The total product, 66 mg., was dissolved in aqueous sodium carbonate solution and extracted with chloroform. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The ether was dried over anhydrous sodium sulfate, and the ether was removed from the filtered solution to leave 32 mg. of crude acid. Crystallization of this material from ether–hexane gave the pure biphenylcarboxylic acid II (R = OMe; R′ = CO_2H), m.p. 161–163°, λ_{max} 217 mμ (log ε 4.53) and 265 (4.11).

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.70; H, 5.42.

Methylation of 6 mg. of the acid with ethereal diazomethane in the usual way afforded 5 mg. of the methyl ester II (R = OMe; R′ = CO_2Me), m.p. 138–139°.

Synthesis of 3,4,5-Trimethoxy-3′-biphenylcarboxylic Acid (II, R = OMe; R′ = CO_2H).—A mixture of 2 g. of 1-iodo-3,4,5-trimethoxybenzene[26] and 1 g. of methyl *m*-iodobenzoate was placed in a 15-in. Pyrex tube equipped with a glass stirring rod. The air was displaced from the tube by a stream of nitrogen and the tube and its contents were placed in a metal bath. The temperature of the bath was raised slowly to 170° while 2.5 g. of copper bronze was added with stirring over 30 min. The temperature was raised to 220° and the mass was stirred occasionally for a period of 3 hr. After cooling, the reaction product was extracted repeatedly with benzene, and the filtered benzene solution was concentrated. Chromatography over aluminum oxide in benzene–hexane (1:2) gave 340 mg. of crude ester II (R = OMe; R′ = CO_2Me), which crystallized from ether to afford pure methyl 3,4,5-trimethoxy-3′-biphenylcarboxylate: m.p. 138–139°; infrared (Nujol) 5.90 (s) (ester carbonyl) μ; p.m.r. three-proton singlet, δ 3.86, six-proton singlet, δ 3.91 (aromatic methoxyls), two-proton singlet, δ 6.77 (C-2 and C-6 hydrogens), and 18-line ABCD pattern, δ 7.41–8.23 (ring-B aromatic hydrogens).

The mixture melting point with the ester obtained from degradation of albomaculine and this sample showed no depression; the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.32; H, 5.81.

Hydrolysis of Ester II (R = OMe, R′ = CO_2Me).—A methanolic solution of 15 mg. of the ester II (R = OMe) obtained by the Ullmann synthesis was refluxed with 2 ml. of 5 *N* potassium hydroxide for 3 hr. After cooling the solution, it was acidified with 2 *N* hydrochloric acid and then extracted with ether. Recovery of the product from ether afforded *ca.* 11 mg. of acidic material, which after two recrystallizations from ether gave 6 mg. of the pure acid II (R = OMe; R′ = CO_2Me), identical in every respect (infrared, mixture melting point) with that obtained from the Hofmann product.

Deoxynerinine (IV).—The diol III (125 mg.) was heated at 90–100° for 3 hr. with 25 ml. of 5% sulfuric acid. After cooling and basifying the solution with 2 *N* ammonium hydroxide, the product was extracted with chloroform. Recovery of the chloroform gave 105 mg. of a colorless oil. Distillation of this material at 110° (0.1 mm.) gave pure deoxynerinine (IV) as an oil: $[\alpha]_D$ +83°; λ_{max}^{EtOH} 280 mμ (log ε 3.09); infrared ($CHCl_3$) 6.20, 6.26 (aromatic ring), 8.90 (s), 9.14 (s) (cyclic ether) μ; p.m.r. six-proton singlet, δ 3.90, three-proton singlets, δ 3.92 (aromatic methoxyls) and 2.03 (N-methyl hydrogens), one-proton multiplets, δ 3.90 (C-5a hydrogen) and 5.50 (C-4 olefinic hydrogen), one-proton doublets δ 4.95 (*J* = 17.5 c.p.s.) and 4.87 (*J* = 17.5 c.p.s. (C-7) methylene group), and one-proton singlet, δ 6.83 (hydrogen).

Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60. Found: C, 68.72; H, 7.83.

Deoxynerinine Perchlorate.—To an ether solution of 25 mg. of the ether III, was added 1 drop of 70% perchloric acid. Trituration of the gum with ether, containing a small amount of methanol, gave a solid which on crystallization from methanol–ether gave the pure hydroperchlorate, m.p. 244–245°.

Anal. Calcd. for $C_{19}H_{26}ClNO_8$: C, 52.84; H, 6.06. Found: C, 52.92; H, 6.36.

Acknowledgments.—The authors are indebted to the South African Council for Scientific and Industrial Research for a bursary (to T. P. T.), and to Professor F. L. Warren for his interest in the early phases of this work.

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[26] This was prepared from gallic acid according to the procedure of Graebe and Suter.[16] The authors are indebted to Messrs. R. D. Haugwitz and W. Pearson, Indiana University, for their assistance with this preparation.

Synthesis of Dicarboximidophosphonothioates

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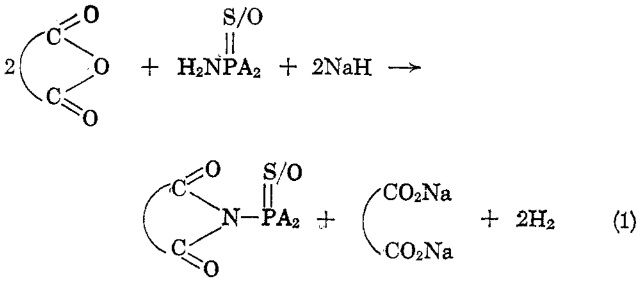
Dicarboximidophosphonothioates derived from a variety of five-membered ring dicarboximides and containing alkoxy, alkylamino, alkylthio, aryloxy, or alkyl groups attached to phosphorus have been prepared, principally by the novel reaction of cyclic anhydrides with phosphoramidothioates and sodium hydride. The reaction of phthalic anhydride with O,O-diethyl phosphoramidothioate and sodium hydride to form O,O-diethyl phthalimidophosphonothioate was shown to involve sodium O,O-diethyl phosphoramidothioate and disodium N-(diethoxyphosphinothioyl)phthalamate as intermediates.

