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PHOSPHOROUS ACID AMIDES—II[1]

SYNTHESIS OF MONOALKYL PHOSPHOROAMIDITES $(RO)(R_2'N)P(O)H$

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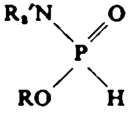
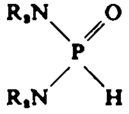
Abstract—Various possible methods for synthesis of monoalkyl phosphoroamidites, $(RO)(R_2'N)P(O)H$, starting from tervalent or pentavalent phosphorus derivatives are described and discussed. New experimental results concerning phosphorylation of secondary amines by means of phosphorous acid anhydrides are presented.

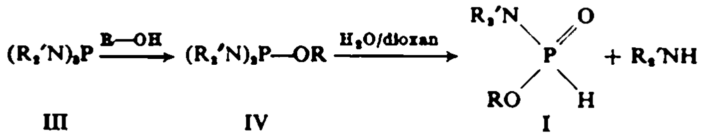
Only in recent years have the syntheses of amidoesters (I) and diamides (II) of phosphorous acid been developed.


I


II

Both types I and II, representing structural analogues of dialkyl phosphites, are relatively unknown, although the first representative of phosphorous acid diamides, viz. the dianilide, was prepared in 1954,[2] other compounds of type (II) have became available only recently.[1,3–5]

Monoalkyl phosphoroamidites (I) can be obtained in relatively high yields by reacting secondary amines with trialkyl esters of phosphorous–phosphoric anhydride (XI).[6] The reaction will be rediscussed later (Part D). Except for the method mentioned, only one compound of type I, namely isopropyl N,N-diethylphosphoroamidite (I; R = i-Pr, R′ = Et), appears to have been reported.[5] Its two-step synthesis was accomplished by means of partial alcoholysis of hexaethyl phosphorus triamide (III; R′ = Et) with isopropanol and subsequents elective hydrolysis of the resulting alkyl phosphorodiamidite (IV; R = i-Pr, R′ = Et) according to the scheme:


R = i-Pr, R′ = Et

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[1] Part I; A. Zwierzak, *Bull. Acad. Polon. Sci., Ser. sci. chim.* **13**, 609 (1965); *Chem. Abstr.* **64**, 9575 (1966). Paper LXX on organophosphorus compounds.

[2] S. Goldschmidt and F. Obermeier, *Liebigs Ann.* **588**, 24 (1954).

[3] E. N. Walsh, Ger. Pat. 1,125,425 (to Stauffer Chem. Co.); *Chem. Abstr.* **57**, 7104 (1962).

[4] G. Oertel, H. Malz and H. Holtschmidt, *Chem. Ber.* **97**, 891 (1964).

[5] D. Houalla, M. Sanchez and R. Wolf, *Bull. Soc. Chim. Fr.* 2368 (1965).

[6] A. Zwierzak, *Bull. Acad. Polon. Sci., Ser. sci. chim.* **12**, 235 (1964).

The purity of the compound obtained was followed by IR as well as P^{31} NMR spectra. The attempts to prepare two other representatives of I by the method described above met with little success. As determined from P^{31} NMR spectra, the appropriate intermediates IV; (R = Et, R' = Me and R = n-Bu, R' = Et) prepared by alcoholysis of the corresponding hexa-alkyl phosphorus triamides III; (R' = Me and R' = Et) were found to be mixtures of IV, III and V.

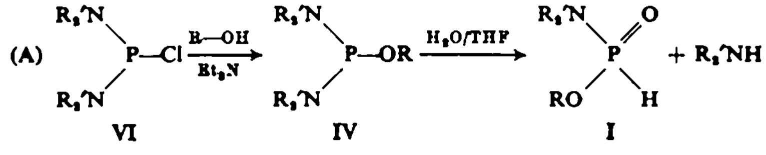
$(R_2'N)_2P{-}OR$ IV $(R_2'N)_3P$ III $R_2'N{-}P(OR)_2$ V

They could not be employed, therefore, as starting materials for the preparation of I. Wolf *et al.*[5] have suggested that the tendency of tervalent phosphorus compounds to redistribute the groups linked to the phosphorus atom may account for the formation of such a mixture.

