propene, 3017-69-4; 2-bromo-3-methyl-2-butene, 3017-70-7; morpholine, 110-91-8; 4-methyl-7-piperidino-1,5-heptadiene, 80698-42-6; bis(acetato-*O*)bis[tris(2-methylphenyl)phosphine]palladium, 69073-98-9; (*N*)-(5-phenyl-2-pentenyl)piperidine picrate, 80698-44-8; *trans*-5-(1-methylethenyl)-3-piperidinocyclohex-1-ene, 80698-45-9; $[CH_2{=}CHCH{=}CHCH_2\text{-}P^*\text{-}CH_2CH_3]^+$ Br^-, 80698-46-0; $CH_2{=}CHCH{=}CH\text{-}P^*$, 19352-92-2; $PhCH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-43-7; $PhCH_2CH_2CH(CH{=}CH_2)\text{-}P^*$, 80698-47-1; (E)-$PhCH(CH_3)CH{=}CHCH_2\text{-}P^*$, 80698-48-2; $PhCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-49-3; $PhCH_2CH_2CH(CH{=}CHCH_3)\text{-}P^*$, 80698-50-6; $PhCH(CH_3)CH{=}CHCH(CH_3)\text{-}P^*$, 80698-51-7; $PhCH_2CH_2CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-52-8; $PhCH(CH_3)CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-53-9; $H_2C{=}CHCH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-54-0; $H_2C{=}CHCH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-55-1; $H_3CCH{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-56-2; $H_3CCH{=}CHCH_2CH_2CH(\text{-}P^*)CH{=}CHCH_3$, 80698-57-3; $P^*\text{-}CH_2C(CH_3){=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-58-4; $H_2C{=}CHCH_2CH_2CH{=}CHCH_2\text{-}M$, 80698-59-5; $H_2C{=}CHCH_2CH_2CH(\text{-}M)CH{=}CH_2$, 80698-60-8; (*X*,*Z*)-$P^*\text{-}CH_2CH{=}CHCH_2CH_2CH{=}CHCH_3$, 80698-61-9; $H_2C{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-62-0; $H_2C{=}CHCH_2CH_2CH(\text{-}P^*)CH{=}CHCH_3$, 80698-63-1; (*E*,*Z*)-$M\text{-}CH_2CH{=}CHCH_2CH_2CH{=}CHCH_3$, 80698-64-2; $H_2C{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}M$, 80698-65-3; $H_2C{=}CHCH_2CH_2CH(\text{-}M)CH{=}CHCH_3$, 80698-66-4; $P^*\text{-}CH_2CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-67-5; $H_2C{=}CHCH(\text{-}P^*)CH_2CH_2C(CH_3){=}CH_2$, 80698-68-6; $P^*\text{-}CH_2C(CH_3){=}CHCH_2CH_2CH{=}CH_2$, 80698-69-7; $H_2C{=}C(CH_3)CH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-70-0; $P^*\text{-}CH_2CH{=}C(CH_3)CH_2C(CH_3){=}CH_2$, 80698-71-1; (*E*)-$M\text{-}CH_2CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-72-2; $H_2C{=}CHCH(\text{-}M)CH_2CH_2C(CH_3){=}CH_2$, 80698-73-3; $M\text{-}CH_2C(CH_3){=}CHCH_2CH_2CH{=}CH_2$, 80698-74-4; $H_2C{=}C(CH_3)CH(\text{-}M)CH_2CH_2CH{=}CH_2$, 80698-75-5; $M\text{-}CH_2CH{=}C(CH_3)CH_2C(CH_3){=}CH_2$, 80698-76-6; (*E*)-$M\text{-}CH_2CH{=}CHCH(CH_3)CH_2CH{=}CH_2$, 80698-77-7; $P^*\text{-}CH(CH_3)CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-78-8; $H_3CCH{=}CHCH(\text{-}P^*)CH_2CH_2C(CH_3){=}CH_2$, 80698-79-9; $H_3CCH{=}CHCH_2CH_2CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-80-2; $H_3CCH{=}CHCH_2CH_2CH(\text{-}P^*)C(CH_3){=}CH_2$, 80698-81-3; $P^*\text{-}C(CH_3)_2CH{=}CHCH_2CH_2CH{=}CH_2$, 80698-82-4; $(H_3C)_2C{=}CHCH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-83-5; $(H_3C)_2C{=}CHCH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-84-6; $(H_3C)_2C{=}CHCH(CH_3)CH{=}CHCH_2\text{-}P^*$, 80698-85-7; $P^*\text{-}C(CH_3)_2CH{=}CHCH_2CH_2CH{=}CHCH_3$, 80698-86-8; $(H_3C)_2C{=}CHCH(\text{-}P^*)CH_2CH_2CH{=}CHCH_3$, 80698-87-9; $(H_3C)_2C{=}CHCH_2CH_2CH{=}CHCH(CH_3)\text{-}P^*$, 80698-88-0; $(H_3C)_2C{=}CHCH(CH_3)CH{=}CHCH(CH_3)\text{-}P^*$, 80698-89-1; $P^*\text{-}C(CH_3)_2CH{=}CHCH_2CH_2C(CH_3){=}CH_2$, 80698-90-4; $(H_3C)_2C{=}CHCH(\text{-}P^*)CH_2CH_2C(CH_3){=}CH_2$, 80698-91-5; $(H_3C)_2C{=}CHCH_2CH_2CH{=}C(CH_3)CH_2\text{-}P^*$, 80698-92-6; $(H_3C)_2C{=}C(CH_3)CH(\text{-}P^*)CH_2CH_2CH{=}CH_2$, 80698-93-7; $(H_3C)_2C{=}C(CH_3)CH_2CH_2CH{=}CHCH_2\text{-}P^*$, 80698-94-8; $(H_3C)_2C{=}C(CH_3)CH_2CH_2CH(\text{-}P^*)CH{=}CH_2$, 80698-95-9; $(H_3C)_2C{=}C(CH_3)CH(CH_3)CH{=}CHCH_2\text{-}P^*$, 80698-96-0.

