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Photolysis of 1-Azido-2,2,3,4,4-pentamethylphosphetane 1-Oxide: Monomeric Metaphosphonimidate[1-3]

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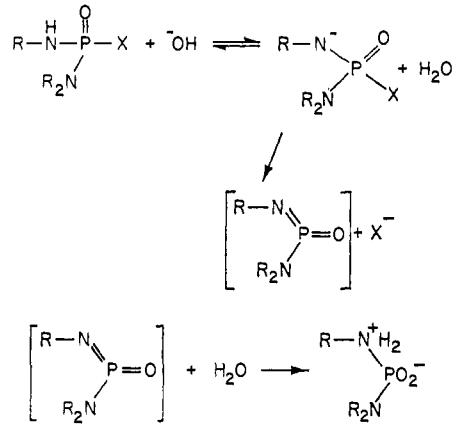
Abstract: Monomeric metaphosphorimidates, O=P(OR)=NR′, have been postulated as reactive intermediates in phosphorus chemistry. Stereochemical evidence for such intermediates has now been obtained by photolysis, in methanol, of *cis*- and *trans*-1-azido-2,2,3,4,4-pentamethylphosphetane 1-oxide to yield the *cis*- and *trans*-2-methoxy-3,3,4,5,5-pentamethyl-1,2-azaphospholidene 2-oxides and eight other products. The starting materials and products have been separated and purified by high-pressure liquid chromatography, and their stereochemistry was established through their nmr spectra. The formation of the principal products has been rationalized on the assumption that photolysis of the azides leads to ring expansion with insertion of a nitrogen atom into the ring to yield a monomeric metaphosphonimidate, or with insertion of an oxygen atom into the ring to yield a new type of chemical intermediate. Consistent with this explanation, the ratio of *cis*- to *trans*-methyl phostamates, obtained as products of photolysis, is essentially independent of whether cis or trans azide is used as starting material. The chemistry and stereochemistry of monomeric metaphosphorimidates are discussed on the basis of these findings. The other products have also been accounted for, in most cases by assuming that a nitrene, or incipient nitrene, is formed in the photolysis.

The mechanisms of hydrolysis of phosphoramidates, like those of other phosphates, are of biochemical interest. Phosphoramidates where one or more hydrogen atoms are attached to nitrogen are particularly sensitive to alkaline hydrolysis,[4] and in 1957 a metaphosphorimidate mechanism was advanced to account for this fact.[5] Kinetic and stereochemical investigations have supported this hypothesis and have placed limits upon its range of applicability.[6] In particular, Gerrard and Hamer[7] showed that the alkaline hydrolysis of methyl *N*-cyclohexylthiophosphorochloridate occurs with racemization, presumably through a metaphosphorimidate intermediate; but when *p*-nitrophenolate ion rather than chloride is the leaving group, chirality is preserved; this fact suggests that a metaphosphorimidate, if it participates in the hydrolytic process, is not entirely free, or that it reacts with solvent in a time short compared with that needed to pass through a planar configuration.



Recently Harger[8] has carried out the photolytic ring enlargement of 1-azido-2,2,3,4,4-pentamethylphosphetane 1-oxide (I) to yield 2-methoxy-3,3,4,5,5-pentamethyl-1,2-azaphospholidene 2-oxide (II).

By taking advantage of high-pressure liquid chromatography, we have now separated the cis and trans isomers of both starting material and products. Photolysis of either the cis or trans azide in methanol leads to the same ratio of cis and trans phostamic esters; this

(1) Preliminary communications: Remsen Lecture, John Hopkins University, May 1973; *Pure Appl. Chem.*, in press.

(2) In this paper, species with the structure O=P(OR)=NR are called metaphosphorimidates and those with the structure O=P(R)=NR′ are called metaphosphonimidates. The arguments in this paper apply to the members of both classes.

(3) Abbreviations used are: Azide, I, 1-azido-2,2,3,4,4-pentamethylphosphetane 1-oxide; methyl phostamate, II, 2-methoxy-3,3,4,5,5-pentamethyl-1,2-azaphospholidene 2-oxide; unsaturated amino ester, III, *O*-methyl (1,1,2,3-tetramethyl-3-butenyl)phosphoramidate; phosphetane ester, IV, 1-methoxy-2,2,3,4,4-pentamethylphosphetane 1-oxide; methyl phostonate, V, 2-methoxy-3,3,4,5,5-pentamethyl-1,2-oxaphospholane 2-oxide; phosphetane hydroxamate, VI, 1-methoxyamino-2,2,3,4,4-pentamethylphosphetane 1-oxide; phostonate amide, VII, 2-amino-3,3,4,5,5-pentamethyl-1,2-oxaphospholane 2-oxide; anhydride, VIII, anhydride of 1-hydroxy-2,2,3,4,4-pentamethylphosphetane 1-oxide; phosphetane chloride, IX, 1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide.

(4) D. R. Heath, *J. Chem. Soc.*, 3796, 3804 (1956).

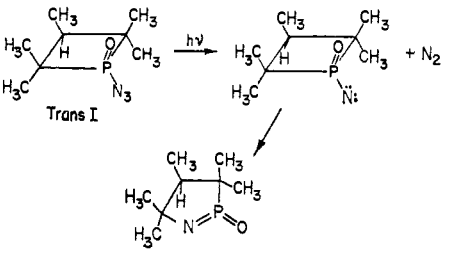
(5) F. H. Westheimer, *Chem. Soc., Spec. Publ.*, **No. 8**, 181 (1957).