In the course of a systematic study on the synthesis and chemistry of phosphorous acid amides, we tried to test this concept of spontaneous redistribution of substituents depending upon the source and kind of reacting species involved in the synthesis. A detailed investigation of the various possible methods of preparation of monoalkyl phosphoroamidites (I) starting from tervalent phosphorus derivatives and some types of pentavalent phosphorus anhydrides is now reported. All the reactions discussed, present potential synthetic routes to monoalkyl phosphoroamidites (I), two of them, however, can be regarded only as a preparative source of pure compounds; others produce complex mixtures which cannot be resolved by any preparative treatment. Final evidence as to the purity of monoalkyl phosphoroamidites (I) or the qualitative composition of the mixtures produced has been obtained in each case from the IR spectra as well as TLC data.

A. *Preparation of monoalkyl phosphoroamidites* (I) *from* N,N,N',N'-*tetraethylphosphorodiamidous chloride* (VI; R' = Et).

The following modification of the procedure originally described[5] was devised in order to elucidate the origin of the compounds III and V contaminating, as claimed, the intermediately formed alkyl phosphorodiamidite (IV):



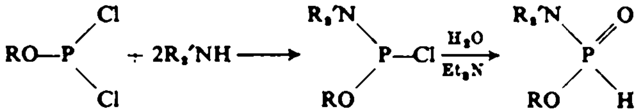
R = n-Bu, R' = Et

When IV was prepared by alcoholysis of III,[5] it seemed likely, that owing to the limited selectivity of P—N bond rupture, V accompanied by some unreacted starting material III, could be also formed. In the reaction sequence proposed (A) this possibility was practically eliminated by reacting pure VI with the stoichiometric amount of the appropriate alcohol in presence of triethylamine. However, according to TLC data, alkyl phosphorodiamidite (IV) produced was in each case contaminated with considerable amounts of III and V. The formation of these compounds in the reaction could be explained only in terms of a tendency for P^{III} derivatives to spontaneously disproportionate. Impure IV affords on hydrolysis in THF solution the corresponding monoalkyl phosphoroamidites (I) admixed with considerable amounts of N,N,N',N'-tetraalkylphosphorous diamides[7] (II) as well as dialkyl phosphites derived from V. For this reason the reaction (A) is of little preparative value.

B. *Preparation of monoalkyl phosphoroamidites* (I) *from alkyl phosphorodichloridites* (VII)

As alkyl N,N-dialkylphosphoroamidochloridites (VIII) are relatively stable and do not exhibit this tendency for disproportionation, it was expected that on hydrolysis monoalkyl phosphoroamidites (I) would be formed.

(B)



VII VIII I

This reaction was found to be the most attractive synthetic procedure devised so far for the preparation of *pure* monoalkyl phosphoroamidites (I).

The synthesis of alkyl N,N-dialkylphosphoroamidochloridites (VIII) was accomplished, according to the modified Michaelis procedure,[8] on adding two molar equivalents of the corresponding amine to the benzene solution of alkyl phosphorodichloridite (VIII) at 0–5°. Physical constants, yields and elemental analysis of the compounds VIII are listed in Table 1. All the compounds are colourless, mobile liquids, fuming in air, and reacting easily, often violently, with water. They are thermally unstable and readily undergo dealkylation on prolonged heating. When hydrolysed by means of a stoichiometric amount of water at 10–15° in presence of triethylamine, alkyl N,N-dialkylphosphoroamidochloridites (VIII) afford monoalkyl phosphoroamidites (I) in relatively high yields (50–80%).

Monoalkyl phosphoroamidites (I) prepared by this method were purified by high vacuum distillation. In a pure state they are colourless, mobile liquids, easily soluble in water and typical organic solvents. Similar to N,N,N',N'-tetraalkylphosphorous diamides (II) they are thermally unstable and cannot be heated above 130–150° without decomposition. On storage at room temperature the samples of I rapidly acquire an orange colour turning brown. With the exclusion of moisture they can, however, be stored at low temperature for an indefinite period without any appreciable change. Physical constants, yields, elemental analysis, and characteristic IR absorption bands of I are summarized in Table 2. As determined by TLC, the samples of I prepared by this method appeared to contain none of the impurities mentioned in connection with method (A). The R_f values of monoalkyl phosphoroamidites (I) and related compounds are given in Table 3.