Dicarboximidophosphonothioates, the N-phosphorothioyl derivatives of dicarboximides, have not been reported, and the related dicarboximidophosphonates have been described only recently and very briefly.[1] These compounds are not easily prepared by the usual methods,[2] but a wide variety of dicarboximidophosphonothioates and a few dicarboximidophosphonates have now been synthesized by the newly discovered reaction of cyclic dicarboxylic anhydrides with phosphorus amides and sodium hydride (reaction 1).



(1)

The obvious method for the preparation of dicarboximidophosphonothioates, the reaction of dicarboximide salts with phosphorus acid chlorides, can be realized, but usually only with fair yields and under exacting conditions. Thus, O,O-diethyl phthalimidophosphonothioate (I) was obtained in 50% yield from potassium phthalimide and O,O-diethyl phosphorochloridothioate (reaction 2) when the reaction was

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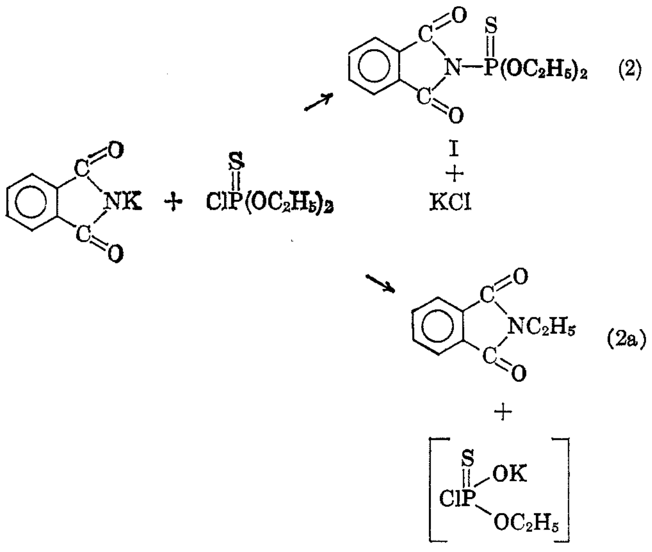
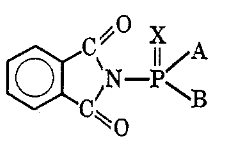
(1) A. K. Tsolis, W. E. McEwen, and C. A. VanderWerf, *Tetrahedron Letters*, No. 43, 3217 (1964); A. K. Tsolis, Dissertation, University of Kansas, 1963.

(2) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 278–300.



carried out in N-methyl-2-pyrrolidone at 0° over a 16-hr. period. Dimethylformamide and hexamethylphosphoramide were also useful solvents (28 and 56% yields, respectively), but less polar and hydroxyl-containing solvents were completely ineffective. The yield decreased with shorter reaction periods owing to incomplete reaction and at higher temperatures because of side reactions. Alkylation of the phthalimide ion by O,O-diethyl phosphorochloridothioate (reaction 2a)[3,4] was indicated to be a significant side reaction by the isolation of N-ethylphthalimide in 11 and 16% yields from two experiments. The product I is a poor alkylating agent[5] and is not likely to be involved in this. Reaction of the phosphorus acid chloride with solvent is suggested by the reactivity of phosphoryl chloride with dimethylformamide[6] and is undoubtedly also important. Despite these difficulties, the method has some synthetic utility and phthalimidophosphonothioates containing alkoxy, alkylamino, alkylthio, and aryloxy groups attached to phosphorus and diethyl phthalimidophosphonate were prepared by it (Table I).

TABLE I
PHTHALIMIDOPHOSPHONOTHIOATES FROM POTASSIUM PHTHALIMIDE



A	B	X	Yield, %[a]	M.p., °C	Anal.
OC_2H_5	OC_2H_5	S	50	82.5–84	*b*
OC_2H_5	OC_2H_5	O	18	62.5–64	*b*
$O\text{-}n\text{-}C_3H_7$	$O\text{-}n\text{-}C_3H_7$	S	11	52–53	*b*
SC_2H_5	SC_2H_5	S	56	59–59.5	*c*
$NH\text{-}i\text{-}C_3H_7$	$OC_6H_3Cl_2(2,4)$	S	46	139–139.5	*d*

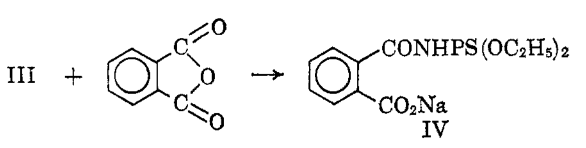
[a] Reactions in N-methyl-2-pyrrolidone at 0° for 16 hr. [b] Analysis is given in Table II. [c] *Anal.* Calcd. for $C_{12}H_{14}NO_2PS_3$: C, 43.5; H, 4.26; N, 4.23. Found: C, 43.6; H, 4.40; N, 4.06. [d] *Anal.* Calcd. for $C_{17}H_{15}Cl_2N_2O_3PS$: C, 47.6; H, 3.52; Cl, 16.5; N, 6.53. Found: C, 47.4; H, 3.57; Cl, 16.6; N, 6.40.