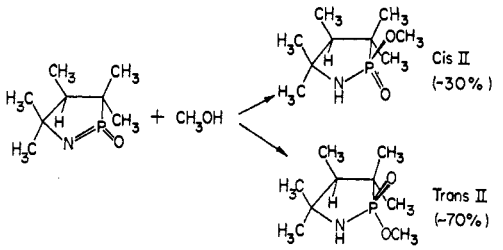
(6) E. W. Crunden and R. F. Hudson, *Chem. Ind. (London)*, 1478 (1958); *J. Chem. Soc.*, 3591 (1962); D. Samuel and F. H. Westheimer, *Chem. Ind. (London)*, 51 (1959); M. A. H. Fahmy, A. Khasawinah, and T. R. Fukuto, *J. Org. Chem.*, 37, 617 (1972); H. K. Hall, *J. Org. Chem.*, 21, 248 (1956); P. S. Traylor and F. H. Westheimer, *J. Amer. Chem. Soc.*, 87, 553 (1965); A. Williams and K. T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 1454 (1972); 318 (1973).

(7) A. F. Gerrard and N. K. Hamer, *J. Chem. Soc. B*, 539 (1968); 1122 (1967).

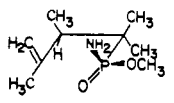
(8) M. J. P. Harger, *Chem. Commun.*, 442 (1971).

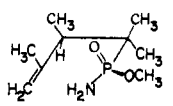
fact strongly suggests the intervention of a monomeric metaphosphonimidate intermediate, as shown below. In this scheme, and those that follow, a nitrene has been written as an intermediate. Although this is convenient for showing the reaction pathway, it need not exist as a free molecular species; ring enlargement may be concerted with the loss of nitrogen.





In addition to the phostamic esters, II, eight other reaction products have been isolated by high-pressure liquid chromatography. These include ring-cleavage products (the stereoisomeric unsaturated amino esters, III) one of which was isolated previously by Harger, as well as the cis and trans phosphetane esters, IV, *cis*- and *trans*-methyl phostonates, V, one isomer of phosphetane hydroxamate, VI, and one of the phostonate amide, VII.


III a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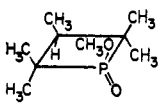
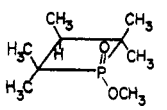
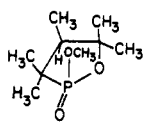
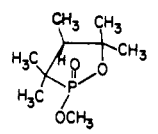
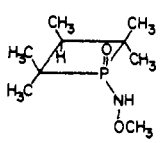
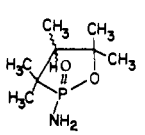

Cis IV


Trans IV


Cis V


Trans V


VI


VII

This paper describes the separation and identification of these products, and offers a discussion of their significance for the monomeric metaphosphonamidate mechanism. The discovery of the cis and trans phostonate esters and of the phostonate amide among the products has led to the postulate of a new kind of unstable intermediate in phosphorus ester chemistry.

Experimental Section

General. High-pressure liquid–solid chromatography (HPLC) was carried out at room temperature on a Waters Associates ALC 202 liquid chromatograph equipped with both uv and refractive index detectors. Analytical columns, 6 ft long and 0.09 in. i.d. packed with Corasil II, were obtained from Waters Associates. Empty preparative scale stainless steel columns (6 ft × 0.307 in. i.d. and 8 ft × 0.843 in. i.d.) were purchased from Waters Associates and dry-packed with Waters' Porasil C.

The 6 ft long, 0.307 in. preparative column was operated at a flow rate of 2.7 ml/min on the Waters chromatograph. Eluent was forced through the large column by a Milton Roy Model DC-1-117R Simplex Milroyal D adjustable stroke pump, at a rate of 30 ml/min; this required pressures of less than 100 psi. The separations obtained with this column were most effectively monitored with the analytical HPLC columns. The preparative columns were usually overloaded relative to conditions for optimum separations, but by recycling various fractions, reasonably pure products could be obtained. Retention times for HPLC are expressed in units, k', of the "dead volume," with the first dead volume being taken as $k = 0$. The k' values are thus related to R_f, where $k' = (1/R_f) - 1$. Peak areas on the chromatograms were measured with a Keuffel and Esser Compensating Polar Planimeter.

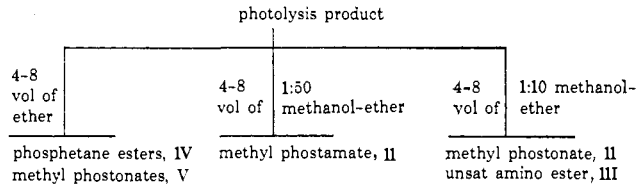
Photolyses were carried out at 253.7 nm in a Srinivasan-Griffin Rayonet photochemical reactor, with RPR-2537A low-pressure mercury lamps as light source. Quartz reaction vessels were surrounded by a quartz cooling jacket.

Melting points were taken with a Hoover capillary melting point apparatus. Ir spectra were obtained with a Perkin-Elmer Infracord, and nmr spectra with a Varian T-60, a Varian HA-100, or a Varian XL-100 nmr spectrometer.

Elementary analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr data for all new compounds were consistent with the structures proposed, and spectra for known compounds agreed with previously published spectra.

Chromatography. For preparative purposes, gross separation of the reaction products was achieved by chromatography[9] on 30–50 g of Woelm neutral alumina/g of product, according to the Scheme I.

Scheme I



The variation in elution volumes, shown in Scheme I, depended on the activity of the alumina. Very active alumina (activity I) was to be avoided, since the photolysis products were to some extent irreversibly adsorbed on it. Best results—and most rapid elution—were obtained with columns that had been used several times. The mixtures of products eluted from the alumina were further separated by HPLC, as described in individual preparations below.