All IR spectra of monoalkyl phosphoroamidites (I) examined, contained a sharp absorption band of medium intensity in the region 2390–2393 cm^{-1}. This band, associated undoubtedly with the P–H stretching vibration, falls between the region

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[7] The name N,N,N',N'-tetra-alkyl phosphorodiamidites proposed previously[1] for the compounds II is not in accord with the IUPAC nomenclature system of organophosphorus compounds.

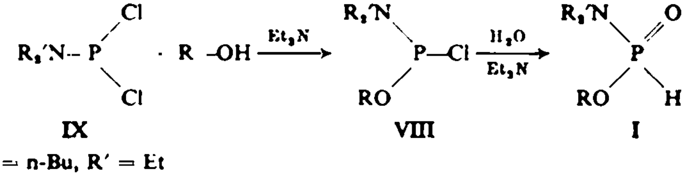
[8] A. Michaelis, *Liebigs Ann.* 326, 153 (1903).

2340–2350 cm^{-1},[9] which seems to be characteristic for N,N,N',N'-tetraalkylphosphorous diamides (II), and reported for dialkyl phosphites (bands near 2440 cm^{-1}).[10] Similarly, the P=O absorption band for I (1246–1253 cm^{-1}) lies between the region characteristic of N,N,N',N'-tetraalkylphosphorous diamides II (1215–1230 cm^{-1})[9] and phosphorus acid esters (1250–1300 cm^{-1})[10]. Both observations are consistent with the accepted dependence of these frequencies upon the inductive effects of substituents linked to the P atom.

C. *Preparation of monoalkyl phosphoroamidites* (I) *from* N,N-*dialkylphosphoroamidous dichlorides* (IX)

Further attempts to synthesize pure monoalkyl phosphoroamidites (I) from tervalent phosphorus derivatives involved the application of N,N-dialkylphosphoroamidous dichlorides (IX) as starting materials according to the scheme:

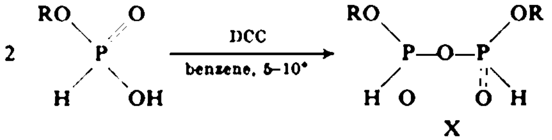
(C)



In spite of the stability of VIII and the limited tendency for disproportionation, the reaction afforded I highly contaminated with N,N,N',N'-tetraalkylphosphorous diamides (II) and dialkyl phosphites as well as minute amounts of two other unidentified impurities. No detailed study has been undertaken to elucidate the origin of these side-products. One of the possible explanations, which can be offered, suggests the formation of some dialkyl phosphoroamidite, $R_2'N-P(OR)_2$, on alcoholysis of IX. This compound and its disproportionation products might be responsible for the formation of impurities produced on hydrolysis of VIII.

D. *Preparation of monoalkyl phosphoroamidites* (I) *by phosphorylation of amines with phosphorous acid anhydrides*

A simple procedure has recently been devised,[11] by which *sym*-dialkyl pyrophosphites (X) are readily obtained on reacting alkyl dihydrogen phosphites with dicyclohexylcarbodiimide:



Highly reactive anhydrides (X) were found to be excellent phosphorylating agents for secondary amines, monoalkyl phosphoroamidites (I) and the corresponding

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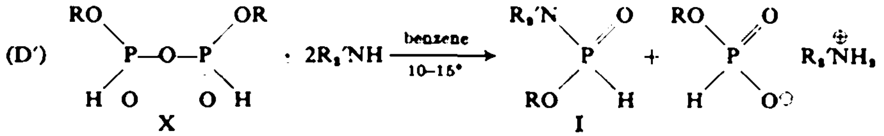
[9] The P—H and P=O frequencies reported previously[1] for II were recently found to be inaccurate. Wolf *et al.*[8] give the value 2338 cm^{-1} as ν_{P-H} for N,N,N',N'-tetraethyl phosphorodiamidite (II; R = Et).

[10] N. B. Colthup, L. H. Daly and S. E. Wiberley, *Introduction to Infrared and Raman Spectroscopy*. Academic Press, New York (1964).

[11] A. Zwierzak, unpublished work.