The two reported dicarboximidophosphonates are succinimide derivatives obtained by the reaction of N-halosuccinimides with trialkyl phosphites.[1] This reaction was easily extendible to N-chlorophthalimide, which gave a 52% yield of diethyl phthalimidophosphonate on treatment with triethyl phosphite. Extension of the reaction to the synthesis of dicarboximidophosphonothionates from phosphorothioites, however, was not expected, since carbon–oxygen rather than carbon–sulfur bond cleavage is usually[7] observed with Arbuzov reaction intermediates[1] containing both. Accordingly, no I was obtained on treatment of N-chlorophthalimide with triethyl phosphorothioite.

The reaction of phosphorus amides with cyclic dicarboxylic anhydrides and sodium hydride (reaction 1), on the other hand, appears to be a very general method of synthesis of both dicarboximidophosphonothioates and phosphonates. The yields obtained in this study were only fair, ranging from 4 to 75% (Table II), but these do not necessarily represent maximum yields as many of the syntheses were carried out under conditions now known to be inferior. The compounds prepared by the method include examples obtained from phosphoramidothioates having alkoxy, alkylamino, alkylthio, and alkyl groups attached to phosphorus and from diethyl phosphoramidate as well as examples obtained from a wide variety of cyclic dicarboxylic anhydrides including maleic, succinic, and phthalic anhydrides and their derivatives. The only limitation encountered is that the anhydride ring must be five membered. Glutaric and naphthalic anhydrides, for example, gave no product.

This remarkable reaction is actually a composite of several simpler reactions (reactions 3–7), each of which has been demonstrated individually for the reaction of phthalic anhydride with O,O-diethyl phosphoramidothioate (II) and sodium hydride to form O,O-diethyl phthalimidophosphonothioate (I). The initial reaction is the formation of sodium O,O-diethyl phosphor-

$$\underset{\text{II}}{(C_2H_5O)_2PSNH_2} + NaH \longrightarrow \underset{\text{III}}{(C_2H_5O)_2PSNHNa} + H_2 \quad (3)$$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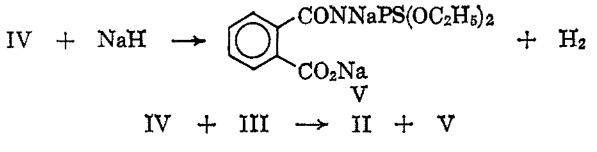
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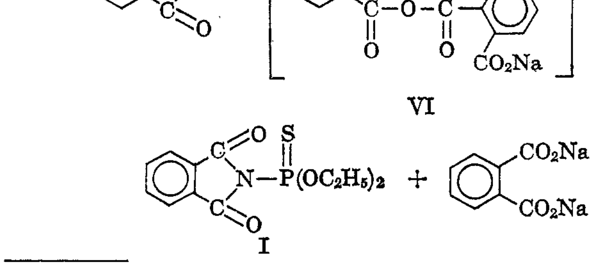
$$\text{IV} + \text{III} \longrightarrow \text{II} + \text{V} \quad (6)$$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[3] J. H. Billman and R. V. Cash, *Proc. Indiana Acad. Sci.*, **63**, 108 (1953); *Chem. Abstr.*, **49**, 8194 (1953).

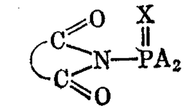
[4] C. Stolzer and A. Simon, *Ber.*, **96**, 453 (1963).

[5] D. W. Osborne, *J. Org. Chem.*, **31**, 197 (1966).

[6] Z. Arnold and J. Zemlicka, *Proc. Chem. Soc.*, **227** (1958).

[7] R. G. Harvey, H. I. Jacobson, and E. V. Jenson, *J. Am. Chem. Soc.*, **85**, 1618 (1963).

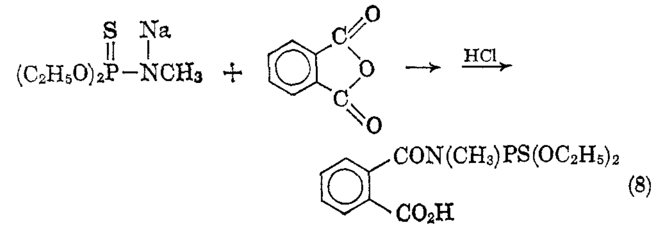
TABLE II
DICARBOXIMIDOPHOSPHONOTHIOATES FROM ANHYDRIDES AND PHOSPHORAMIDOTHIOATES