Materials. ***trans*-1-Chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide (IXa)** was prepared according to McBride, *et al.*,[10] and recrystallized five times from hexane, mp 74.5–76° (lit. 72–75°). The cis isomer was prepared from the trans, by way of the corresponding acid as intermediate, according to Cremer and Trivedi;[11] the crude product (78–85% cis by nmr) was used without purification.

***cis*-1-Azido-2,2,3,4,4-pentamethylphosphetane 1-oxide (Ib)** was prepared from crude cis chloride. The latter (3.3 g, 17 mmol) was

(9) M. J. P. Harger and S. Trippett, private communication.

(10) J. J. McBride, E. Jungermann, J. V. Killheffer, and R. J. Clutter, *J. Org. Chem.*, 27, 1833 (1962).

(11) S. E. Cremer and B. C. Trivedi, *J. Amer. Chem. Soc.*, 91, 7200 (1969).

dissolved in 30 ml of methanol and added to a solution of 10.5 g (9–10-fold excess) of sodium azide in 36 ml of water; the resulting homogeneous solution had a pH of 7.4 (more alkaline solutions should be avoided). After 2.5 hr at room temperature, the solution was extracted three times with equal volumes of ether. The ether extracts were dried, the solvent was evaporated, and the resulting oil was suspended in 25 ml of water and reextracted into ether to remove traces of sodium azide. The ether was then carefully dried with calcium sulfate and finally with 4 Å molecular sieves. After evaporation of the ether, the residue was twice distilled from 5 Å molecular sieves; the colorless product boiled at 72° (0.15 mm), and consisted (nmr analysis) of 78% cis and 22% trans azide. Pure cis azide was obtained in small quantities by high-pressure liquid chromatography of 40-μl samples on a 0.307 in. × 6 ft column filled with Porasil C and eluted with 1:30 acetonitrile–methylene chloride. Four recycles were required to obtain a sample of cis that was pure both chromatographically and by nmr. The analytical sample (15 μl) was distilled at 0.15 mm. *Anal.* Calcd for $C_8H_{16}N_3OP$: C, 47.76; H, 8.02; N, 20.88; P, 15.39. Found, *cis*-Ib: C, 47.96; H, 8.22; N, 20.72; P, 15.43.

The trans azide,[8] Ia, prepared in a similar manner from pure trans chloride, distilled at 65° (0.1 mm) and after four crystallizations from ether at Dry Ice temperatures, with precautions against adventitious moisture, melted at 32–33°.

***trans*-2-Methoxy-3,3,4,5,5-pentamethyl-1,2-azaphospholidine 2-Oxide (IIa).** The 1:50 methanol–ether fraction from chromatography of the photolysis products from the cis or trans azide melts at 123–127° after crystallization from hexane; it consists (nmr analysis) of 26:74 mixture of *cis*- to *trans*-methyl phostonates. The isomers can easily be separated by HPLC on a 0.307 in. × 6 ft column of Porasil C with ethyl acetate as eluent. A 100-mg sample of *trans*-methyl phostamate that had been purified by HPLC was recrystallized three times from 0.5 to 1 ml of hexane to yield white needles, mp 140.0–141.0°. A 50-mg sample of *cis*-methyl phostamate, IIb, from HPLC was recrystallized once from ethyl acetate and then three times from hexane to give small granular white crystals, mp 124.0–125.0°. *Anal.* Calcd for $C_9H_{20}NO_2P$: C, 52.67; H, 9.82; N, 6.82; P, 15.09. Found *trans*-IIa: C, 52.89; H, 9.69; N, 6.81; P, 15.30; *cis*-IIb: C, 52.37; H, 9.86; N, 6.61; P, 14.89.

"*trans*"-*O*-Methyl(1,1,2,3-tetramethyl-3-butenyl)phosphonamidate (IIIa). (The stereochemical designation refers to the isomeric azide from which this diastereomer is stereoselectively formed.) Photolysis of pure trans azide and subsequent chromatography as indicated above leads to a relatively pure sample of a single isomer of the unsaturated ester amide, IIIa. Repeated crystallization from hexane (6 ml/g) gave pure material, mp 112.5–115.0° (lit.[8] 107–115°). The corresponding "cis" isomer was obtained from the photolysis of a sample of 50% cis azide. The fraction from chromatography over alumina that contained the cis and trans isomers of the unsaturated ester amide was further chromatographed by HPLC on a $^3/_8$ in. × 6 ft column of Porasil C, eluting with acetonitrile. The sample had to be recycled three times in order to obtain satisfactory separation of the isomers. In this manner, 0.1 g of crude "cis" III was obtained from 3 g of mixed azide isomers; this material was recrystallized to constant melting point (131.5–132.5°) from 2 ml of hexanes plus a few drops of methylene chloride, and appeared pure by nmr. *Anal.* Calcd for $C_9H_{20}NO_2P$: C, 52.67; H, 9.82; N, 6.82; P, 15.09. Found "*cis*"-IIIb: C, 52.67; H, 9.85; N, 6.83; P, 15.15.

***trans*-1-Methoxy-2,2,3,4,4-pentamethylphosphetane 1-oxide (IVa)** was prepared from 1 g of the trans acid chloride according to Hawes and Trippett.[12] The pure trans ester melted at about 20°. Crude, cis phosphetane ester, IVb, was similarly prepared from crude cis acid chloride.[11] Distillation of the crude cis product gave a 15% yield of phosphetane ester that was 57% cis by nmr analysis. Both cis and trans phosphetane esters were also obtained by further chromatography of the ether fractions from a photolysis mixture (*vide supra*) on a 0.843 in. × 8 ft Porasil C column with ethyl acetate as eluent, and a single recycle. Although the cis and trans phosphetane esters were incompletely separated, the forward and trailing edges of the joint peak gave trans and cis material, respectively, of 90% purity by nmr.

