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Thermal Decomposition of 1-(Dialkylphosphoryl)imidazoles[1,2]

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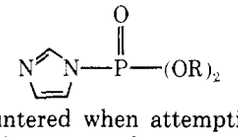
Received June 23, 1978

A number of 1-(dialkylphosphoryl)imidazoles, $(RO)_2PONC_3H_3N$, were synthesized in order to gain information requisite to a systematic search for compounds of this type in biological systems. Compounds containing short straight alkyl chains (R = methyl, ethyl, *n*-butyl, allyl) decompose at temperatures below 80 °C, giving 1-alkylimidazole, trialkyl phosphate, and 1,3-dialkylimidazolium polyphosphate. The di-*tert*-butyl ester decomposes to isobutylene and imidazolium polyphosphate, while the diisopropyl ester is thermally stable. The decomposition appears to result from an initial nucleophilic attack by the 3-nitrogen of one 1-(dialkylphosphoryl)imidazole on the α-alkyl carbon of another 1-(dialkylphosphoryl)imidazole.

Although a number of 1-phosphorylimidazole protein derivatives have been reported,[3-9] naturally occurring 1-(dialkylphosphoryl)imidazoles[1] have not been found. Interest in these compounds arises from the expectation that they would have a high phosphate group transfer potential and therefore might function as biological "high energy" intermediates. As a first step toward developing techniques whereby a search for compounds of this type in biological systems could be systematically undertaken, a number of 1-(dialkylphosphoryl)imidazoles were synthesized. An unanticipated property of these compounds is the ease with which lower members of the series spontaneously decompose at temperatures only slightly above room temperature. This communication concerns the products and mechanism of the decomposition.

Although thermal decomposition of a variety of phosphate esters has been known for many years, most take place at reasonably high temperatures.[10] Instability of 1-(dialkylphosphoryl)imidazoles of the general structure



was initially encountered when attempting to purify the compounds by high vacuum distillation. Nikolenko and Degterev[11] reported that the diethyl ester could be distilled at 79–80 °C (0.3 torr) with accompanying decomposition, but in our hands this compound decomposed completely within minutes at 40–45 °C (0.3 torr) and no 1-(diethylphosphoryl)-imidazole was ever detected in the distillate. The diisopropyl ester can be distilled at approximately 110 °C (0.3 torr) without significant decomposition as previously reported.[12,13] However, this compound appears to be unique among the short alkyl chain diesters in regard to thermal stability.

All of the straight chain dialkyl esters decompose at temperatures increasing with increasing chain length. 1-(Dimethylphosphoryl)imidazole decomposes explosively at temperatures only slightly above room temperature, whereas the dibutyl ester decomposes rapidly at 50–55 °C. With the exception of the diisopropyl and dilauryl esters, all of the compounds undergo extensive decomposition within a matter of hours at room temperature. However, the rate of decomposition is much slower in dilute anhydrous CCl_4 or $CHCl_3$ solution.

The products of the decompositions were separated and characterized and are listed in Table I. Two products, the corresponding 1-alkylimidazole and the trialkyl phosphate, were obtained by high vacuum distillation of the straight chain esters. After distillation, a highly viscous residue remained which dissolved completely in water to give an acidic solution showing a faintly positive reaction with ammonium molybdate. The phosphorus-containing product could be converted completely to orthophosphate by heating at 100 °C for 10 min in 2 N sulfuric acid, suggesting that the residue is mainly a polyphosphate. Thin-layer chromatography of the residue on cellulose powder eluting with either an acidic[14] or basic[15] solvent system showed essentially no material with chromatographic mobility. This behavior is characteristic of polyphosphates with a degree of polymerization greater than 4. The cationic component of the residues was identified as a 1,3-dialkylimidazolium ion from their characteristic NMR spectra; the C-4 and C-5 protons are equivalent, and in D_2O at pH approximately 9 the C-2 proton exchanged completely with deuterium within 10 min, consistent with the previous report of Olofson et al.[16] for the 1,3-dimethylimidazolium ion.

It should be noted that since the products are easily isolated in a pure form, the synthesis of 1-(dialkylphosphoryl)imidazoles followed by thermal decomposition provides a convenient single-step preparative method for both 1-alkylimidazoles and 1,3-dialkylimidazolium salts. The corresponding reaction was not observed with 1-(diphenylphosphoryl)imidazole, and therefore the method is not applicable to diaryl esters.