Supplementary Material Available: Table IV containing the physical properties, NMR spectral data, and molecular weights of the products prepared (11 pages). Ordering information is given on any current masthead page.

α-Diazophosphonic Acids as Potential Photoaffinity Labeling Reagents: Synthesis, Stability, and Photochemistry

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Received October 27, 1981

A series of α-diazophosphonic acid salts ($Et_2NSO_2CN_2PO_3^{2-}$, $i\text{-}Pr_2O_3PCN_2PO_3^{2-}$, and $RR'NCOCN_2PO_3^{2-}$) have been synthesized by diazo transfer to a diester precursor followed by ester cleavage with trimethylsilyl bromide. These compounds show disparate stabilities: the sulfamoyl- and phosphono-substituted derivatives decompose slowly even at pH 6.0 (21 °C, 0.2 M phosphate buffer; $t_{1/2} \approx 5$ h), whereas the *N*,*N*-dimethylcarbamoyl-substituted analogue decomposes rapidly even at pH 9.0 ($t_{1/2} \approx 40$ min). For all three derivatives the decomposition reaction involves initial loss of the PO_3^{2-} group to give the neutral diazo compound, $ZCHN_2$. The photochemical behavior of the α-diazophosphonic diester precursors $ZCN_2PO_3Me_2$ and the dianions $ZCN_2PO_3^{2-}$ (Z = Et_2NSO_2 and $i\text{-}Pr_2O_3P$) was also investigated by using light of $\lambda > 300$ nm. In alcohol or water as solvent, the neutral esters undergo the expected hydroxyl insertion and photoreduction reactions. In contrast, on photolysis in methanol, the anions undergo neither of these reactions; the major products appear to be those of 1,2-migration of one of the phosphate oxygens, leading to the α-hydroxy monoesters $ZCHOHPO_3Me^-$. This represents the first report of a photochemical study of a diazo compound with an anionic substituent. Although it is also the first example of formal Wolff rearrangement of an oxygen substituent from phosphorus to an adjacent carbene, we suggest that the migration proceeds via an oxaphosphirane intermediate instead of the classical Wolff-type mechanism. Unfortunately, the intervention of this transformation means that α-diazophosphonate dianions are unlikely to be useful as photoaffinity labeling reagents.

Since its invention by Westheimer some 20 years ago,[1] the technique of photoaffinity labeling has become an important one for probing macromolecular binding sites and biological targets.[2] The photolabile moieties employed for this purpose have for the most part been α-diazo esters or aryl azides, although diazirine derivatives are finding increasing use.[3] In recent years, a number of steps have been taken to "fine tune" the diazo functionality, modifying the substituents to optimize acid stability, minimize self-destructive Wolff rearrangement of the carbene intermediate, and obtain adequate light absorbance outside the envelope of a biological target.[4] Five years ago, Goldstein, McKenna, and Westheimer[5] and then we[6] reported the synthesis and characterization of several α-diazophosphonic acids as potential photolabile mimics of phosphate derivatives. We report here the full details of

(1) A. Singh, E. Thornton, and F. H. Westheimer, *J. Biol. Chem.*, **237**, PC3007 (1962).

(2) Inter alia: V. Chowdhry and F. H. Westheimer, *Annu. Rev. Biochem.*, **48**, 293 (1979); A. M. Tometsko and F. M. Richards, Eds., *Ann. N. Y. Acad. Sci.*, **346** (1980); H. Bayley and J. R. Knowles, *Methods Enzymol.*, **46**, 69 (1977); J. R. Knowles, *Acc. Chem. Res.*, **5**, 155 (1972).

(3) R. A. G. Smith and J. R. Knowles, *J. Am. Chem. Soc.*, **95**, 5072 (1973); *J. Chem. Soc., Perkin Trans. 2*, 686 (1975); H. Bayley and J. R. Knowles, *Biochemistry*, **17**, 2420 (1978); **19**, 3883 (1980); *Ann. N. Y. Acad. Sci.*, **346**, 45 (1980); F. M. Richards and J. Brunner, *ibid.*, **346**, 144 (1980); R. Radhakrishnan et al., *ibid.*, **346**, 165 (1980).

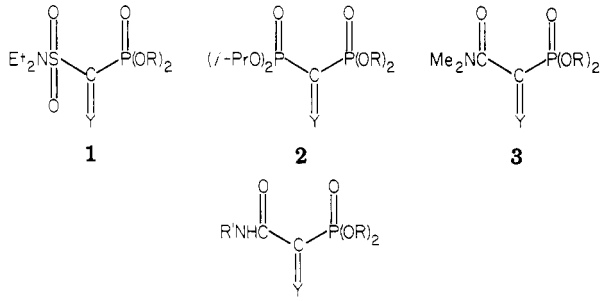
(4) (a) V. Chowdhry, R. Vaughan, and F. H. Westheimer, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 1406 (1976); (b) V. Chowdhry and F. H. Westheimer, *J. Am. Chem. Soc.*, **100**, 309 (1978); (c) *Bioorg. Chem.*, **7**, 189 (1978); (d) J. Stackhouse and F. H. Westheimer, *J. Org. Chem.*, **46**, 1891 (1981).