2-Methoxy-3,3,4,5,5-pentamethyl-1,2-oxaphospholane 2-Oxide (V). The chromatography of the ether fractions from a photolysis mixture (*vide supra*) on a 0.843 in. × 8 ft Porasil C column also yielded the *cis*- and *trans*-methyl phostonates with ethyl acetate as solvent. The isomerically pure materials recovered after a single recycle were vacuum distilled to give analytical samples. *Anal.* Calcd for $C_9H_{19}O_3P$: C, 52.42; H, 9.29; P, 15.02. Found: *trans*-Va, C, 52.42; H, 9.16; P, 14.88; *cis*-Vb, C, 52.42; H, 9.28; P, 14.93.

1-Methoxyamino-2,2,3,4,4-pentamethylphosphetane 1-Oxide (VI). A solution of 583 mg of distilled methoxyamine (prepared from Eastman methoxyamine hydrochloride) and 1.2 g of trans acid chloride in 2 ml of acetonitrile was allowed to stand at room temperature for 3 days. Acetonitrile was evaporated from the resulting suspension (containing methoxyamine hydrochloride); the residue was suspended in 10 ml of 10% aqueous sodium carbonate solution and extracted twice with 10 ml of methylene chloride. After the methylene chloride solution had been dried with Drierite and the solvent evaporated, the product was recrystallized from 13 ml of 1:3 benzene–hexane; yield 0.6–0.7 g, mp 151–152.5°. *Anal.* Calcd for $C_9H_{20}NO_2P$: C, 52.67; H, 9.82; N, 6.82; P, 15.09. Found: C, 52.79; H, 9.80; N, 6.77; P, 15.03.

2-Amino-3,3,4,5,5-pentamethyl-1,2-oxaphospholane 2-Oxide (VII). The mixture of photolysis products eluted from neutral alumina with 1:10 methanol–ether was rechromatographed on neutral alumina, activity I, using 40 g of alumina/g of product. The earliest fractions eluted with 1:50 methanol–ether contain methyl phostamate, while elution with 1:10 methanol–ether yields, first, the unsaturated ester amides IIIa and IIIb, and then finally, a mixture rich in the amino phostonate, VII. The impure phostonate recovered from these last fractions of the eluate was easily purified by a single crystallization from 1:1 methylene chloride–benzene (1 l/40 mg) by gently evaporating the solution until crystallization began, and then cooling the solution overnight. The white needles melted at 183.3–184.4°. The stereochemistry of this isomer is uncertain. *Anal.* Calcd for $C_8H_{18}NO_2P$: C, 50.25; H, 9.49; P, 7.33. Found: C, 50.34; H, 9.33; P, 7.22.

Anhydride of 1-hydroxy-2,2,3,4,4-pentamethylphosphetane 1-oxide (VIII) was formed from the hygroscopic acid chloride on storage at room temperature as reported by Emsley, *et al.*[13] The anhydride was purified by chromatography with ethyl acetate on silica gel (activity I) and then crystallized three times from hexane; the mixture of stereoisomers melted at 151.0–152.5°.

Dimethyl ether was identified by gas chromatography as a product of the photolysis of the phosphetane azides in dry methanol. Chromatography was conducted at 130° with a Hewlett-Packard 5750 research chromatograph and flame ionization detector, with helium as the carrier gas at 25 ml/min on a 6 ft × 0.25 in. Porapak T column (Waters Associates). Direct injection of the methanol solutions gave satisfactory analyses; the output was calibrated with pure dimethyl ether.

Results

Product Yields. The yields of products (Table I) were determined by HPLC on 0.09 in. i.d. Corasil II columns, using the solvent systems listed in Table II for elution. The products were identified by comparison of their retention times in these systems with those of pure compounds synthesized or isolated as described in the Experimental Section. In general, the photolysis mixtures for analysis were prepared for chromatography by evaporation of the solvent (methanol), and the residue was dissolved to make a 10% solution in the chromatog-

Table I. Yields of Photolysis Products from Trans Azide

Product	Yield by HPLC[a]	Yield by isolation[b]
Methyl phostonates	11	10
Phosphetane esters	6	8
Phosphetane hydroxamate	1	1
Anhydride[c]	1	3
Methyl phostamates	65	58
Unsaturated ester amides	14	17
Phostonate amide	2	3

[a] % total peak area. [b] % by weight. [c] An impurity in the azide, not a photolysis product.

(12) W. Hawes and S. Trippett, *J. Chem. Soc. C*, 1465 (1969).

(13) J. Emsley, T. B. Middleton, J. K. Williams, and M. F. Cook, *Phosphorus*, 3, 45 (1972).

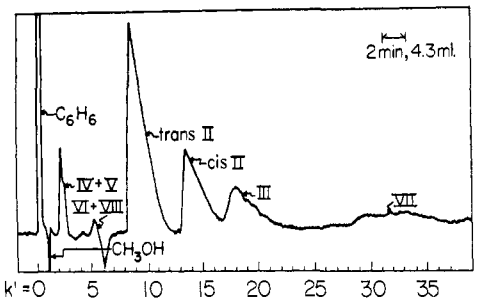


Figure 1. Chromatographic separation of *cis*- and *trans*-methyl phostamates, II, and of the unsaturated amino ester, III, on Corasil II with methanol–hexane–acetone in the ratio of 1:250:50 as eluent at a flow rate of 2.1 ml/min. Index of refraction detector; 5-mg sample.