The formation of 1-phosphorylimidazole from orthophosphate in the autoxidation of diimidazole ferroheme[17] appears to occur by a free-radical mechanism,[18,19] and therefore it was considered possible that the thermal decomposition of 1-(dialkylphosphoryl)imidazoles might also be a free-radical reaction. However, the observation that the diallyl ester decomposes without formation of any polymeric carbon compounds would appear to exclude a free-radical mechanism for the decomposition. Supporting this conclusion, free radicals were not detected by ESR in neat samples of the dibutyl ester heated to 60 °C for 1 min and then plunged into liquid nitro-

Table I. Summary of Thermal Decomposition Products of 1-(Dialkylphosphoryl)imidazoles

1-(dialkylphosphoryl)-imidazole	registry no.	decomposition temp range, °C (torr)	composition of distillate (% yield)	registry no.	polyphosphate in the nondistillable residue	registry no.	^{1}H NMR of residue in D_2O (ppm from DSS)[a]
dimethyl	67723-07-3	20–25 (760)	1-methylimidazole[a]	616-47-7	1,3-dimethylimidazolium	45470-32-4	4.2 (s, 6 H, NCH_3), 7.8 (s, 2 H, C-4,5), 9.2 (s, 1 H, C-2)
			trimethyl phosphate[b]	512-56-1			
diethyl	16913-98-7	40–45 (0.3)	1-ethylimidazole (55)[c]	7098-07-9	1,3-diethylimidazolium	67711-49-3	1.3 (t, 6 H, CH_3), 4.0 (q, 4 H, CH_2), 7.6 (s, 2 H, C-4,5), 8.8 (s, 1 H, C-2)
			triethyl phosphate (11)[c]	78-40-0			
diallyl	67711-46-0	42–47 (0.3)	1-allylimidazole (43)[c]	31410-01-2	1,3-diallylimidazolium	67711-50-6	4.9 (m, 4 H, $N(CH_2)$), 5.3–5.7 (m, 4 H, $=CH_2$), 5.8–6.5 (m, 2 H, $=CH$), 7.6 (s, 2 H, C-4,5), 8.9 (s, 1 H, C-2)
			triallyl phosphate (19)[c]	1623-19-4			
di-*n*-butyl	67711-47-1	50–55 (0.3)	1-*n*-butylimidazole[d] (47)	4316-42-1 126-73-8	1,3-di-*n*-butylimidazolium	67711-51-7	1.03 (t, 6 H, CH_3), 1.4 (h, 4 H, CH_2), 2.0 (p, 4 H, CH_2), 4.3 (t, 4 H, CH_2), 7.6 (s, 2 H, C-4,5), 8.9 (s, 1 H, C-2)
			tri-*n*-butyl phosphate[e] (14)				
di-*tert*-butyl	67711-48-2	45–65 (0.3)	isobutylene[f] (100)	115-11-7	imidazolium	17009-90-4	7.8 (s, 2 H, C-4,5), 9.1 (s, 1 H, C-2)

[a] Proton NMR spectrum in $CDCl_3$ was identical with that of an authentic sample. [b] Proton NMR spectrum was composed of one signal at 3.9 ppm (d) from Me_4Si. [c] Determined from relative areas under appropriate signals in the NMR spectrum of total distillate. [d] Bp 62 °C (0.3 torr); satisfactory elemental analysis for C, H, N, and P (C, 67.24; H, 9.65; N, 22.32. Calcd for $C_7H_{12}N_2$: C, 67.74; H, 9.86; N, 22.58.); mass spectrum parent peak, *m/e* 124. NMR spectrum was identical with that of an authentic sample. [e] Bp 95 °C (0.3 torr); satisfactory elemental analysis for C, H, and P (C, 54.02; H, 10.27; P, 11.53. Calcd for $C_{12}H_{27}O_4P$: C, 54.12; H, 10.22; P, 11.63.); mass spectrum parent peak, *m/e* 266. NMR spectrum was identical with that of a commercial sample. [f] Identified by its NMR spectrum and by bromination in CCl_4 to 1,2-dibromo-2-methylpropane. [g] Abbreviations are listed in legend for Table II.

gen, or in samples heated from room temperature to 60 °C in the ESR cavity. Thus, the mechanism of the decomposition appears to be exclusively ionic.

It has been observed previously that thermal decomposition of phosphoramidates results in alkylation of the nitrogen. Cadogan[20] reported that diethyl *N*-phenylphosphoramidate decomposes at 260 °C to give *N*-ethylaniline and *N,N*-diethylaniline as well as other products identified only as polyphosphates. Given the much greater basicity of the 3 nitrogen of 1-(dialkylphosphoryl)imidazoles compared to the nitrogen of a simple phosphoramidate, it is not surprising that the decomposition of 1-(dialkylphosphoryl)imidazoles occurs at lower temperatures. The reported appearance of a major peak at *m/e* 158 (1-benzylimidazole) in the mass spectrum of 1-(dibenzylphosphoryl)imidazole[21] is almost certainly due to a decomposition analogous to those described herein.