(5) J. A. Goldstein, C. McKenna, and F. H. Westheimer, *J. Am. Chem. Soc.*, **98**, 7327 (1976).

(6) P. A. Bartlett and K. P. Long, *J. Am. Chem. Soc.*, **99**, 1267 (1977).

0022-3263/82/1947-1284$01.25/0

Chart I[a]



1 2 3

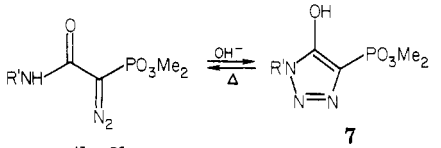
4, R′ = *i*-Pr
5, R′ = c-C_6H_{11}
6, R′ = $PhCH_2$

a, Y = H; R = Me
b, Y = N_2; R = Me
c, Y = N_2; R = $SiMe_3$
d, Y = N_2; R = e^-
e, Y = H_2; R = e^-
f, Y = H, OMe; R = Me
g, Y = H, OEt; R = Me
h, Y = H, OMe; R = e^-

our synthetic work in this area, and the results of our photochemical studies of both the esters and the phosphonic acid salts.

Synthesis of α-Diazophosphonic Acid Diesters 1–6. The precursor to each of the diazo compounds was the corresponding methylene analogue. The sulfonamide **1a** and methylenediphosphonate **2a** (Chart I) were prepared from *N,N*-diethylmethanesulfonamide[7] and diisopropyl methylphosphonate,[8] respectively, by alternate deprotonation (1 equiv of *n*-butyllithium), phosphorylation (0.5 equiv of dimethyl phosphorochloridate), deprotonation (0.5 equiv of base), phosphorylation (0.25 equiv of phosphorochloridate), etc. During each phosphorylation step, half of the carbanion is quenched by protonation by the more acidic product, hence the necessity of alternating addition of base and phosphorylating agent for efficient consumption of starting material. An alternative procedure, involving the addition of the phosphorochloridate to equimolar amounts of carbanion and lithium diisopropylamide, led to significant quantities of dimethyl *N,N*-diisopropylphosphoramidate. The phosphonoacetamide derivatives **3a–6a** were prepared from the bromoacetamides by Arbuzov reaction with trimethyl phosphite.

Diazo transfer to each of these activated methylene derivatives was accomplished in excellent yield by treating the sodium salt with *p*-toluenesulfonyl azide in THF.[9] Complications arose only in the case of the secondary amides **4a–6a** because the alkaline reaction conditions resulted in isomerization of the diazo product to the hydroxytriazoles **7**.[10] After neutralization and isolation,

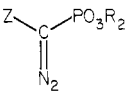


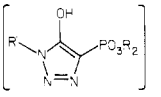
4b-6b 7

however, these isomers could be converted back to the diazo tautomers by heating, as previously observed by Regitz and Anschütz in related systems.[10]

In addition to possessing spectral properties which are consistent with the structures depicted, the diazo compounds **1b** and **3b** were further characterized by their

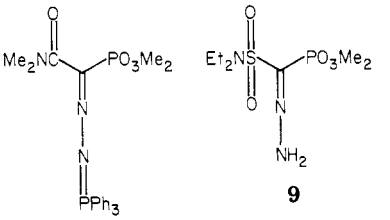
Table I. ^{13}C NMR Resonances of α-Diazophosphonates



series	Z	chemical shift (J_{CP}, Hz) of diazo carbon[a] b (R = Me)[b]	d (R = e^-)[c]
1	Et_2NSO_2	59.4 (216)	60.9 (152)
2	*i*-Pr_2O_3P	37.6 (204)[d]	37.9 (147, 200)[e]
3	Me_2NCO	49.7 (220)	55.0 (165)
4	*i*-PrNHCO	50.5 (209)	55.4 (162)
		112 (247; R′ = c-C_6H_{11})	126.9 (211; R′ = *i*-Pr)

[a] Chemical shifts reported in parts per million downfield from Me_4Si. [b] In $CDCl_3$ solvent, referenced to $CDCl_3$ as 77.0 ppm. [c] In H_2O, pH > 9, referenced to dioxane as 66.5 ppm. [d] Triplet. [e] Double doublet.

reactions with triphenylphosphine.[11] Diphosphonate **3b** afforded a crystalline phosphazene **8**; chromatography of



8 9

the analogous product from the sulfonamide **1b** resulted in its hydrolysis[11c] and isolation of the crystalline hydrazone **9**.

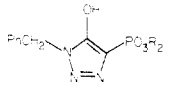
Ester Hydrolysis. The methyl esters were cleaved with trimethylsilyl bromide as described by McKenna et al.[12] The resulting bis(trimethylsilyl) esters were hydrolyzed by extraction from carbon tetrachloride solution into aqueous base or buffer. This procedure avoids acid-catalyzed decomposition of the α-diazophosphonate and affords an aqueous solution of the dianion which is essentially free from impurities. Alternatively, the sulfamoyl silyl ester **1c** was cleaved in methanol containing 2 equiv of base (sodium hydroxide or an amine). Evaporation then provided the corresponding salt of **1d** as a pale yellow solid which was stable when stored at 4 °C in the dark for extended periods.