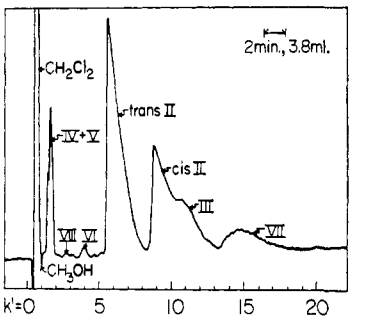


Figure 2. Chromatographic separation of the phosphetane hydroxamate, VI, phostonate amide, VII, and anhydride, VIII, on Corasil II with hexane–acetone in the ratio of 2:1 as eluent at a flow rate of 1.9 ml/min. Index of refraction detector; 3-mg sample.

Table II. Analytical HPLC Solvent Systems

Solvent system	Products separated as individual peaks
A Methanol–hexane–acetone, 1:250:50	*cis*- and *trans*-methyl phostamates, unsaturated ester amides
B Hexane–acetone 2:1	*trans*-Methyl phostamate, amino phostonate, phosphetane hydroxamates, anhydride
C Ethyl acetate–hexane, 2:1	*trans*-Methyl phostamate, *cis*- and *trans*-methyl phostonates, cis and trans phosphetane esters
D Ethyl acetate	*cis*- and *trans*-methyl phostonates, phosphetane esters, *trans*-methyl phostamate
E Acetonitrile	Cis phostamate ester, *cis*- and *trans*-methyl phostonates, phosphetane esters, phosphetane hydroxamates, anhydride

raphy solvent or in benzene; this solution of the mixture of products was then injected onto the column. Control experiments using acetonitrile as solvent showed that all the compounds here identified produced about the same peak area (±20%) per millimole with the refractive index detector, and stereoisomers showed identical areas within experimental error. Although slightly more precise results might be obtained by taking the small differences in sensitivity into account, the results here reported were obtained by equating peak area with product yield; note that this is strictly accurate for the vital ratios of stereoisomers. "Yield by isolation" refers to the percentage of products obtained from a preparative experiment begun with 5 g of trans azide, where the products were separated, with about 80% recovery, on the large (*i.e.*, 0.843 in.) preparative column packed with Porasil C and eluted first with 2:1 hexane–acetone. These fractions were assayed by the appropriate analytical HPLC system, and the appropriate fractions were rechromatographed on the same preparative column with ethyl acetate to obtain the first four products and with 2:1 hexane–acetone to obtain the last three. The numbers in the table are for products at this stage containing 0.1–0.2 g of impurity; corrections were made for the amount of impurities detected by HPLC analysis.

The data in Table I for "yield by HLPC" were obtained under various chromatographic conditions

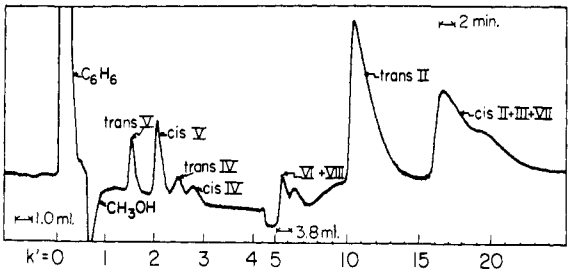


Figure 3. Chromatographic separation of cis and trans phosphetanes esters, IV, and *cis*- and *trans*-methyl phostonates, V, on Corasil II with ethyl acetate–hexane in the ratio of 2:1 as eluent at a flow rate of 0.5 ml/min. Index of refraction detector; 0.6-mg sample.

chosen so as to maximize particular separations at the expense of others; the various eluents are listed in Table II, and examples of the separations are shown in Figures 1–3. The agreement between analyses and isolation is good but not perfect; presumably the analytical data are much the better, since the fractions obtained in preparative chromatography are not pure and quantitative recovery was difficult. The yields of cis and trans isomers or other diastereomeric pairs are combined in Table III; the isomer ratios obtained are discussed below.

Yields of methyl phostonate, V, and of the phostonate amide, VII, proved variable. The variability appears

Table III. Per Cent Trans Isomers in Products

Azide photolyzed	Methyl phostamate[a]	Methyl phostonate[b]	Phosphetane ester[b]	Unsaturated ester amide[c]
Trans	67 ± 1[d,e]	55	77	79
78% trans, 22% cis	68 ± 1	60	20[f]	
28% trans, 72% cis	70 ± 1	55	2[f]	39[g]
Cis	71			

[a] Solvent system A. [b] Solvent system C. [c] Isolated by chromatography over alumina, followed by preparative HPLC on Corasil II with 2% ethanol in chloroform as eluent. Isomer distribution determined by HLPC on Corasil II with solvent system E or by nmr analysis. [d] Average of eight determinations. [e] Independent of added methoxide, acetic acid, acetate buffer, or water. [f] This apparently anomalous results arises because the cis azide is solvolyzed much more rapidly than the trans, and the effect of this solvolysis is magnified since the total yield of phosphetane ester is small. [g] 22% trans, 78% cis azide photolyzed.