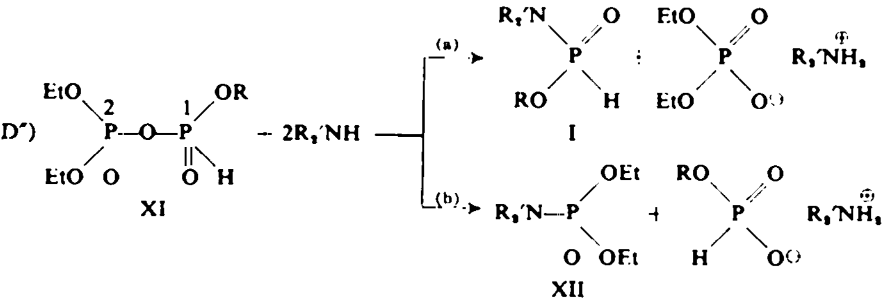
ammonium salts of alkyl dihydrogen phosphites being formed under very mild condition



R = Et, R′ = Et, n-Bu

No difficulty was encountered in the synthesis of pure I by this method, providing the anhydride (X) purified by molecular distillation has been used as starting material. The wide applicability of the method (D′) as an elegant route to monoalkyl phosphoroamidites (I) is limited by the tedious purification of X.

It has been reported[6] that the easily available O-alkylphosphorous-0,0-diethylphosphoric anhydrides (XI) are selective phosphorylating agents for secondary amines:



Two directions (a) and (b) of the reaction (D″) are possible, the path (a) being suggested as predominant owing to the strongly enhanced electrophilicity of the P^1 phosphorus atom. The reaction (D″) has been reinvestigated and the earlier statements proved to be inaccurate in the light of TLC and IR spectroscopy. All distillable products prepared by the method referred to are mixtures consisting of I and the corresponding diethyl N,N-dialkylphosphoroamidates (XII).

It is noteworthy to point out the difference in the behaviour of the anhydride (XI) towards amines and alcohols. The latter can attack predominantly the more electrophilic P^1 phosphorus atom of the anhydride molecule, giving rise to dialkyl phosphites. No such selectivity is observed on aminolysis.

EXPERIMENTAL

Solvents were purified by conventional methods. Amines were dried over KOH and fractionally distilled. B.ps are uncorrected. IR spectra were recorded using an UR-10 spectrophotometer (C. Zeiss). Measurements were made on samples of analytical purity. All compounds were examined in chf solns at ca. 0·2 molar concentrations using standard NaCl cells. TLC was carried out on standard glass plates covered with 0·5 mm of Kieselgel G (E. Merck). All compounds were developed by spraying with 5% AgNO$_3$aq. With this reagent compounds containing N—P—N bonds give black colouration, while with those containing O—P—N linkages brown spots are observed. Dialkyl phosphites are detected as white spots, which can be easily distinguished from organophosphorus amides. Purity control was accomplished in all cases by running chromatograms of neat liquids.

Table 1. Alkyl N,N-dialkylphosphoroamidochloridites $(RO)(R_2'N)PCl$(VIII)

R, R′	B.p. °C/mm Hg*	n_D^{20}	Yield %	Analyses (%) Required C	H	P	N	Found C	H	P	N
R = Et, R′ = Et	44–45/1·3 (65–70)	1·4680	47	39·1	8·2	16·8	7·6	39·2	8·5	16·6	8·2
R = n-Bu, R′ = Et	62–63/1·2 (90–95)	1·4655	83	45·3	9·0	14·6	6·6	45·3	9·3	14·8	6·6
R = R′ = n-Bu	73–76/0·08 (95–100)	1·4675	64	53·7	10·1	11·6	5·2	53·6	10·4	11·5	5·7
R = Et, R′ = n-Bu	64–65/0·05 (100–105)	1·4672	78	50·1	9·7	12·9	5·9	50·1	9·8	13·0	6·3
R = Et, R′ = morpholine residue	51–54/0·03 (75–80)	1·4990	50	36·4	6·6	15·9	7·1	36·0	6·7	—	7·4
R = i-Pr, R′ = Et	39–42/0·8 (70–75)	1·4626	68	—	—	—	7·1	—	—	—	7·0

* Bath temp given in parenthesis.