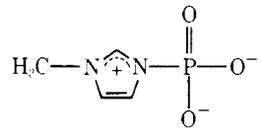
In this connection, pyridine,[22] iodide ion,[23] and *N*-methylmorpholine[24] react with tetrabenzyl pyrophosphate to abstract a benzyl group, demonstrating that the carbon α to a phosphoryl group is particularly susceptible to nucleophilic attack by a variety of bases. Other reactions of this general type are well known in phosphorus chemistry, the classic example being the Arbuzov reaction.[25]

From these considerations, it seems probable that the initial reaction in the thermal decomposition involves nucleophilic attack by the 3 nitrogen of one 1-(dialkylphosphoryl)imidazole on the α carbon of another, generating an ion pair (I, Scheme I). A number of alternatives can be considered for the next step, and it is likely that a number of competing reactions occur simultaneously. However, the anion of I would not be expected to decompose readily to generate alkyl metaphosphate because the imidazole anion is such a poor leaving group. Nucleophilic attack by the oxygen of the anion on the phosphorus of the cation to produce 1-(trialkylpyrophosphoryl)imidazole (II) and 1-alkylimidazole is a possible reaction, but it probably would be relatively slow due to steric interference by the alkyl groups and the imidazole ring. Moreover, the same steric restraints will be operative in the subsequent chain elongation steps of Scheme I. Nucleophilic attack on the phosphorus of phosphate esters is known to be more susceptible to steric hindrance than are reactions of analogous carbonyl compounds.[26]

A second step, which is less subject to steric effects and therefore considered more likely, is the loss of an ester alkyl group from the cation of I (a, Scheme II). This could occur by reaction of the I cation with either the accompanying anion or with a molecule of 1-(dialkylphosphoryl)imidazole, generating the dipolar ion III plus an identical cation in the first case and 1-(dialkylphosphoryl)imidazole in the second case. The dipolar ion III is a monoalkyl ester of phosphoryl-*N*-methylimidazolium ion (IV), the product obtained by Jencks and Gilchrist[27] from the reaction of phosphoramidate with 1-methylimidazole. The phosphoryl group of IV probably remains completely ionized in aqueous solution to pH's at

Scheme I

least as low as 5. The stability of IV in aqueous solution is surprising ($t_{1/2}$ of hydrolysis approximately 10 h at 39 °C),[27] but it is likely due to the doubly negative charge on the phosphoryl group and the polarity of the solvent. In the case of the monoester III, a relatively nonpolar environment and



IV

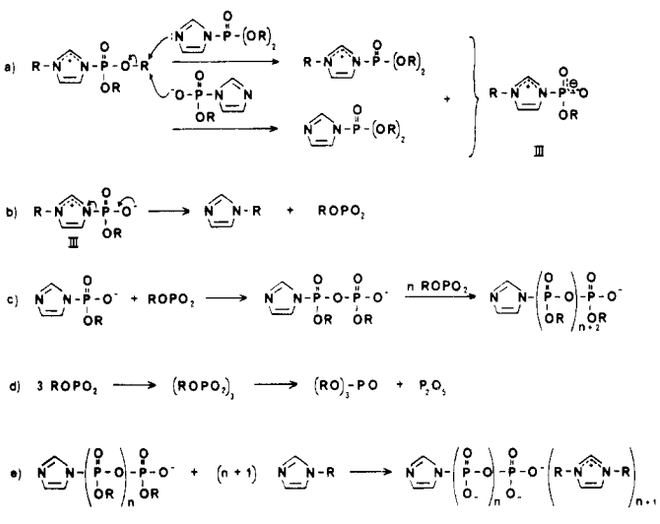
elevated temperature would be expected to facilitate decomposition into two neutral molecules, *N*-alkylimidazole and monomeric alkyl metaphosphate (b, Scheme II). If monomeric alkyl metaphosphate was formed in the decomposition, it would be expected to react rapidly with the anion of I to form the corresponding 1-pyrophosphorylimidazole and with itself to form cyclic trimers and tetramers (c and d, Scheme II).

