(-NHC_6H_4-SO_2NH_2-4)_2$	20	216–218	$C_{18}H_{19}N_4O_4PS_3$
XXI	$C_6H_5P(=S)-NHCH_2CH_2O$	18[f]	217–218	$C_8H_{10}NOPS$
XXII	$C_6H_5P(=S)NHCH_2CH_2CH_2O$	20[f]	88–91	C_9HL_2NOPS
XXIII	$C_6H_5P(=O)NHCH_2CH_2O$	12[e]	257–258	$C_8H_{10}NO_2P\cdot H_2O$
XXIV	$C_6H_5P(=S)NHC_6H_4S-1,2$	30[f]	103–106	$C_{12}H_{10}NPS_2$
XXV	$1\text{-}C_{10}H_7CH_2P(=O)(-NC_5H_{10})_2$	23[b]	168–170	$C_{21}H_{29}N_2OP\cdot H_2O$
XXVI	$2,4\text{-}(CH_3)_2C_6H_3COCH_2P(=O)(OC_2H_5)_2$	50	C	$C_{14}H_{21}O_4P$
XXVII	$C_6H_5OCH_2CH_2OCH_2CH_2CH_2P(=O)(OC_2H_5)_2$	59	C	$C_{14}H_{25}O_5P$
XXVIII	$OC(C_6H_5)=C(C_6H_5)N=CCH_2P(=O)(OC_2H_5)_2$	33	[d]	$C_{20}H_{22}NO_4P$
XXIX	$[ClCH_2P(=O)(OH)O]^-[NH_2NH_3]^+$	100	80–82	$CH_8ClN_2O_3P$
XXX	$[ClCH_2P(=O)(OH)O]^-[H_2NC(=NH)NHNH_3]^+$	100	127–129	$C_2H_{10}ClN_4O_3P$
XXXI	$[ClCH_2P(=O)(OH)O]^-[NH_4]^+$	20	142–144	CH_7ClNO_3P
XXXII	$[ClCH_2P(=O)(OH)O]^-[C_6H_5NHNH_3]^+$	73	136–139	$C_7H_{12}ClN_2O_3P$
XXXIII	$[ClCH_2P(=O)(OH)O]^-[C_6H_5NH_3]^+$	80	196–198	$C_7H_{11}ClNO_3P$
XXXIV	$OC(CH_3)=CHC(CH_3)_2-P(=S)NHNHC_6H_5$	40	121–123	$C_{12}H_{17}N_2OPS$
XXXV	$OC(CH_3)=CHC(CH_3)_2-P(=S)NH(CH_2)_3N(CH_3)_2.HCl$	16	116–118	$C_{11}H_{24}ClN_2OPS$
XXXVI	$OC(CH_3)=CHC(CH_3)_2-P(=S)-NC_2H_4$	75	C	$C_8H_{14}NOPS$
XXXVII	$OC(CH_3)=CHC(CH_3)_2P(=S)-NC_5H_{10}$	98	C	$C_{11}H_{20}NOPS$
XXXVIII	$OC(CH_3)=CHC(CH_3)_2P(=S)-N(-CH_2CH_2-)_2O$	60	63–65	$C_{10}H_{18}NO_2PS$
XXXIX	$[OC(CH_3)=CHC(CH_3)_2P(N_2H_4)=N-]_2$	70	190–192	$C_{12}H_{26}N_6O_2P_2$
XXXX	*N*-Methylpiperazide of dibenzophosphazinic acid	33	230–235	

[a] Melting points are uncorrected. [b] Prepared in benzene using excess amine. [c] A. Michaelis and G. Schlüter, *Ber.*, **31**, 1042 (1898), m.p. 92°. [d] Liquid, b.p. 160°/0.001 mm. [e] Undistillable oil. [f] Prepared in benzene using triethylamine.

To 0.03 mole of dibenzophosphazinic acid[3] in 150 ml. of dry toluene was added dropwise with stirring a fivefold excess of thionyl chloride. The mixture was then heated at reflux for 2 hrs. during which time a green oil separated from the solution. After cooling the toluene was decanted and the oil triturated several times with toluene. *N*-Methylpiperazine (0.09 mole) was added with stirring to the oil and this mixture was heated at 120° for 8 hr. When the reaction had cooled to room temperature, it was triturated with water and the resulting solid was collected by filtration. Recrystallization from ethanol-water gave XXXX as the dihydrate.