Dicarboximide	A	X	Reacn. cond.[a]	Yield %	M.p. or b.p. (μ), °C.	Formula	Calcd., %				Found, %			
							C	H	N	Other	C	H	N	Other
Phthalimide	OCH_3	S	B	45	126.5–128	$C_{10}H_{10}NO_4PS$	44.3	3.72	5.17	11.4 (P)	44.3	3.81	5.14	11.2
Phthalimide	OC_2H_5	S	A	75	82.5–84	$C_{12}H_{14}NO_4PS$	48.2	4.72	4.68	10.4 (P)	48.4	4.44	4.48	10.3
			B	66										
			C	76										
			D	61										
Phthalimide	OC_2H_5	O	A	36	62.5–64	$C_{12}H_{14}NO_5P$	50.9	4.98	4.95		51.2	4.84	5.00	
Phthalimide	O-n-C_3H_7	S	A	61	54–54.5	$C_{14}H_{18}NO_4PS$	51.3	5.54	4.28		51.3	5.54	4.42	
Phthalimide	O-i-C_3H_7	S	A	70	78–80	$C_{14}H_{18}NO_4PS$	51.3	5.54	4.28		51.1	5.60	4.34	
Phthalimide	O-i-C_4H_9	S	A	16	38–41	$C_{16}H_{22}NO_4PS$	54.1	6.24	3.94		53.9	6.22	3.93	
Phthalimide	OCH_2CCl_3	S	A	48	132–133.5	$C_{12}H_8Cl_6NO_4PS$	28.5	1.59	2.77	42.0 (Cl)	28.3	1.72	2.76	42.0
Phthalimide	$N(CH_3)_2$	S	B	21	168.5–170	$C_{12}H_{16}N_3O_2PS$	48.5	5.42	14.1		48.2	5.39	14.1	
Phthalimide	C_2H_5	S	A	36	137–138.5	$C_{12}H_{14}NO_2PS$	54.0	5.28	5.25		54.1	5.24	5.02	
Tetrachloro-P[b]	OC_2H_5	S	B[c]	17	162–165	$C_{12}H_{10}Cl_4NO_4PS$	33.0	2.30	3.20	7.08 (P)	33.5	2.56	3.08	7.01
Tetrachloro-P[b]	SC_2H_5	S	A	62	131–133	$C_{12}H_{10}Cl_4NO_2PS_3$	30.7	2.15	2.99	30.2 (Cl)	31.1	2.30	3.15	30.2
3-Nitro-P	OC_2H_5	S	B[c]	5	91–92	$C_{12}H_{13}N_2O_6PS$			8.14				8.23	
3-Nitro-P	SC_2H_5	S	A	43	90–92	$C_{12}H_{13}N_2O_4PS_3$	38.3	3.48	7.44		38.2	3.66	7.42	
4-Bromo-P	OC_2H_5	S	B	22	69–70	$C_{12}H_{13}BrNO_4PS$			3.70	21.1 (Br)			3.69	21.3
4-Bromo-P	SC_2H_5	S	C	18	90–92	$C_{12}H_{13}BrNO_2PS_3$	35.1	3.19	3.41	19.5 (Br)	35.3	3.12	3.70	19.3
4-Chloro-P	OC_2H_5	S	A	48	88.5–89	$C_{12}H_{13}ClNO_4PS$	43.2	3.98	4.20		43.6	3.95	4.27	
4-Methyl-P	OC_2H_5	S	A	73	69.5–70	$C_{13}H_{16}NO_4PS$	49.8	5.14	4.47		49.5	5.23	4.40	
4-Methyl-P	O-n-C_3H_7	S	C	39	35–37	$C_{15}H_{20}NO_4PS$	52.8	5.90	4.10		52.8	5.84	3.97	
4-Methyl-P	SC_2H_5	S	C	54	87.5–88.5	$C_{13}H_{16}NO_2PS_3$	45.2	4.67	4.06	8.97 (P)	45.7	4.35	3.95	9.18
4-Acetamido-P	OC_2H_5	S	C	26	138–138.5	$C_{14}H_{17}N_2O_5PS$	47.2	4.81	7.86		47.2	4.72	7.80	
Cyclohexane-1,2-D[d]	OC_2H_5	S	A	46	$n^{25}\mathrm{D}$ 1.5100	$C_{12}H_{20}NO_4PS$	47.2	6.60	4.59		46.6	6.52	4.89	
1-Cyclohexene-1,2-D	OC_2H_5	S	A	63	65–66	$C_{12}H_{18}NO_4PS$	47.5	5.98	4.62		47.6	6.05	4.34	
4-Cyclohexene-1,2-D	OC_2H_5	S	B[e]	4	$n^{25}\mathrm{D}$ 1.5205	$C_{12}H_{18}NO_4PS$			4.62				4.62	
4-Cyclohexene-1,2-D	SC_2H_5	S	A	39	45–46	$C_{12}H_{18}NO_2PS_3$	43.0	5.41	4.18	28.7 (S)	43.0	5.48	4.22	28.4
4-Methyl-4-cyclohexene-1,2-D	OCH_3	S	A	20	42–43	$C_{11}H_{16}NO_4PS$	45.7	5.58	4.84		49.5	5.78	4.91	
(*endo*)(*cis*)-Bicyclo[2.2.1]hept-5-ene-2,3-D	OC_2H_5	S	B	51	88–89.5	$C_{13}H_{18}NO_4PS$	49.5	5.75	4.44		49.6	5.78	4.31	
(*exo*)(*cis*)-7-Oxabicyclo[2.2.1]heptane-2,3-D	OC_2H_5	S	D[c]	37[f]	67–68	$C_{12}H_{18}NO_5PS$	45.1	5.68	4.39	9.71 (P)	45.1	5.78	4.33	9.91
Succinimide	OC_2H_5	S	A	34	61.5–62	$C_8H_{14}NO_4PS$	38.2	5.62	5.58		38.5	5.79	5.48	
Maleimide	OC_2H_5	S	A	37	83–84 (30)[g]	$C_8H_{12}NO_4PS$	38.5	4.85	5.62		38.8	4.95	5.82	
Dichloromaleimide	OCH_3	S	C	8	115–116	$C_6H_6Cl_2NO_4PS$	24.8	2.08	4.83		24.6	2.03	4.78	
Dichloromaleimide	OC_2H_5	S	A	59	65–68 (0.2)[h]	$C_8H_{10}Cl_2NO_4PS$	30.2	3.17	4.40	22.3 (Cl)	30.2	8.26	4.43	22.0
Dichloromaleimide	OC_2H_5	O	A	24	79–81 (0.4)	$C_8H_{10}Cl_2NO_5P$	31.8	3.34	4.63		31.9	3.53	4.50	
Dichloromaleimide	SC_2H_5	S	A	31	108–110 (0.8)	$C_8H_{10}Cl_2NO_2PS_3$	27.4	2.88	4.00		27.9	3.03	3.82	
Dichloromaleimide	$N(CH_3)_2$	S	A	36	110–112	$C_8H_{12}Cl_2N_3O_2PS$	30.4	3.82	13.3		30.1	3.78	13.5	