Selective cleavage of the methyl esters of the diazomethylenediphosphonate **2b** was possible by careful temperature control ($T < 20$ °C) in the ester-exchange reaction. Selectivity for less hindered methyl esters is expected from the mechanism of the cleavage process and has been demonstrated in a variety of systems previously.[12b]

The diazophosphonates were readily characterized by ^{13}C NMR spectroscopy, as indicated in Table I. Because of the dipolar nature of the diazo functionality, the resonances of these carbons are found at exceedingly high field for the formally sp^2-hybridization state. They undergo a 0.3–5.0-ppm downfield shift and a significant decrease in carbon–phosphorus coupling constant on conversion of the diester to the dianion. The diazo species were, moreover,

(7) W. F. Erman and H. C. Kretschmar, *J. Org. Chem.*, **26**, 4841 (1961).
(8) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).
(9) M. Regitz, *Synthesis*, 351 (1972).
(10) (a) M. Regitz, W. Anschütz, and A. Liedhegener, *Chem. Ber.*, **101**, 3734 (1968); (b) M. Regitz and W. Anschütz, *ibid.*, **102**, 2216 (1969).
(11) (a) H. Staudinger and G. Lüscher, *Helv. Chim. Acta*, **5**, 75 (1922); (b) H. J. Bestmann, H. Buckschewski, and H. Leube, *Chem. Ber.*, **92**, 1345 (1959); (c) M. Regitz, *ibid.*, **99**, 3129 (1966).
(12) (a) C. E. McKenna, M. T. Higa, N. H. Cheung, and M.-C. McKenna, *Tetrahedron Lett.*, 155 (1977); (b) C. E. McKenna and J. Schmidhauser, *J. Chem. Soc., Chem. Commun.*, 739 (1979).

Table II. UV Spectral Characteristics of α-Diazophosphonates

series	Z[c]	λmax (log ε), nm b (R = Me)[a]	d (R = H)[b]
1	Et_2NSO_2	227 (3.85), 373 (1.65)	233 (3.85), 393 (1.64)
2	i-Pr_2O_3P	227 (3.83), 337 (1.08)	238 (3.85), 367 (1.71)
3	Me_2NCO	244 (3.86), 357 (1.58)	263 (4.17), 381 (1.81)
		256 (3.43)	

[a] In water. [b] In 0.2 M phosphate buffer, pH 9. [c] See Table I for structure.

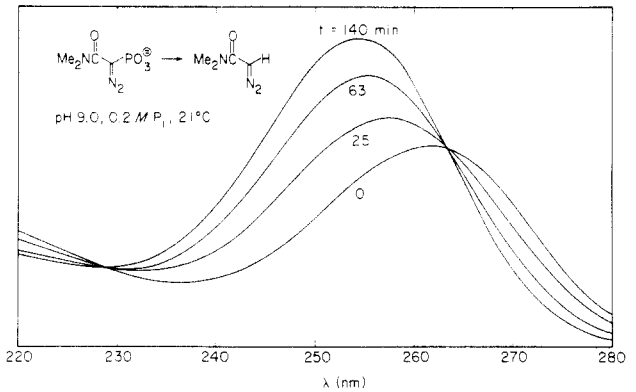
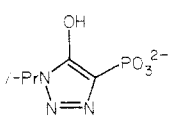


Figure 1. UV spectral changes associated with dephosphorylation of **3d**.

readily distinguished from the hydroxytriazole tautomers.

The diazo compounds were further characterized by UV spectroscopy (Table II), exhibiting a strong absorbance at short wavelength and a weak band between 360 and 400 nm. A significant bathochromic shift in both maxima is seen on conversion of the diester to the dianion; moreover, for the dimethylcarbamoyl derivatives **3** there is a significant increase in extinction coefficient on ester hydrolysis.

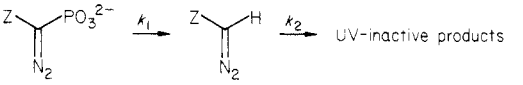
In view of the ease with which the secondary amides **4b–6b** tautomerize to the hydroxytriazoles **7** under the influence of base, it was of interest to determine whether this isomerization could be avoided during the ester cleavage process. We pursued this point only briefly because of the lability of carbamoyl-substituted α-diazophosphonates (see below), but we were able to ascertain that hydroxytriazoles were not formed in the ester hydrolysis sequence. The major driving force for the base-catalyzed isomerization is clearly the acidity of the hydroxytriazoles **7** (they are readily extracted into aqueous sodium bicarbonate, for example). When the phosphonate moiety is ionized, and therefore less electron withdrawing, this driving force is necessarily reduced. On the other hand, we saw no evidence for tautomerization of the (hydroxytriazolyl)phosphonate dianion **10** back to the diazo carboxamide **4** either.[13]



10

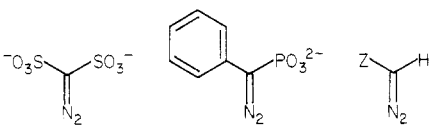
Stability of α-Diazophosphonic Acids. Of major importance for the potential use of α-diazophosphonic acids as photoaffinity labels is their stability in neutral aqueous solution. Although diazo derivatives substituted with electron-withdrawing groups are significantly more stable than the parent diazoalkanes, those which are substituted with anionic substituents are considerably less stable.[14-16] Diazoacetate ion decomposes to glycolate with a half-life of less than 3 min at pH 7.3,[14] for example, and diazomethanedisulfonate **11** decomposes in water in a matter of hours.[16] The phenyl-substituted α-diazophosphonic acid **12** decomposes readily by a general-acid-catalyzed process, although with the optimal choice of buffer (0.01 M collidine/collidine perchlorate), the half-life can be extended to 1.5 h at pH 8.[5]