TABLE 2. MONOALKYL PHOSPHOROAMIDITES $(RO)(R_2N)P(O)H(I)$

R, R′	B.p. °C/mm Hg[1]	n_D^{20}	Yield %	Analyses (%) Required C	H	P	N	Found C	H	P	N	Characteristic IR absorption maxima[2] cm^{-1}
R = R′ = Et	44–45/0·5 (65–70)	1·4344	60	43·6	9·7	18·8	8·5	43·3	9·7	18·7	8·1	2393 m (P—H), 1252 s (P=O), 1213 s (P—NEt$_2$), 955 s, 982 s (P—N—C)
R = n-Bu, R′ = Et	52–54/0·05 (85–90)	1·4390	65·5	49·7	10·4	16·1	7·25	49·5	10·6	15·8	6·6	2390 m (P—H), 1250 s (P=O), 1213 s (P—NEt$_2$), 956 s, 980 s (P—N—C)
R = R′ = n-Bu	72–74/0·05 (115–120)	1·4421	40	57·8	11·2	12·5	5·6	57·6	11·3	12·5	5·6	2390 m (P—H), 1249 s (P=O), 930 s, 980 s (P—N—C)
R = Et, R′ = n-Bu	68–70/0·03 (95–105)	1·4421	53	54·2	10·9	14·0	6·3	54·1	10·9	14·0	6·5	2390 m (P—H), 1246 s (P=O), 930 s, 992 s (P—N—C)
R = Et, R′ = morpholine residue	66–67/0·01 (100–105)	1·4630	51	40·2	7·4	17·3	7·8	40·5	7·8	17·1	7·8	2392 m (P—H), 1253 s (P=O), 974 s, 995 s (P—N—C)
R = i-Pr, R′ = Et	52–53/0·5 (85–90)	1·4320	61	46·8	10·1	17·3	7·8	46·7	10·0	—	7·6	2390 m (P—H), 1251 s (P=O), 1213 s (P—NEt$_2$), 960 s, 982 s (P—N—C)

[1] Bath temp given in parenthesis; [2] Abbreviations used: s, strong; m, medium.

TABLE 3. THE R_f VALUES OF MONOALKYL PHOSPHOROAMIDITES (I) AND RELATED COMPOUNDS*

Formula	R_f values		
	Solvent system C_6H_6—CH_3COCH_3—$CHCl_3$ (20:10:3)	Solvent system CH_3CN—$CH_3COOC_2H_5$—CH_2Cl_2 (4:1:2)	Solvent system CH_3COCH_3—C_6H_6—CH_2Cl_2 (20:10:3)
$(EtO)(Et_2N)P(O)H$	0·32	0·38	0·48
$(n\text{-}BuO)(Et_2N)P(O)H$	0·42	0·46	0·56
$(n\text{-}BuO)(n\text{-}Bu_2N)P(O)H$	0·56	0·64	—
$(EtO)(n\text{-}Bu_2N)P(O)H$	0·45	0·51	—
(EtO)(O  N)P(O)H	0·18	0·23	—
$(i\text{-}PrO)(Et_2N)P(O)H$	0·36	0·49	—
$(Et_2N)_2P(O)H$	0·19	0·25	0·33
$(n\text{-}Bu_2N)_2P(O)H$	0·54	0·59	—
$(EtO)_2P(O)H$	0·38	0·55	—
$(n\text{-}BuO)_2P(O)H$	0·64	0·69	—
$(i\text{-}PrO)_2P(O)H$	0·46	0·55	—
$(EtO)_2P(O)NEt_2$	0·39	0·40	0·57
$(EtO)_2P(O)NBu_2\text{-}n$	0·52	0·55	0·66

* 5% benzene solns were applied for all determinations.