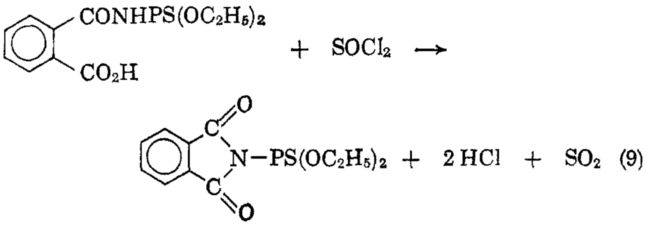
[a] A is procedure A of Experimental Section, phosphoramidothioate and anhydride added consecutively to sodium hydride; B is procedure B of Experimental Section, sodium hydride added to a mixture of phosphoramidothioate and anhydride; C is procedure C of Experimental Section, procedure A except acetic anhydride used for half of the anhydride; D is isolation of the intermediate N-(diethoxyphosphinothioyl)amido acid and subsequent treatment with thionyl chloride. [b] P = phthalimide. [c] Tetrahydrofuran solvent and a 1:1:1 ratio of reactants employed. [d] D = dicarboximide. [e] Tetrahydrofuran solvent. [f] Intermediate, m.p. 153–155°, 61% yield; ring closure, 60% yield. [g] $n^{25}\mathrm{D}$ 1.5106. [h] $n^{25}\mathrm{D}$ 1.5260.

amidothioate (III) from the amide and sodium hydride (reaction 3). Similar reactions[8] and the further reactions of the anions formed with alkyl halides[8] and with phosphorochloridates[9] have been reported. Phosphoramidate anions have also been prepared in this manner and their reactions with some carbonyl groups have been reported.[10] Under the conditions of this reaction, 1 mole of hydrogen was evolved on addition of II to excess sodium hydride and an impure salt could be obtained on evaporation of the solvent. This anion, being an excellent nucleophilic reagent, reacts exothermally with phthalic anhydride to form sodium N-(diethoxyphosphinothioyl)phthalamate (IV) in the next step of the reaction (reaction 4). Compound IV, however, contains an acidic proton (pK_a = 10.6)[5] and is rapidly converted to the disodium salt V by means of reactions 5 and 6. Thus, 1 mole of hydrogen was produced on the slow addition of 1 mole of phthalic anhydride to a mixture of III and sodium hydride and, after acidification, N-(diethoxyphosphinothioyl)phthalamic acid[5] was obtained in 73% yield. In the absence of sodium hydride the same reactants formed considerable amounts of II, and the yield of I (after the addition of more phthalic anhydride) was essentially halved. Because of this acid–base exchange, 2 moles of sodium hydride/mole of II must be used to obtain good yields in the over-all reaction. Further confirmation of reaction 4 was obtained by the synthesis of N-(diethoxyphosphinothioyl)-N-methylphthalamic acid (VII) from sodium O,O-diethyl methylphosphoramidothioate and phthalic anhydride (reaction 8). The final step in the reaction, the cyclization of V (reaction 7), is formally a transfer of sodium oxide from V to phthalic anhydride and can best be understood by postulating the mixed anhydride VI as an intermediate. The cyclization would then take place through two simple reactions, a base-catalyzed anhydride interchange and an acylation by anhydride. Experimentally, V, prepared either as above or by treatment of the corresponding acid with sodium hydride, is converted to I in good yield by phthalic anhydride under the reaction conditions. The disodium phthalate formed as a by-product in this step was isolated from the over-all reaction in 87% yield (as the acid).


(8)

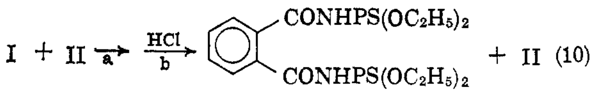
VII

Many of the compounds of Table II were prepared by the addition of sodium hydride to a solution containing the anhydride and phosphorus amide, conditions under which reactions 3–7 occur simultaneously and no intermediates could be isolated. It is preferable, however, to add the phosphorus amide and anhydride consecutively to sodium hydride suspended in a polar solvent, such as dimethylformamide or dimethyl sulfoxide. Under these conditions reaction 3 takes place on addition of the phosphorus amide, reactions 3–6 on the addition of half of the anhydride, and reaction 7 on addition of the remaining anhydride. This procedure not only allows a more controlled reaction with improved yields (75% *vs* 66% for I), but also permits two valuable variations on the general procedure. Thus, half of the cyclic anhydride can be replaced by other organic or inorganic anhydrides such as acetic anhydride, acetyl chloride, or phosphoryl chloride. The yields of I obtained using this variation were actually somewhat improved (76–87%), probably because the final reaction mixtures were more fluid. This procedure is particularly useful for the synthesis of dicarboximidophosphonothioates from uncommon anhydrides and it was used in several cases (Table II). These cyclization reactions are probably closely related in mechanism to reaction 7. The second variation consists of isolating the intermediate disodium (N-phosphinothioyl)amidates (exemplified by V) as the acids and subsequently effecting the ring closure by other methods. In the case of compound I, this was easily accomplished with thionyl chloride (89% yield, reaction 9), acetyl chloride (80% yield), or acetic anhydride and sodium acetate (93% yield). The over-all yield of I by this route was about 61%.