Experiments were not carried out in an effort to demonstrate that monomeric alkyl metaphosphates are actually formed in these decompositions. However, a considerable body of evidence has accumulated implicating monomeric metaphosphates as intermediates in numerous transphosphorylation reactions,[28] and more recently Clapp and Westheimer[29] demonstrated convincingly that monomeric methyl metaphosphate was produced in the gas-phase thermal decomposition of methyl 2-butenylphostonate. Of course, the intermediacy of monomeric metaphosphates remains to be demonstrated in other reactions where they have been proposed, but the postulate is no longer so speculative.

The trialkyl phosphate formed in the decomposition can be seen to arise by way of an intramolecular rearrangement of trialkyl trimetaphosphate (d, Scheme II) in a manner analogous to the thermal decomposition of "Langheld esters".[30,31] Stoichiometry requires that phosphorus pentoxide also be a product of the reaction. The presence of phosphorus pentoxide would account for the observed acidity and the positive molybdate reaction of aqueous solutions of the residue from the distillation. Phosphorus pentoxide is very likely a product of the Langheld ester decomposition as well since Hull and Snodgrass[30] reported that the residue remaining after removal of triethyl phosphate from a Langheld ester preparation could be treated again with diethyl ether to generate additional triethyl phosphate.

In addition to the reaction shown in e in Scheme II, the possibility also exists that the dialkylimidazolium ion could arise by reaction of 1-alkylimidazole with trialkyl phosphate. However, this possibility is excluded by the observation that the reactants were reisolated in 92% yield from an equimolar

Scheme II



mixture of 1-butylimidazole and tributyl phosphate which had been refluxed for 2 h at 210 °C.

The following result also shows clearly that the 1,3-dialkylimidazolium ion does not result by way of an intramolecular process. When 1-(diethylphosphoryl)imidazole was allowed to decompose in the presence of an equimolar amount of 1-methylimidazole, the yield of 1-ethylimidazole was 74% opposed to 55% from the neat decomposition, and 1-methyl-3-ethylimidazolium ion predominated over 1,3-diethylimidazolium ion by a factor of approximately 5 as judged from the relative areas under the δ 1.58 (ethyl CH_3 of 1-methyl-3-ethylimidazolium) and 1.28 (ethyl CH_3 of 1,3-diethylimidazolium) signals. The proton NMR spectrum of the residue was consistent with that previously reported by Borne et al.[32] for 1-methyl-3-ethylimidazolium iodide.

The above mechanistic considerations also account for the formation of isobutylene from 1-(di-*tert*-butylphosphoryl)imidazole and the enhanced thermal stability of the diisopropyl ester. In both cases the α carbon is sterically protected from nucleophilic attack, but in the former case proton abstraction from an α carbon by N-3 of 1-(dialkylphosphoryl)imidazole can result in an elimination reaction, yielding isobutylene and ultimately imidazolium polyphosphate.

Experimental Section

Materials. Reagent grade CCl_4 was dried over P_2O_5 and doubly distilled. Imidazole (Aldrich) was twice recrystallized from anhydrous benzene, mp 91 °C. Bromotrichloromethane (spectrophotometric grade), dimethyl phosphite, diethyl phosphite, diisopropyl phosphite,

Table II. Properties of 1-(Dialkylphosphoryl)imidazoles

1-(dialkylphosphoryl) imidazole	% yield[a]	refractive index, 23 °C	^{1}H NMR in CCl_4 (ppm from Me_4Si)[b] imidazole[c] C-2 H	C-4,5 H[d]	alkyl
dimethyl	58[f]	1.4705	7.6	6.9	3.7 (d, CH_3)
diethyl	88	1.4605	7.6	6.9	1.3 (t, CH_3), 4.0 (p, CH_2)
diisopropyl[g]	83	1.4539	7.6	7.0	1.3 (m, CH_3), 4.6 (m, CH)
diallyl	40[f]	1.4845	7.6	7.0	4.6 (m, CH_2O), 5.0–6.1 (m, $-CH=CH_2$)
di-*n*-butyl[e]	95	1.4580	7.6	7.0	1.1 (t, CH_3), 1.8 (m, CH_2), 4.0 (m, CH_2O)
di-*tert*-butyl	82	1.4470	7.5	6.8	1.6 (d, CH_3)
dilauryl[h]	95	1.4620	7.6	7.0	0.9 (t, CH_3), 1.0 (m, C-11 CH_2), 1.2–1.8 (m, C-2–C-10), 4.0 (m, CH_2O)