Table III. Pseudo-First-Order Rate Constants and Half-lives for the Decomposition of α-Diazophosphonates[a]



Z (substrate)	pH	k_1, min^{-1} ($t_{1/2}$)	k_2, min^{-1} ($t_{1/2}$)
Et_2NSO_2 (**1d**)	6.0	2.4×10^{-3} (4.8 h)	1.3×10^{-3} (8.8 h)
	7.5	6×10^{-5} (8 days)	[b]
i-Pr_2O_3P (**2d**)	6.0	5.5×10^{-4} (21 h)	3.5×10^{-5} (14 days)
	7.5	8.8×10^{-5} (5.4 days)	[b]
Me_2NCO (**3d**)	6.0	[b]	4.2×10^{-3} (2.7 h)
	7.5[c]	0.23 (3 min)	[b]
	9.0	1.7×10^{-2} (40 min)	[b]

[a] 0.2 M potassium phosphate buffer, 21–22 °C. [b] Not determined. [c] 0.01 M buffer.



11 **12** **13**, Z = Et_2NSO_2; **14**, Z = i-Pr_2O_3P; **15**, Z = Me_2NCO

The decomposition of the α-diazophosphonates **1d–3d** was followed spectrophotometrically in 0.2 M phosphate buffer at 21–22 °C (Table III). In each case, the first step in the decomposition process involves loss of the phosphonic acid moiety to give the neutral diazo compounds **13–15**. Subsequent loss of the diazo group and the UV chromophore of these intermediates are slower processes. For the phosphonate and carboxamide derivatives **14** and **15**, the difference in rate between the two decomposition steps is sufficiently great that clean isosbestic points are observed on following the process by UV spectroscopy, as shown by the representative curve in Figure 1. In the sulfonamide case, decomposition of **13** occurs at a comparable rate to dephosphorylation of **1d**; hence, the entire process was followed to completion to determine the relative rates.

The intermediacy of **13–15** in the decomposition sequence was proven by their isolation and spectroscopic

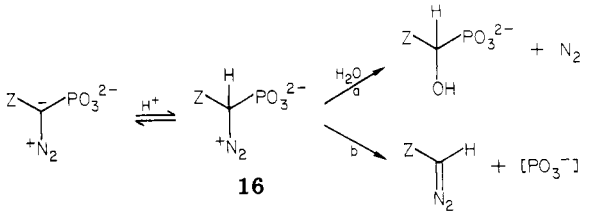
(13) D. J. Brunswick and B. S. Cooperman, *Biochemistry*, **12**, 4074 (1973).

(14) M. M. Kreevoy and D. E. Konasewich, *J. Phys. Chem.*, **74**, 4464 (1970).

(15) W. J. Albery, C. W. Conway, and J. A. Hall, *J. Chem. Soc., Perkin Trans. 2*, 473 (1976).

(16) J. M. Young, *J. Chem. Soc., Perkin Trans 1*, 2541 (1974).

Scheme I



16

characterization or comparison with authentic material. Extraction of the aqueous solution with methylene chloride after completion of the first step, or near completion in the case of the sulfonamide **1d**, gave the neutral diazo compounds. The carboxamide **15** was compared by UV spectroscopy and TLC with an authentic sample and also shown to decompose at the same rate at pH 6.0. *N,N*-Diethyldiazomethanesulfonamide (**13**) showed a strong diazo band in the IR spectrum (2110 cm^{-1}) and appropriate UV absorbance bands [λ_{max} nm (log ϵ) 226 (3.93), 390 (1.78)]. The diazomethylphosphonate **14** was identified on the basis of its similarity to the dimethyl ester[17] by UV: λ_{max} nm (log ϵ) 225 (4.09), 360 (1.14).

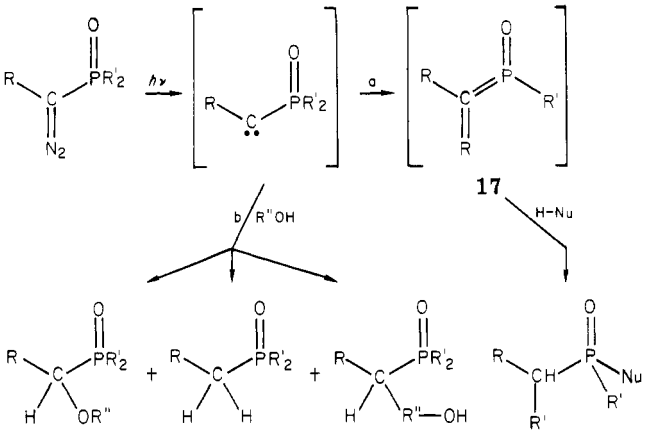
This mode of decomposition is well precedented. Methyl diazomalonic acid, for example, decomposes with loss of carbon dioxide and formation of the diazoacetic ester.[15] Dephosphorylation of phosphonic acids has similarly been observed in cases in which the carbon moiety is a good electrofuge.[18] Recently, in fact, such a process has been employed as a route to the metaphosphate ion.[19] The hydroxytriazole **10** is also dephosphorylated on being allowed to stand at pH 8.