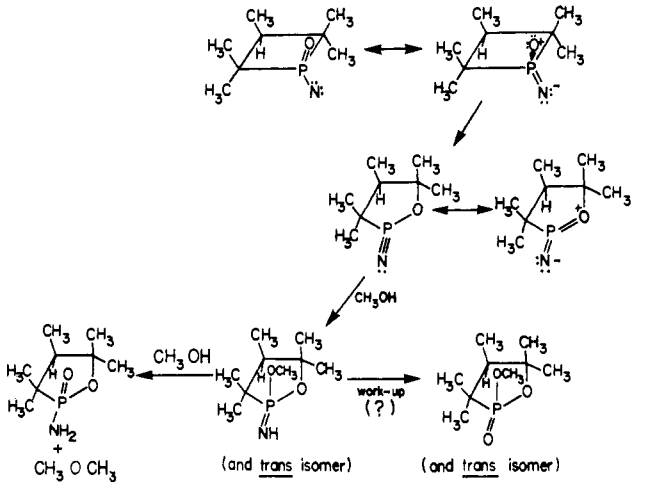
to be caused by traces of water in the methanol used as solvent in the photolyses. When the methanol was freshly dried with magnesium, when the photolysis tubes were sealed with serum caps that had never been punctured, and when care was taken to dry the apparatus thoroughly, then the yield of the methyl phostonate was fairly consistently about 12–13% and that of the phostonate amide only around 1–2%. When 0.4 equiv of water was deliberately added, the yield of methyl phostonate fell to 2% and that of the phostonate amide rose to 17%. When varying amounts of water, from 0.08 to 0.5 equiv, were added, the yields of the two products were anticorrelated with the sum generally around 17%.

Discussion

The products obtained from the photolysis of the phosphetane azides in methanol can be rationalized by assuming that a nitrene or incipient nitrene is an intermediate. As pointed out in the introduction, the ring enlargements may, however, occur concurrently with the evolution of nitrogen, in a concerted reaction. This formulation would parallel that for the rearrangements that accompany the photolysis of sulfonyl azides and of carboxylic acid azides.[14] The nitrene is, however, a convenient conceptual device, and may be the true intermediate in some of the processes here described. In the photolyses the major products consist of the *cis*- and *trans*-methyl phostamates in the ratio of about 31:69. The ratio is almost invariant; nearly the same yields are obtained from either the cis or the trans azide, and the ratio is unaffected by the addition of various reagents to the methanol (water, acetic acid, methoxide). Slightly more trans product (71% rather than 68%) is formed from cis azide than from trans and this difference may be beyond experimental error; even if this is so, however, the tendency toward stereoselectivity (stereochemical inversion) is small, and the reaction proceeds as if the same intermediate is formed from either cis or trans azide. This intermediate is most probably a monomeric metaphosphonimidate, where the molecule is either planar around the phosphorus atom or else rapidly inverts at phosphorus from one pyramidal structure to its opposite.

Other data also support this mechanism. In dry methanol the *cis*- and *trans*-methyl phostonates are formed in the ratio of 40:60 from either the cis or the trans azide; here again a common intermediate is indicated. Furthermore, along with the methyl phostonates, the corresponding phostonate amide is produced; since the yield of amide increases and that of the ester falls when water is added to the reaction mixture, they presumably are formed from a common intermedate. A partial mechanism for the formation of these products is shown below.

This mechanism postulates that the nitrene, or incipient nitrene, produced in the photolysis is a resonance hybrid with an electron-deficient oxygen atom (oxenium ion) as well as an electron-deficient nitrogen atom. The oxenium ion can insert into an adjacent carbon to phosphorus bond, and so produce the five-membered phostone ring. The immediate product of the ring expansion would be a new type of intermediate with the electrophilic characteristics of a monomeric metaphosphorimidate; it is here tentatively named as a "metaphosphazile." The subsequent fate of this intermediate is uncertain. If large quantities of water are present, the "metaphosphazile" might directly add H_2O to yield the phostonate amide, but this direct pathway is improbable in dry (or almost dry) methanol where a large excess of methanol over water is present. Furthermore, some evidence suggests that the common intermediate for the formation of the phostonate ester and phosphonate amide occurs further along in the reaction pathway, since the addition of water not only increases the yield of amide, but also skews the 40:60 cis:trans ratio of esters to as much as 60:40 cis:trans, as if an intermediate related to the trans phostonate amide reacted more rapidly with water than did its cis counterpart.



This interpretation is supported by the isolation of dimethyl ether, from photolyses conducted in superdry methanol, in amounts approximately stoichiometric with that of the phostonate amide. The ether is the logical product to be formed in the decomposition of the postulated intermediate to yield a product (phostonate amide) with a phosphoryl group. Furthermore, the amount of dimethyl ether formed is diminished toward zero when water is added to the photolysis solutions, as would be expected. Be this as it may, the occurrence of the phostonate esters and the amide strongly suggests that the oxygen atom of the phosphoryl nitrene or incipient nitrene is electron deficient, and inserts to form a new type of intermediate that is effectively planar about the phosphorus atom.

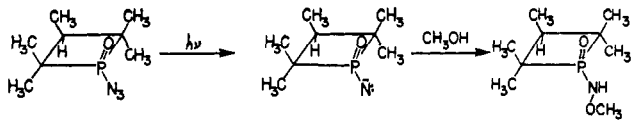
Only one of the stereoisomeric phostonate amides has so far been isolated, although quite possibly the other isomer is present in the photolysis products but has not yet been successfully isolated.

Another product that suggests a nitrene intermediate is the phosphetane hydroxamate, VI. This product would be formed if the postulated nitrene inserts into methanol; the product and mechanism parallel those for the photolysis of carboxylic acid azides.[14a,c,15]

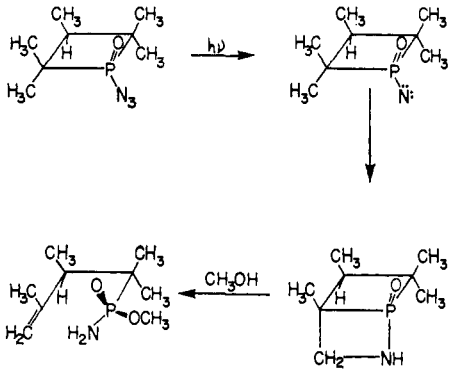
Other products can also be accounted for provided

(14) (a) W. Lwowski, "Nitrenes," Interscience, New York, N. Y., 1970; (b) W. Lwowski and E. Scheiffele, *J. Amer. Chem. Soc.*, **87**, 4359 (1965); (c) R. Kreher and G. H. Bockhorn, *Angew. Chem.*, **76**, 681 (1964); (d) L. Horner, G. Bauer, and J. Doerges, *Chem. Ber.*, **98**, 2631 (1965); (e) R. Puttner and K. Hafner, *Tetrahedron Lett.*, **31**, 9 (1964); (f) M. Regitz, A. Liedhegener, W. Anschuetz, and H. Eckes, *Chem. Ber.*, **104**, 2177 (1971).