Materials

Alkyl phosphorodichloridites (VII). Modified literature procedures were employed. Alcohol (1 mole) was added dropwise with efficient stirring and cooling to phosphorus trichloride (1·5 mole) at −10°. The stirring was then continued for 1 hr at room temp, HCl was removed under reduced press, and the residue distilled *in vacuo*. Ethyl phosphorodichloridite was fractionated twice under normal press. The following phosphorodichloridites (VII) were prepared: ethyl[12] (32%), b.p. 116–118°, n_D^{20} −1·4660; isopropyl (36%), b.p. 39°/28 mm Hg, n_D^{20} −1·4610; n-butyl[13] (56%), b.p. 55°/14 mm Hg, n_D^{20} −1·4679. Compound IX was prepared as described previously[14] in 71% yield, b.p. 69–70°/10 mm Hg, n_D^{20} −1·4932. Compound VI was obtained by the previously described procedure[1]; XII[15] was prepared in 85% yield by the action of diethylamine (2 moles) on diethyl phosphorochloridate (1 mole) in benzene solution at 5–10°, b.p. 55°/0·3 mm Hg, n_D^{20} −1·4228 and XII[16] was similarly prepared, yield −87%, b.p. 90°/0·4 mm Hg, n_D^{20} −1·4330.

A. *Preparation of n-butyl* N,N-*diethylphosphoroamidite from* N,N,N′,N′-*tetraethylphosphorodiamidous chloride* (VI)

A soln of n-butanol (10·4 g, 0·14 mole) in benzene (15 ml) was added gradually with stirring and cooling to a mixture of N,N,N′,N′-tetraethylphosphorodiamidous chloride (30·0 g, 0·14 mole) and triethylamine (14·2 g, 0·14 mole) in benzene (150 ml) at 20–30°. The stirring was continued for a further 2 hr at 30–35°. The mixture was cooled, triethylamine hydrochloride removed by filtration, and the filtrate refrigerated overnight. Filtration was then repeated and the filtrate distilled *in vacuo* to give IV (31·2 g, 54%) as colourless liquid, b.p. 49°/0·1 mm Hg, n_D^{20} −1·4556.

Refluxing IV (12·4 g, 0·05 mole) with an equivalent quantity (0·9 g, 0·05 mole) of water in THF (20 ml) for 1 hr afforded 4·0 g (42%) of n-butyl N,N-diethylphosphoroamidite, b.p. 49°/0·1 mm Hg, n_D^{20} −1·4354. The product could not be satisfactorily analysed. TLC revealed the presence of considerable amounts of II (R = Et) and di-n-butyl phosphite.

B. *Preparation of monoalkyl phosphoroamidites* (I) *from alkyl phosphorodichloridites* (VII)—*General procedure*

1. *Preparation of alkyl* N,N-*dialkylphosphoroamidochloridites* (VIII). A modified procedure described by Michaelis[8] was applied. Dialkylamine (0·4 mole) in benzene (40 ml) was added dropwise with efficient stirring to the soln of the corresponding alkyl phosphorodichloridite (0·2 mole) in benzene (200 ml) at 0–5° (ice-salt bath). The stirring was continued for a further 4 hr at 0–5°. Dialkylamine hydrochloride was then filtered off and washed with benzene (2 × 50 ml). After removal of solvent the residue was distilled *in vacuo*.

2. *Hydrolysis of alkyl* N,N-*dialkylphosphoroamidochloridites* (VIII). The mixture of water (3·6 g, 0·2 mole), triethylamine (20·2 g, 0·2 mole), and THF (10 ml) was added dropwise with efficient stirring and cooling to the soln of alkyl N,N-dialkylphosphoroamidochloridite (0·2 mole) in benzene (200 ml) at 10–15°. The mixture was kept for 1 hr at room temp and then filtered. Triethylamine hydrochloride was washed with benzene (2 × 50 ml). Evaporation of the filtrate and flash distillation of the residue in high vacuo yielded the corresponding I in a chromatographically pure state. Some of the compounds I obtained were contaminated with traces of dialkyl phosphites.

C. *Preparation of n-butyl* N,N-*diethylphosphoroamidite from* N,N-*diethylphosphoroamidous dichloride* (IX)

A mixture of n-butanol (14·8 g, 0·2 mole), triethylamine (20·2 g, 0·2 mole) and benzene (20 ml) was added portionwise with stirring and cooling to a soln of N,N-diethylphosphoroamidous dichloride (34·8 g, 0·2 mole) in benzene (200 ml) at 0–5°. After the addition, stirring was continued for 4 hr at 0–5°. Triethylamine hydrochloride was then filtered off and washed with benzene (2 × 50 ml). The solvent was removed under reduced press and the residue distilled *in vacuo* to give VIII (31·2 g, 73%),

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[12] J. E. Malowan, D. R. Martin and P. J. Pizzolato, *Inorg. Synth.* **4**, 63 (1953).