Because of their appreciable stability, the half-lives of the sulfamoyl- and phosphoryl-stabilized derivatives **1d** and **2d** were determined at both pH 6.0 and 7.5. At the higher pH, these compounds are essentially stable except from the point of view of long-term storage. Even at pH 6.0, decomposition is sufficiently slow that they could serve readily in biochemical experiments. In contrast, the carbamoyl derivative **3d** decomposes in less than 1 h at pH 9.0 and in minutes at pH 7.5, even at a buffer concentration of 0.01 M. Such instability would clearly reduce the utility of carbamoyl-substituted α-diazophosphonates as photoaffinity labels.

We can only speculate as to the reason for the large difference in stability between the sulfamoyl- and phosphoryl-stabilized diazo compounds **1d** and **2d** on the one hand and the carbamoyl- and phenyl-substituted analogues **3d** and **12** on the other, but the mechanistic sequence depicted in Scheme I is plausible. As we[6] and Goldstein et al.[5] proposed previously, decomposition is initiated by protonation of the diazo carbon to form the zwitterionic intermediate **16**. Two pathways are available for subsequent reaction: (a) displacement of nitrogen by water or via an α-lactone[20] or (b) dephosphorylation by expulsion of the neutral diazo compound, conceivably with formation of metaphosphate.[19]

For the case Z = phenyl, path a is apparently favored,[5] which is not surprising in view of the benzylic nature of the diazonium ion. In contrast, nucleophilic substitution adjacent to sulfonyl and phosphoryl groups is notoriously difficult,[21] and decomposition of **1d** and **2d** therefore takes place via path b. Decomposition of the carbamoyl derivative **3d** also involves dephosphorylation (path b), and the fact that it occurs so much faster than for the other cases probably reflects the greater electron-withdrawing ability of the carbamoyl group and therefore the greater leaving group ability of the substituted diazo moiety. Although this effect should influence the position of the equilibrium leading to **16** as well, in this reaction the doubly charged PO_3^{2-} group may exert the dominant effect and minimize the differences between the other substituents.

Scheme II



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Photochemical Behavior of α-Diazophosphonates. Of obvious importance for a potential photoaffinity label is its photochemical behavior: the carbene intermediate must react preferentially by intermolecular insertion or addition instead of by intramolecular processes such as Wolff-type rearrangement. The photochemistry of α-diazophosphine oxides and phosphonic esters has been extensively investigated by Regitz and others,[22] and recently the photolysis of a sulfonyl-stabilized α-diazophosphinate in alcohol was reported by Stackhouse and Westheimer.[4d] Only for the phosphine oxides (phenyl migration)[22a] and a phosphinate thiol ester (RS migration)[4d] has Wolff-type rearrangement to give a methylenephosphane oxide, **17**, been observed (path a, Scheme II). No such migration of a phosphorus alkoxy substituent has been demonstrated, as it has for esters of α-diazo carboxylic acids.[23] α-Diazophosphonic acid diesters do, on the other hand, undergo O–H and C–H insertion and photoreduction (path b) when irradiated in alcohols.[22]

The photochemistry of diazo compounds with anionic substituents has remained unexplored, presumably because of their instability (see above). The α-diazophosphonate anions provided us, therefore, with a unique opportunity to study the behavior of carbenes with adjacent, negatively charged oxygen substituents.

Photochemical studies were initiated with the diesters **1b** and **2b** in order to provide readily characterized products which could serve as spectroscopic models for subsequent study of the dianions. All experiments were carried out with a Pyrex filter by using light of wavelength >300 nm in order to best simulate conditions of an actual

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(19) A. C. Satterthwait and F. H. Westheimer, *J. Am. Chem. Soc.*, **103**, 1177 (1981), and references cited therein.

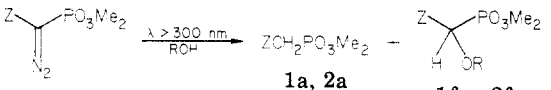
(20) A. T. Austin and J. Howard, *J. Chem. Soc.*, 3278 (1961); P. Brewster, F. Hiron, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature (London)*, **166**, 179 (1950).

(21) (a) A. Lawson and R. B. Tinkler, *J. Chem. Soc. C*, 652 (1969); J. A. Cade, *J. Chem. Soc.*, 2266 (1959); (b) T. B. Johnson and I. B. Douglass, *J. Am. Chem. Soc.*, **63**, 1571 (1941).

(22) (a) M. Regitz, *Angew. Chem., Int. Ed. Engl.*, **14**, 222 (1975), and references cited therein; (b) H. Tomioka, T. Inagaki, S. Nakamura, and Y. Izawa, *J. Chem. Soc., Perkin Trans. 1*, 130 (1979).

(23) H. Chaimovich, R. J. Vaughan, and F. H. Westheimer, *J. Am. Chem. Soc.*, **90**, 4088 (1968).

Table IV. Photolysis of α-Diazophosphonic Esters in Alcohols[a]

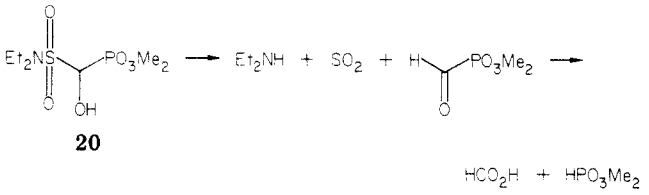


1b,2b 1a, 2a 1f,g, 2f,g

Z	R	% yield 1a, 2a	% yield 1f,g, 2f,g
Et_2NSO_2 (1)	Me (f)	17	31
	Et (g)	24	33
i-Pr_2O_3P (2)	Me (f)	41	44
	Et (g)	>95[b]	

[a] Yields of chromatographed products. [b] Only compound detected in crude product.