(9)

I

Two side reactions have also been identified in the synthesis of I from phthalic anhydride. Thus, reaction 10a was indicated to occur by the isolation of O,O,O′,O′-tetraethyl phthaloyldiphosphoramidothioate (VIII) in 11–16% yields after acidification of the reaction mixture. In a separate experiment VIII was actually obtained in high yield after acidification of the product obtained by treatment of I with III and sodium hydride.[5] This reaction can be avoided by the use of conditions under which all the III is converted to V before any product is formed; that is, by following the preferred procedure and adding the anhydride very slowly with good mixing. Another probable side reaction, which actually was observed only in the unsuccessful attempt to extend the reaction to saccharic anhydride, is the reaction of III with the normally employed solvent, dimethylformamide (reaction 11). A 37% yield of O,O-diethyl (dimethyl-


(10)

VIII

$$(C_2H_5O)_2PSNHNa + HCON(CH_3)_2 \longrightarrow (C_2H_5O)_2PSN{=}CHN(CH_3)_2 + (NaOH) \quad (11)$$

IX

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aminomethylene)phosphoramidothioate (IX), a phosphorylated amidine,[11] was obtained. This reaction is somewhat surprising in view of the phosphorus–nitrogen bond cleavage observed in reactions of phosphoramidate anions with some other carbonyl compounds.[10]

Compound I was shown to be a phthalimidophosphonothioate in structure rather than the isomeric O-phosphorothioyl derivative of phthalimide or N-phosphorothioyl derivative of phthalisoimide[12] by its spectral properties as well as through its synthesis by diverse methods and its chemical reactivity.[5] Thus, I has carbonyl infrared absorptions at 1785 (weak) and 1740 (strong) cm.$^{-1}$ [13] which are also present in the Raman spectrum, but with the relative intensities inversed as expected for the cyclic, symmetrical dicarboximide structure.[14] The n.m.r. spectrum has a singlet at -7.76, an octet at -4.43 (J = 7.1, 10.3 c.p.s.), and a sextet at -1.43 p.p.m. (J = 7.1, 0.96 c.p.s.) in a 4:4:6 ratio and is also best accommodated by the symmetrical structure I. The structures of the other dicarboximidophosphonothioates and phosphonates were confirmed by their similar carbonyl infrared spectra and their similarly appropriate n.m.r. spectra.

Experimental Section

The proton n.m.r. spectra were obtained with a Varian A-60 spectrometer using tetramethylsilane as an internal standard and the critical infrared spectra were obtained with a prism-grating spectrophotometer.[15] The elemental analyses are by L. E. Swim of The Dow Chemical Co.

I from Potassium Phthalimide.—O,O-Diethyl phosphorochloridothioate (18.85 g., 0.10 mole) was added dropwise to a mixture containing 18.50 g. (0.10 mole) of potassium phthalimide in 175 ml. of N-methyl-2-pyrrolidone at 0–2° with stirring. Another 25 ml. of solvent was added and the mixture was stirred for 16 hr. at 0–2°. It was then poured into 500 ml. of ice–water and, after standing for 1 hr., the white solid was removed by filtration, washed with water, dried, and recrystallized from hexane to obtain 15.0 g. (50.2% of theory) of O,O-diethyl phthalimidophosphonothioate, m.p. 82.5–84°. The aqueous filtrate was extracted twice with carbon tetrachloride and the solid obtained on evaporation of the combined organic layers was recrystallized from hexane and then ethanol to obtain N-ethyl phthalimide, 1.88 g. (11% of theory), m.p. 76–76.5° (lit.[16] m.p. 78–79°). The other compounds of Table I were prepared similarly except that diethyl phthalimidophosphonate was extracted from the aqueous solvent with methylene chloride.

Diethyl Phthalimidophosphonate from N-Chlorophthalimide.—Triethyl phosphite (16.62 g., 0.10 mole) was added over a 15-min. period to a suspension of 18.16 g. (0.10 mole) of N-chlorophthalimide in 200 ml. of benzene at 21–33°. The reaction was exothermic and the mixture was cooled with cold water. The mixture was stirred for 6 hr. and then the benzene was evaporated under reduced pressure and the residue was recrystallized twice from hexane to obtain 14.6 g. (52.0% of theory) of diethyl phthalimidophosphonate, m.p. 62.5–64°.

I from Phthalic Anhydride. Procedure A.—O,O-Diethyl phosphoramidothioate (16.9 g., 0.10 mole) was added dropwise to a stirred mixture of 8.75 g. (0.20 mole) of a 55.0% mineral oil dispersion of sodium hydride in 125 ml. of dimethylformamide under nitrogen at 19–25°. When the evolution of hydrogen ceased, a solution of 29.6 g. (0.20 mole) of phthalic anhydride in 100 ml. of dimethylformamide was added over a 20-min. period. The mixture became gelatinous toward the end of this addition. After stirring for 2 hr. this mixture was poured into 250 ml. of ice water. The white solid formed was removed by filtration, washed with water, dried, and recrystallized from hexane to obtain 22.4 g. (75.0% of theory) of O,O-diethyl phthalimidophosphonothioate, m.p. 82.5–84°.

Procedure B.—A 51.2% dispersion of sodium hydride in mineral oil (9.85 g., 0.21 mole) was added in small portions from a solids addition tube over a 2-hr. period to a stirred solution of 29.6 g. (0.20 mole) of phthalic anhydride and 16.9 g. (0.10 mole) of O,O-diethyl phosphoramidothioate in 200 ml. of dimethylformamide at 0–4° under nitrogen. The mixture was stirred for 21 hr. at 0° and was then poured into 500 ml. of ice–water and the O,O-diethyl phthalimidophosphonothioate was isolated and purified as in procedure A to obtain 19.8 g. (66.2% of theory). The aqueous filtrate was acidified with dilute hydrochloric acid and the precipitate which formed was removed by filtration, washed with water, and recrystallized from carbon tetrachloride to obtain O,O,O′,O′-tetraethyl phthaloyldiphosphoramidothioate,[5] 3.51 g. (15.0% of theory), m.p. 111.5–113°.