[13] W. Gerrard, *J. Chem. Soc.* 1464 (1940).

[14] K. Issleib and W. Seidel, *Chem. Ber.* **92**, 2681 (1959).

[15] B. Loev and J. T. Massengale, *J. Org. Chem.* **22**, 1186 (1957).

[16] A. Debo, Ger. Pat. 1,033,200 (to J. A. Benckiser GmbH); Chem. Zentr. 3641 (1959).

b.p. 60°/0·6 mm Hg, n_D^{20} –1·4658. Hydrolysis of this material was carried out as described in the Exp. B-2 and afforded n-butyl N,N-diethylphosphoroamidite (9·0 g, 30%), b.p. 60°/0·1 mm Hg, n_D^{20} –1·4382. TLC revealed that the compound was contaminated with N,N,N′,N′-tetraethylphosphorous diamide, di-n-butyl phosphite as well as two other unidentified products.

D. *Preparation of monoalkyl phosphoroamidites* (I) *by phosphorylation of amines with* sym-*diethyl pyrophosphite* (X, R = Et).

sym-*Diethyl pyrophosphite* (X)[11]. A soln of dicyclohexylcarbodiimide (41·3 g, 0·2 mole) in benzene (100 ml) was added dropwise to a stirred soln of crude ethyl dihydrogen phosphite[17] (44·0 g, 0·4 mole) in benzene (80 ml) at 5–10°. Precipitation of dicyclohexylurea commenced at once. The mixture was allowed to stand for 1 hr at room temp, and then filtered. After removal of solvent the residue was refrigerated overnight, filtered, and evaporated in Utzinger's short-way distillation apparatus at 0·01 mm Hg (bath temp —85–95°) to give pure *sym*-diethyl pyrophosphite (19·2 g, 47·5%) as colourless, mobile liquid, n_D^{20} –1·4313. (Found: C, 24·1; H, 6·0; P, 30·5; $C_4H_{12}O_5P_2$ requires: C, 23·8; H, 5·9; P, 30·7%.) The IR spectrum showed bands at 2440 m (unresolved d), 1482 m, 1448m, 1397 m, 1374 m, 1262 s (sh), 1230 s, 1168 s, 1103 s, 1082 s, 1060 s, 1008 s, 990 s, 913 s, 817 s. The anhydride is relatively unstable. When stored, even at low temperature (0–5°), it acquires a yellow colour after 2 weeks and then deposits a yellow ppt.

1. *Reaction between* sym-*diethyl pyrophosphite and diethylamine. Ethyl* N,N-*diethylphosphoroamidite* (I, R = R′ = Et). Diethylamine (7·3 g, 0·1 mole) in benzene (10 ml) was added dropwise with stirring and cooling to a soln of *sym*-diethyl pyrophosphite (10·1 g, 0·05 mole) in benzene (50 ml) at 10–15°. The mixture was then kept for 1 hr at room temp and distilled *in vacuo* to give chromatographically pure ethyl N,N-diethylphosphoroamidite (5.0 g, 61%), b.p. 41–42°/0·03 mm Hg, n_D^{20} –1·4330. The diethylammonium salt of ethyl dihydrogen phosphite remained in the distillation flask as a thick syrup.

2. *Reaction between* sym-*diethyl pyrophosphite and di-n-butylamine. Ethyl* N,N-*di-n-butylphosphoroamidite* (I, R = Et, R′ = n-Bu). The reaction was carried out as described in the previous experiment starting from the anhydride (9·0 g, 0·045 mole) and di-n-butylamine (11·6 g, 0·09 mole) in benzene (50 ml). After removal of solvent the crystalline, strongly hygroscopic di-n-butylammonium salt of ethyl dihydrogen phosphite was filtered off and the mother liquor distilled *in vacuo* to afford chromatographically pure ethyl N,N-di-n-butylphosphoroamidite (2·5 g, 25%), b.p. 62–63°/0·01 mm Hg, n_D^{20} –1·4422.

[17] J. Michalski, T. Modro and A. Zwierzak, *J. Chem. Soc.* 4904 (1961).