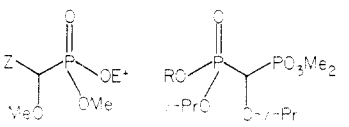
Scheme III



20

photoaffinity labeling experiment. Under these conditions, irradiation of the diesters in alcohol solvent afforded quite cleanly products of insertion into the hydroxyl group and/or reduction (see Table IV).

As would be expected for a process involving hydrogen atom abstraction,[22] more reduction product is observed in ethanol than in methanol. The diphosphonate **2b** in fact reacts exclusively by this pathway in ethanol. The absence of methyl ether ethyl esters **18** or of isopropyl ethers **19**



18 19

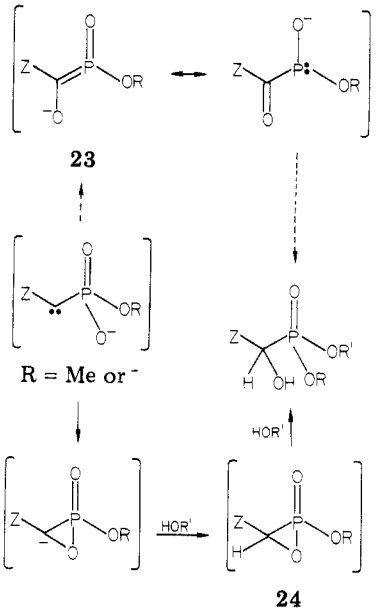
in the photolysis products rule out the occurrence of any Wolff rearrangement pathways. Although we cannot definitively rule out their presence, we saw no evidence in the ^{13}C NMR spectra of crude reaction mixtures for the products of diethylamino migration or intramolecular C–H insertion.[24]

In addition to the clear-cut NMR structure assignment of the alcohol insertion products, the methoxymethylenediphosphonate **2f** was synthesized unambiguously by phosphorylation of the lithium salt of dimethyl (methoxymethyl)phosphonate[25] with diisopropyl phosphorochloridate.

Photolysis of sulfonamide **1b** in water gave cleanly a single product which proved to be too unstable for chromatographic purification. On the basis of its ^1H and ^{13}C NMR spectrum, we assign it structure **20**, the expected product of insertion into water. Facile decomposition of this material as illustrated in Scheme III can be easily envisaged.[21b,26]

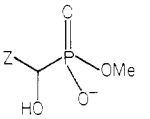
In contrast to the diesters **1f** and **2f**, we were unable to fully characterize the products from photolysis of the α-diazophosphonate *dianions* **1d** and **2d** in methanol.

Scheme IV



23 24

However, ^1H and ^{13}C NMR spectroscopy clearly showed formation of *α-hydroxy monomethyl esters* **21** and **22** to



21, Z = $Et_2NS(O)_2$
22, Z = $(i\text{-PrO})_2P{=}O$

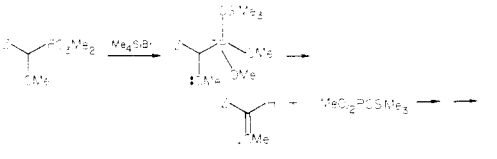
be a major reaction pathway. Most definitive was the appearance of methyl ester doublets in the ^1H (δ 3.7, J_{PH} = 10 Hz) and ^{13}C NMR (δ 53, J_{CP} = 6 Hz) and the absence of resonances expected for the ether methyl groups of **1h** and **2h**.[27]

To our knowledge this represents the first report of migration of an oxygen substituent from phosphorus in a formal Wolff-type process. However, although this behavior is consistent with the increased tendency for Wolff rearrangement of electron-rich substituents on phosphorus, as noted by Breslow,[28] we think it unlikely that the Wolff intermediate **23** (Scheme IV) is actually involved in the rearrangement we observe. This structure is simply a resonance structure of an acyl phosphonite, which is unlikely to undergo nucleophilic attack on phosphorus with formation of the observed product.

On the other hand, a mechanism involving cyclization of the carbene intermediate, protonation, and subsequent reaction of the oxaphosphirane **24** by nucleophilic attack on phosphorus is an attractive alternative. Mechanisms similar to this have in fact been postulated by Westheimer for the Wolff-type rearrangement of an α-diazophosphinate

(24) H. Tomioka, H. Kitagawa, and Y. Izawa, *J. Org. Chem.*, **44**, 3072 (1979); R. Rando, *J. Am. Chem. Soc.*, **92**, 6706 (1970).
(25) A. E. Arbuzov and V. S. Abramov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 35 (1959); M. Green, *J. Chem. Soc.*, 1324 (1963).
(26) E.g., G. R. Moe, L. M. Sayre, and P. S. Portoghese, *Tetrahedron Lett.*, 537 (1981).

(27) We tried to prepare authentic samples of methyl ethers **1h** and **2h** for spectral comparison, but the normally clean ester cleavage process with trimethylsilyl bromide[12] appeared to proceed nonselectively with **1f** and **2f**. One conceivable reason for this anomalous behavior is the potential fragmentation mode depicted below:



(28) R. Breslow, A. Feiring, and F. Herman, *J. Am. Chem. Soc.*, **96**, 5937 (1974).

thiol ester and for side reactions in the photolysis of a tosyl-substituted (diazomethyl)phosphinate.[4c,d]

Such an intramolecular quenching of the carbene moiety severely reduces the potential of α-diazophosphonates as photoaffinity labels, since the postulated intermediate **24** will only react with nucleophiles. On the other hand, that such a reactive phosphonylating agent could be generated photochemically in a protein binding site remains an intriguing possibility.