Procedure C.—The reaction portion of procedure A was followed except that only 16.3 g. (0.11 mole) of phthalic anhydride was added. After stirring for 30 min., 10.2 g. (0.10 mole) of acetic anhydride was added over a 25-min. period at 5–15° with vigorous stirring. The mixture, which became gelatinous, was stirred for 1 hr. and worked up as in procedure A to obtain 22.7 g. (76.0% of theory) of O,O-diethyl phthalimidophosphonothioate. When acetyl chloride (7.85 g., 0.10 mole) was used in place of the acetic anhydride, a 26.0-g. (86.6% of theory) yield was obtained, and, when phosphoryl chloride (15.3 g., 0.10 mole) was used, a 24.0-g. (80% of theory) yield was obtained.

Most of the compounds of Table II were prepared by one of these procedures. The liquid and low-melting products were isolated from the aqueous dimethylformamide by extraction with carbon tetrachloride, and the solid products, except diethyl phthalimidophosphonate which was extracted with chloroform, were isolated by filtration.

Isolation of N-(Diethoxyphosphinothioyl)phthalamic Acid.—A reaction mixture was prepared according to procedure A except that only 14.8 g. (0.10 mole) of phthalic anhydride was added and the temperature was controlled at 0–2°. After stirring for 1 hr. the solution was poured into 500 ml. of ice–water. There was no precipitate. The aqueous solution was extracted with hexane and then acidified with 50 ml. of 5 *N* hydrochloric acid. The white solid that slowly formed was removed by filtration, washed with water and hexane, and dried to obtain N-(diethoxyphosphinothioyl)phthalamic acid,[5] 23.1 g. (72.8% of theory), m.p. 160–161°. Recrystallization from ethyl acetate raised the melting point to 166–167.5°.

N-(Diethoxyphosphinothioyl)-N-methylphthalamic Acid.—To a solution containing 18.3 g. (0.10 mole) of O,O-diethyl methylphosphoramidothioate and 14.8 g. (0.10 mole) of phthalic anhydride in 200 ml. of dimethylformamide under nitrogen was added 4.93 g. (0.105 mole) of a 51.2% mineral oil dispersion of sodium hydride in small portions with stirring. After stirring for 17 hr. the resulting solution was poured into 200 ml. of ice–water and 50 ml. of 5 *N* hydrochloric acid was added. The resulting mixture was extracted with carbon tetrachloride and the organic layer was evaporated under reduced pressure to obtain 27.6 g. of yellow oil. This was dissolved in 250 ml. of 5 *N* sodium hydroxide, and, after extracting with carbon tetrachloride, was recovered by neutralizing the solution with hydrochloric acid. This reprecipitation was repeated to obtain the product as white crystals, 10.75 g. (32.5% of theory), m.p. 94.5–95.5° dec. This compound reverts on heating to phthalic anhydride and O,O-diethyl methylphosphoramidothioate.

Anal. Calcd. for $C_{13}H_{18}NO_5PS$: C, 47.1; H, 5.48; N, 4.23. Found: C, 46.9; H, 5.37; N, 4.24.

I from Disodium N-(Diethoxyphosphinothioyl)phthalamate.—To a stirred solution of 15.85 g. (0.050 mole) of N-(diethoxyphosphinothioyl)phthalamic acid in 150 ml. of dimethylformamide under nitrogen at 0° was added consecutively 4.92 g. (0.105 mole) of a 51.2% mineral oil dispersion of sodium hydride and 7.77 g. (0.052 mole) of phthalic anhydride. The mixture was stirred 22 hr. at 0° and was then poured into 200 ml. of ice–water. The precipitate was removed by filtration, washed with water, and recrystallized from hexane to obtain O,O-diethyl phthalimidophosphonothioate, 8.28 g. (55.4% of theory).

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I from N-(Diethoxyphosphinothioyl)phthalamic Acid and Thionyl Chloride.—A mixture containing 9.61 g. (0.030 mole) of N-(diethoxyphosphinothioyl)phthalamic acid, 2.40 ml. (0.033 mole) of thionyl chloride, and 100 ml. of methylene chloride was heated at reflux overnight. The resulting solution was filtered, the filtrate was evaporated under reduced pressure, and the solid residue was recrystallized from hexane to obtain 8.00 g. (89.0% of theory) of O,O-diethyl phthalimidophosphonothioate.

I from N-(Diethoxyphosphinothioyl)phthalamic Acid and Acetic Anhydride.—A solution containing 6.34 g. (0.020 mole) of N-(diethoxyphosphinothioyl)phthalamic acid, 2.46 g. (0.030 mole) of sodium acetate, and 3.06 g. (0.030 mole) of acetic anhydride in 50 ml. of dimethylformamide was stirred for 4 hr. at 25°. It was then poured into 200 ml. of ice water and after standing for 30 min., the solid was removed by filtration, washed with water, and dried to obtain 5.57 g. (93.1% of theory) of O,O-diethyl phthalimidophosphonothioate.