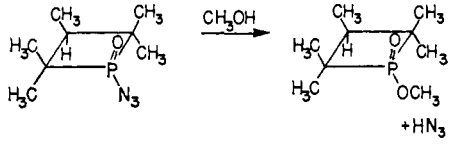
(15) W. Lwowski, R. DeMauriac, T. W. Mattingly, Jr., and E. Scheiffele, *Tetrahedron Lett.*, 3285 (1964).



that a nitrene is the first intermediate formed in photolysis. The unsaturated amino esters, III, are formed stereoselectively, but not quite stereospecifically. Photolysis of pure trans azide produces a mixture that contains the diastereomeric unsaturated ester amides, in a ratio of 9:1. Although a similar experiment has not been carried out with pure cis azide, photolysis of mixtures rich in the cis isomer leads to products where the ratio of stereoisomers is such as to suggest that the reaction of pure cis would produce the stereoisomeric unsaturated ester amides in the inverse ratio to that given above. A possible if highly speculative mechanism for the stereoselective formation of these products involves insertion of the postulated nitrene into a carbon–hydrogen bond, followed by a methanol-induced cleavage of the resulting bicyclic ring system.



Finally, among the products formed in the photolysis are the methyl esters of the phosphetane oxides, formed stereospecifically with retention of configuration from the corresponding azides; *e.g.*



The reaction is base sensitive. In the dark, displacement with methoxide ion is rapid and quantitative, but methanolysis is slow in neutral solution; the photolytic reaction is inhibited by acid and by water. The detailed mechanism for the process that accompanies photolysis has not yet been worked out.

Throughout this paper, cis or trans stereochemistry has been specified for various starting materials or products. These designations are reasonably secure, but it should be noted that the essential conclusions concerning mechanism are independent of these assignments. The evidence for a monomeric metaphosphonimidate rests on the finding that both *cis*- and *trans*-methyl phostamates are formed in the same ratio from either cis or trans azide; this conclusion would not be altered no matter how the specific stereochemical assignments for the starting materials and products might be scrambled. The assignments nevertheless are probably correct; the evidence for them rests primarily on the X-ray analysis that specifies the trans configuration for the isomer of 1-chloro-2,2,3,4,4-pentamethyl-

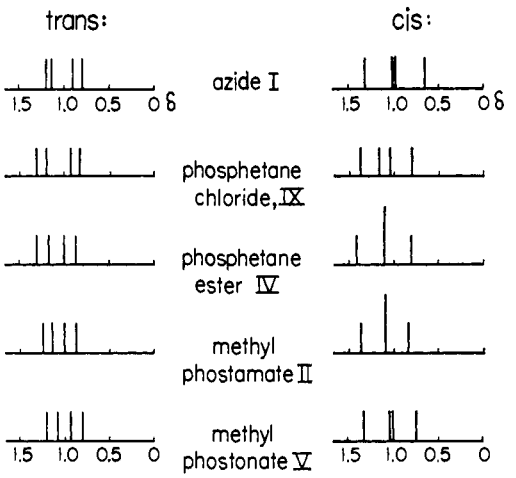


Figure 4. Schematic representation of the nmr spectra in benzene of the azide, I, the phosphetane chloride, IX, the phosphetane ester, IV, the methyl phostamate, II and the methyl phostonate, V. The signals shown are only those for the two methyl groups α to the phosphorus; these signals were distinguished from others in the spectra as described in the Discussion.

phosphetane 1-oxide[16] that melts at 74.5–76.0°. Several stereochemical cycles[11,17] and consideration of the changes in nmr spectra induced by lanthanide shift reagents have led to the conclusions that the phosphetane acid chlorides react with good nucleophiles with retention of configuration. Consistent assignments can be made for the other cyclic products, where their nmr spectra serve to classify them in two series; the spectrum of the known trans acid chloride defines the trans series. No stereochemical assignments, however, are yet possible for the diastereomeric unsaturated ester amides. The requisite nmr spectra are presented schematically in Figure 4. The assignments here used follow and are in agreement with those of DeBruin, *et al.*,[18] for the phosphetanes, and follow the same patterns for our new assignments for the five-membered ring compounds (phostamates and phostonates). The nmr spectra of the latter are, of course, much more complicated than those for the phosphetanes, but the assignments of the signals to particular methyl groups could nevertheless be made unambiguously by inspection of the spectra both at 60 and at 100 MHz. These spectra could all be rationalized by assigning J_{H-P} = 15–16 Hz (five-membered rings) or 18–22 Hz (four-membered rings) for the hydrogen atoms of the methyl groups α to the phosphorus atom; these are the signals shown in Figure 4.

In summary, photolyses of the *cis*- and *trans*-1-azido-2,2,3,4,4-pentamethylphosphetane 1-oxides yield about ten products. The major series of products can be rationalized as formed from a nitrene–oxenium ion resonance hybrid that results from loss of molecular nitrogen from the azide. Rearrangement and ring enlargement then leads to the formation of monomeric metaphosphonimidate and of a new type of closely related chemical intermediate, a "metaphosphazile." The

(16) Mazhar-ul-Haque, *J. Chem. Soc. B*, 934 (1970).