[a] Based on weight of material remaining after removal of solvent under high vacuum. [b] Abbreviations: s, singlet; d, doublet, t, triplet; q, quartet; p, pentet; m, multiplet; sm, sharp multiplet. [c] All signals are multiplets. [d] In more concentrated CCl_4, $CDCl_3$, C_6D_6, Me_2SO-d_6, and acetone-d_6 and in neat samples, the C-4 and C-5 protons were observed as distinct signals separated by 0.1–0.2 ppm; e.g., for dibutyl ester in CCl_4, 6.96 (sm, 1 H, C-4) and 7.04 (sm, 1 H, C-5) ppm. [e] Satisfactory elemental analysis for C, H, N, and P (C, 51.22; H, 8.35; N, 10.74; P, 11.57. Calcd for $C_{11}H_{22}N_2O_3P$: C, 50.77; H, 8.13; N, 10.76; P, 11.90.); mass spectrum parent peak *m/e* 260. [f] Some decomposition occurred during removal of solvent. [g] Registry no., 67711-52-8. [h] Registry no., 67711-53-9.

diallyl phosphite, di-*n*-butyl phosphite, dilauryl phosphite, and 1-methylimidazole were all obtained from Aldrich and used without purification. Di-*tert*-butyl phosphite was synthesized from freshly distilled PCl_3, *tert*-butyl alcohol, and pyridine according to the procedure of Goldwhite and Saunders.[33] 1-*n*-Butylimidazole was prepared by the reaction of imidazole with *n*-butyl bromide according to the procedure of Haring[34] and by the procedure of Yamauchi and Kinoshita[35] through a reaction of tri-*n*-butyl phosphate with imidazole.

General Method for the Synthesis of 1-(Dialkylphosphoryl)-imidazoles. The procedure employed was essentially the method described by Atherton and co-workers[36] for phosphorylation of alcohols and amines with the modification that an extra equivalent of imidazole was employed instead of another base for trapping the HBr that formed during the course of the reaction.

A 300-mL round-bottom flask equipped with a magnetic stirrer, $CaCl_2$ drying tube, and 125-mL separatory funnel was charged with 0.02 mol of imidazole and 0.01 mol of bromotrichloromethane in 100–125 mL of anhydrous CCl_4. The dialkyl phosphite (0.01 mol) in 75 mL of anhydrous CCl_4 was added dropwise over 2 h with stirring. After stirring overnight, the precipitated imidazole hydrobromide was removed by vacuum filtration, and a sample of the filtrate was withdrawn for NMR analysis. Disappearance of phosphite half-proton peaks and appearance of the $CHCl_3$ peak confirmed that the reaction had gone to completion. The solvent was removed from the filtrate by flash evaporation at below room temperature under high vacuum. The product was stored in a desiccator in the cold and used the same day.

The compounds prepared, along with relevant analytical data, are listed in Table II.

Methods. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Nuclear magnetic resonance spectra were obtained using a Varian XL-100-15 spectrometer. Tetramethylsilane (Me_4Si) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as an internal standard depending on the solvent. Electron spin resonance spectra were obtained with a modified Varian V4500-10A X-Band spectrometer through the courtesy of Mr. George Kemmer, Physics Department, Temple University. The mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6 spectrometer through the courtesy of the Chemistry Department, Drexel University, Philadelphia, Pa. Refractive indices were determined on an Abbe-3L B&L refractometer water-jacketed for temperature control.

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Some New Spiro Penicillins

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Received June 23, 1978

New spiro penicillins have been synthesized using the reaction between diazomethyl compounds and dipolarophiles or aldehydes.

Several reports of spiro structures generated at C_6 and C_7 of penicillins[1-4] and cephalosporins[3,5] to form an overall tricyclic structure have appeared. There are different approaches to these types of structures. One involves the addition of a dipolarophile to a 1,3-dipolar group, such as a diazo group. Another involves the addition of diazo compounds to carbonyl compounds to give epoxides, among other products.[6] We have used these concepts for the synthesis of new spiro penicillins and related compounds.

β,β,β-Trichloroethyl 6-diazopenicillanate (**1**)[7] reacted with acrylonitrile, ethyl acrylate, and *tert*-butyl acrylate to give isomeric compounds **2** and **3** (Scheme I). The isomeric pairs were separated by column chromatography to give pure compounds whose NMR and IR spectra are in good agreement with structures **2** and **3** (see Experimental Section). The main spectral dissimilarity between the major product and the minor product appeared in the NMR signals of their *gem*-dimethyl groups: both methyl groups of the former have the same δ value, while those of the latter gave rise to two distinct singlets ($\Delta\nu$ = δ 0.07–0.11).

The preferred mode of addition is from the sterically less hindered α side[8,9a] and assignment of the structures of the major and minor (6:1) products was made on that basis. Thus, compound **2** was expected to be the major isomer. Compound

0022-3263/78/1943-4856$01.00/0