O,O-Diethyl (Dimethylaminomethylene)phosphoramidothioate.—O,O-Diethyl phosphoramidothioate (16.9 g., 0.10 mole) was added dropwise to a stirred mixture of 8.80 g. (0.20 mole) of a 55.0% mineral oil dispersion of sodium hydride in 300 ml. of dimethylformamide under nitrogen at 3–8°. When the evolution of hydrogen ceased, 36.8 g. (0.20 mole) of saccharic anhydride was added over a 30-min. period at 0–10° and the solution was stirred for 2 hr. at 0–10°. It was then poured into 500 ml. of ice-water and the resulting mixture was extracted with carbon tetrachloride. The organic layer was evaporated under reduced pressure and the 13.5 g. of yellow oil remaining was distilled through a Claisen head still to obtain 8.25 g. (36.8% of theory) of the title compound, b.p. 65–68° (0.3 μ), $n^{25}\text{D}$ 1.5140. The substance has an infrared absorption at 1630 cm.$^{-1}$ assigned to C=N stretching[14] and its n.m.r. spectrum contains a triplet at -1.28 (J = 7.1 c.p.s.), a doublet at -3.10 (J = 8.5 c.p.s.), an octet at -3.96 (J = 7.1, 8.8 c.p.s.), and a doublet at -7.95 p.p.m. (J = 24.6 c.p.s.) in a 6:6:4:1 ratio.

Anal. Calcd. for $C_7H_{17}N_2O_2PS$: C, 37.5; H, 7.64; N, 12.5. Found: C, 37.4; H, 7.56; N, 12.3.

Diethylphosphinothioic Amide.—Anhydrous ammonia (10.0 g., 0.59 mole) was added as a vapor to a stirred solution of 36.0 g. (0.23 mole) of diethylphosphinothioic chloride in 150 ml. of benzene at 2–10° by means of a dip tube. The addition required 1.3 hr. and the mixture was stirred for another 2 hr. and allowed to warm to 23°. It then was filtered and the insoluble solid was extracted with hot chloroform. Diethylphosphinothioic amide crystallized on cooling the chloroform extract, 25.5 g. (80.8% of theory), m.p. 81–82.5°.

Anal. Calcd. for $C_4H_{12}NPS$: C, 35.0; H, 8.82; N, 10.2. Found: C, 35.3; H, 8.56; N, 10.2.

O,O-Bis(2,2,2-trichloroethyl) Phosphoramidothioate.—Anhydrous ammonia (16.0 g., 0.94 mole) was added as a vapor to a stirred solution of 74.3 g. (0.188 mole) of O,O-bis(2,2,2-trichloroethyl)phosphorochloridothioate in 250 ml. of methylene chloride at −15 to −30° by means of a dip tube. The addition required 20 min. and the mixture was stirred for another 1.5 hr. and allowed to warm to 16°. It was then extracted with water and the organic layer was evaporated under reduced pressure to obtain 92.3 g. of white solid. This was recrystallized from ethylcyclohexane, then aqueous methanol, to obtain 42.4 g. (59.3% theory) of the title compound, m.p. 90–91.5°.

Anal. Calcd. for $C_4H_6Cl_6NO_2PS$: C, 12.8; H, 1.61; Cl, 56.6; N, 3.73. Found: C, 13.3; H, 1.82; Cl, 56.4; N, 3.55.

Diethyl phosphoramidotrithioate was also prepared in this manner, but the colorless oil remaining after evaporation of the methylene chloride was unstable to heat so the crude product was used without further purification. A 99.5% yield of product and 97.3% yield of chloride ion were obtained.

N,N,N′,N′-Tetramethylphosphorothioic Triamide.—N,N,N′,-N′-Tetramethylphosphorochloridothioic diamide (160 g., 0.86 mole) was added over a 50-min. period to about 250 ml. of liquid ammonia at −30 to −40° with stirring. The mixture was allowed to stir for 16 hr. at this temperature. The residue obtained after evaporation of the ammonia was diluted with chloroform and the resulting mixture was filtered. Evaporation of the filtrate left a crude product which was washed with hexane and recrystallized from cyclohexane to obtain white crystals, 56 g. (39% of theory), m.p. 58–66° (raised to 64.5–66.5° by further recrystallization). Much of the crude product was shown to be unreacted acid chloride by vapor phase chromatography.

Anal. Calcd. for $C_4H_{14}N_3PS$: N, 25.1. Found: N, 25.0.

Acknowledgment.—O,O-Diethyl phthalimidophosphonothioate was first obtained by Dr. H. Tolkmith of this laboratory during a yet unpublished part of his studies on the nucleophilicity of phosphoramidothionates toward carbon.[17] The authors wish to express their appreciation to Professors J. C. Martin and J. W. Crump for helpful discussions and to H. C. Page for technical assistance.

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Reactions of Dicarboximidophosphonothioate Esters with Nucleophilic Reagents

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O,O-Diethyl phthalimidophosphonothioate reacts with aniline, isopropylamine, *p*-nitrophenylhydrazine, sodium methoxide, potassium hydroxide, and sodium borohydride by displacement on the carbonyl carbon to produce N-(diethoxyphosphinothioyl)phthalamic acid derivatives, with sodium *p*-chlorophenate by displacement on phosphorus, and with thiourea by displacement on saturated carbon. The alkaline hydrolysis is first order in both hydroxide ion and substrate.

Dicarboximidophosphonothioate esters[1] and the related dicarboximidophosphonates[1-3] contain three different electrophilic centers capable of reaction with nucleophilic reagents: the carbonyl carbon atoms,[4,5] the phosphorus atom,[6,7] and the saturated carbon atoms adjacent to ester oxygen.[6,8] Reaction at a carbonyl carbon atom would result in acylation of the nucleophile and the formation of an N-(dialkoxyphosphinothioyl)amido acid derivative (reaction 1a), while reaction at the phosphorus atom would result in phosphorylation of the nucleophile with the elimination of a dicarboximide (reaction 1b), and reaction at a saturated carbon atom would result in alkylation of the

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