Preparation of salts of chloromethylphosphonic acid. These salts were prepared by mixing cautiously one mole of chloromethylphosphonic acid with one mole of amine. Considerable heat was evolved and the solid which formed was recrystallized from ethanol-water.

Esters of phosphonic acids were prepared by means of the Michaelis-Arbuzov reaction. ω-Chloro-2,4-dimethylacetophenone and phenoxyethoxyethyl chloride, used in the preparation of XXVI and XXVII, respectively, are commercially available. 2-Bromomethyl-4,5-diphenyloxazole used in the preparation of XXVIII was prepared by bromination of 2-methyl-4,5-diphenyloxazole[7] with *N*-bromosuccinimide.[8]

Acknowledgment. The authors are indebted to Mr. L. Dorfman and his associates of these laboratories for the elemental analyses and infrared determinations.

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TABLE I (*Continued*)

Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %		Phosphorus, %		Chlorine, %	
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
60.16	59.67	6.58	6.59	4.39	4.53			9.70	9.30		
				9.08	8.65	10.39	11.05				
				13.04	13.27					16.51	16.29
				11.42	11.10						
				15.81	15.93	9.05	9.31				
				7.12	6.84	8.15	8.57	7.88	7.39	17.78	16.74
				9.68	9.37	5.54	5.35	5.36	4.70		
				8.97	9.11	10.26	10.42	9.91	9.40		
37.49	37.89	5.11	5.40	32.79	32.79						
44.70	44.63	3.94	4.04	11.61	11.36						
48.24	48.12	5.06	5.25	7.03	6.90						
50.75	50.88	5.68	5.82	6.58	6.61						
47.80	47.97	6.02	6.37	6.97	7.21						
				5.32	5.59	24.35	24.27				
67.36	67.50	8.35	8.60	7.48	7.53						
59.14	59.52	7.44	7.21								
55.63	55.65	7.67	7.75								
64.67	64.58	5.97	6.07	3.77	3.73						
7.39	7.50	4.96	5.10	17.34	17.90						
11.86	11.89	4.97	5.11	27.65	27.54						
8.17	8.61	4.80	4.78	9.53	9.43						
35.23	35.03	5.08	5.12	11.77	12.32						
37.62	37.13	4.87	5.00	6.28	6.42						
53.72	53.68	6.39	6.46								
44.05	43.66	8.40	8.17	9.34	8.80						
47.02	46.54	7.40	6.98	6.86	6.61						
53.86	53.24	8.22	8.02	5.71	6.00						
48.56	48.62	7.34	7.55	5.67	5.70						
34.28	33.88	8.15	8.30	19.99	20.11						
				12.04	12.01	8.55	7.97				

Substituted 5-Nitrobenzimidazoles[1]

LIONEL JOSEPH AND JIM JULCA[2]

Received October 2, 1961

In connection with studies on the physical and physiological properties of benzimidazole derivatives and continuing our studies[3] on this group of heterocycles we have synthesized a number of substituted 5-nitrobenzimidazoles, 5-nitro-2-methylbenzimidazoles, and 5-nitro-2-hydroxymethylbenzimidazoles. In particular these derivatives are characterized by the presence of alkyl, aryl, and alkaryl substituents on the imino nitrogen of the benzimidazole nucleus.

Benzimidazoles without a substituent group on the imino nitrogen constitute a prototropic system. Monosubstitution in the benzene ring results in only two isomeric forms, a 5- or 6-isomer and a 4- or 7-isomer. Substitution on the imino nitrogen eliminates the possibility for the proton shift between the nitrogen atoms of the imidazole ring and in the case of monosubstitution in the benzene ring identity no longer exists between the 5- and 6-isomers or the 4- and 7-isomers.

The preparation of benzene-ring substituted benzimidazoles in which the hydrogen on the imino

(1) This study was supported by the San Diego County Heart Association.

(2) Taken in part from the M. S. thesis of Jim Julca, 1960.

(3) M. Rope, R. W. Isensee, and L. Joseph, *J. Am. Chem. Soc.*, **74**, 1095, (1952); G. Sandera, R. W. Isensee, and L. Joseph, *J. Am. Chem. Soc.*, **76**, 5173 (1954).