(17) J. R. Corfield, R. K. Oram, D. J. H. Smith, and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, 713 (1972); K. E. DeBruin, G. Zon, K. Naumann, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 7027 (1969); J. R. Corfield, N. J. De'ath, and S. Trippett, *Chem. Commun.*, 1502 (1970).

(18) K. E. DeBruin, A. G. Padilla, and M. Campbell, *J. Amer. Chem. Soc.*, **95**, 4681 (1973).

data here presented strengthen the assumption that monomeric metaphosphorimidates can participate in the chemistry of phosphoramides.

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Supplementary Material Available. A listing of the nmr data for compounds Ib, IIb, IIIb, Va, Vb, VIa, and VII will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-4262.

Synthesis of Nonclassical Thiophenes[1]

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Abstract: Phosphorus pentasulfide treatment of suitable vicinal dibenzoyl heterocycles has been established as a convenient pathway to three nonclassical thiophene systems: tetraphenylthieno[3,4-*c*]thiophene, 5-methyl-1,3,4,6-tetraphenylthieno[3,4-*c*]pyrrole, as well as hexaphenylthieno[3,4-*f*]isothianaphthene. 1,3-Dipolar cycloaddition reactions with dibenzoylacetylene, utilizing the "masked" 1,3-dipole of several mesoionic systems, readily provided the precursors to the 10π-electron heterocycles. 5-Methyl-1,3,4,6-tetraphenylthieno[3,4-*c*]pyrrole formed 1:1 primary cycloadducts with activated olefins across both the 4 and 6 positions (azomethine ylide) and 1 and 3 positions (thiocarbonyl ylide), these additions being examples of kinetic and thermodynamic product control. In some cases, the thiocarbonyl ylide adducts underwent thermal elimination of the elements of hydrogen sulfide giving rise to bicyclic heteroaromatics. The addition of dibenzoylacetylene occurred only across the azomethine ylide affording a stable 1:1 adduct. Tetraphenylthieno[3,4-*c*]thiophene and dibenzoylacetylene formed an unstable 1:1 adduct which decomposed by the elimination of sulfur forming 5,6-dibenzoyl-1,3,4,7-tetraphenylisothianaphthene which, in turn, afforded hexaphenylthieno[3,4-*f*]isothianaphthene upon treatment with P_4S_{10}. This novel 14π-electron system underwent cycloaddition reactions with olefins across the 1 and 3 positions.

Nonclassical condensed thiophenes, because of their unusual electronic structure, have been the subject of several recent investigations.[2-4] Tetraphenylthieno[3,4-*c*]thiophene (**4**), initially reported[2e,c] in 1969, was the first stable example of a bicyclic heterocycle containing 10π electrons and a so-called "tetravalent sulfur" atom. Other representatives of this class of compound have since been described,[2a,b,d,f] and in several preliminary communications[1d] we have described an approach to the synthesis of nonclassical thiophenes based upon the cycloaddition reactions of mesoionic ring systems[5] with dibenzoylacetylene. The full details of this work are reported in this and the following publication.[6]

Tetraphenylthieno[3,4-*c*]thiophene (4). The synthesis of **4** was first effected by the acetic anhydride dehydration of *cis*-1,3,4,6-tetraphenyl-1*H*,3*H*-thieno[3,4-*c*]thiophene 2-oxide.[2c,e] It has now been prepared by P_4S_{10} treatment of 3,4-dibenzoyl-2,5-diphenylthiophene. This dibenzoylthiophene is readily available from anhydro-4-hydroxy-2,3,5-triphenylthiazolium hydroxide (**1**), itself formed by acetic anhydride cyclization of the acid formed from thiobenzanilide and α-bromophenylacetic acid.[5c] This system is generally represented as a hybrid of various charged separated structures (**1** and **1a**) though, in terms of the bonding concepts currently being discussed, contribution from a "tetravalent sulfur" structure (**1b**) must also be considered.[7] When **1** was treated with dibenzoylacetylene in refluxing benzene, 3,4-dibenzoyl-2,5-diphenylthiophene (**3**) was formed in 42% yield. This reaction presumably involves the initial addition of dibenzoylacetylene across the thiocarbonyl ylide (or 2 and 5 positions) of **1** affording the primary cycloadduct **2**, which then decomposes to **3** by the elimination of phenyl isocyanate. Analytical and spectral data (Experimental Section) clearly established the assigned structure.

When **3** was treated with phosphorus pentasulfide in

(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute is gratefully acknowledged; (b) abstracted from the Ph.D Thesis of D. McKeough, Rensselaer Polytechnic Institute, 1973; (c) Sterling-Winthrop Fellow, 1971-1973; (d) preliminary communications: K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **95**, 2749, 2750 (1973).

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(3) M. D. Glick and R. E. Cook, *Acta Crystallogr., Sect. B*, **28**, 1336 (1972).

(4) M. O. Calculations on the thieno[3,4-*c*]thiophene system [D. T. Clark, *Tetrahedron*, **24**, 2567 (1968)] ignoring d orbital participation, predict a high energy for this system as well as a triplet ground state.

(5) *E.g.*, see (a) R. Huisgen, G. Gotthardt, and R. Grashey, *Chem. Ber.*, 101, 536 (1968); (b) K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061, 1062 (1968); (c) K. T. Potts, E. Houghton, and U. P. Singh, *ibid.*, 1129 (1969).

(6) K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **96**, 4276 (1974).

(7) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3189 (1956).