Experimental Section

General Methods. Unless otherwise indicated, IR spectra were recorded as neat films, and the NMR solvent was 1% $Me_4Si/CDCl_3$. ^1H NMR data are presented as chemical shifts on the δ scale, relative to internal Me_4Si as 0 ppm (multiplicity, number of protons, phosphorus–proton coupling constant if relevant). ^{13}C NMR data are presented as chemical shifts on the δ scale, relative to $CDCl_3$ solvent as 77.0 ppm (multiplicity, phosphorus–carbon coupling constant if relevant; multiplicity in off-resonance decoupled mode). ^{13}C NMR spectra recorded in D_2O are referenced to internal dioxane as 66.5 ppm. Microanalyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley. The photochemical apparatus was an Ace-Hanovia apparatus with a 450-W medium-pressure Hg immersion lamp equipped with a Pyrex sleeve.

Diethyl [[(Diethylamino)sulfonyl]methyl]phosphonate (1a). To a stirred solution of 10.6 g (70 mmol) of *N,N*-diethylmethanesulfonamide[7] in 70 mL of dry THF under nitrogen at −75 °C was added alternately, at 10-min intervals, 29.2 mL of 2.4 M *n*-butyllithium in hexane (70 mmol), 3.78 mL (5.1 g, 35 mmol) of dimethyl phosphorochloridate, 14.6 mL of butyllithium, 1.89 mL of dimethyl phosphorochloridate, 7.3 mL of butyllithium, 0.95 mL of dimethyl phosphorochloridate, 3.65 mL of butyllithium, and, finally, 0.47 mL of dimethyl phosphorochloridate (total 131 mmol of butyllithium, 65.7 mmol of dimethyl phosphorochloridate). The mixture was brought to 21 °C, partitioned between 250 mL each of $CHCl_3$ and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with 50 mL of $CHCl_3$, and the combined organic layer was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 14.7 g of crude product. Recrystallization from 15 mL of ethyl acetate gave 11.1 g (66% yield) of the sulfonamide **1a**: mp 110–111 °C; IR (KBr) 2850, 1320, 1260, 1140, 1020 cm^{-1}; ^1H NMR δ 1.25 (t, 6), 3.28 (q, 4), 3.5 (d, 2, J_{PH} = 16 Hz), 3.81 (t, 6, J_{PH} = 12 Hz); ^{13}C NMR δ 14.2 (q), 42.2 (t), 47.8 (d, J_{CP} = 138 Hz; t), 53.2 (d, J_{CP} = 6.4 Hz; q). Anal. Calcd for $C_7H_{18}NO_5PS$: C, 32.43; H, 7.00; N, 5.40; P, 11.95; S, 12.37. Found: C, 32.41; H, 6.98; N, 5.48; P, 11.98; S, 12.26.

Dimethyl [[Bis(1-methylethoxy)phosphinyl]methyl]phosphonate (2a). In a similar manner, 10.0 g (55.6 mmol) of diisopropyl methylphosphonate[8] in 40 mL of THF was treated with a total of 104 mmol of *n*-butyllithium and 46 mmol of dimethyl phosphorochloridate to give 15.24 g of crude product as a golden syrup. Fractional distillation afforded 1.02 g of starting material [bp ~30 °C (0.1 torr)] and 10.25 g (71% yield based on unrecovered starting material) of methylenediphosphonate **2a**: bp 103 °C (0.06 torr); ^1H NMR δ 1.4 (d, 12), 2.4 (t, 2, J_{PH} = 22 Hz), 3.8 (d, 6, J_{PH} = 12 Hz), 4.8 (d of septets, 2); ^{13}C NMR δ 23.2, 23.45 (d, J_{CP} = 5.5 Hz, diastereotopic $(CH_3)_2CH$; q), 25.2 (t, J_{CP} = 138 Hz; t), 52.3 (d, J_{CP} = 6.4 Hz; q), 70.8 (d, J_{CP} = 6.5 Hz; d). Anal. Calcd for $C_9H_{22}P_2O_6$: C, 37.50; H, 7.64; P, 21.53. Found: C, 37.65; H, 7.48; P, 21.48.

Dimethyl [2-(Dimethylamino)-2-oxoethyl]phosphonate (3a). To a solution of 41 g (0.2 mmol) of bromoacetyl bromide in 100 mL of CH_2Cl_2 at 0 °C was added anhydrous dimethylamine until an aliquot of the reaction mixture gave an alkaline suspension when shaken in water. The mixture was filtered, concentrated under reduced pressure, slurried in ether, filtered, and evaporated again to give 29 g of crude *N,N*-dimethylbromoacetamide. Addition of 25 g (0.2 mol) of trimethyl phosphite and gentle heating initiated an exothermic reaction. When this abated, the mixture was kept at 85 °C for 30 min and distilled. After a forerun of excess trimethyl phosphite and dimethyl methylphosphonate, 10 g (26% yield) of phosphonoacetamide **3a** was obtained: bp 120 °C (0.1 torr); IR ($CHCl_3$) 3000, 2100, 1620 cm^{-1}; ^1H NMR δ 3.0 (s, 3), 3.1 (s, 3), 3.13 (d, 2, J_{PH} = 21 Hz), 3.8 (d, 6, J_{PH} = 11 Hz); ^{13}C NMR δ 31.4 (d, J_{CP} = 135 Hz; t), 34.6 (q), 37.4 (q), 52.0 (d, J_{CP} = 6.5 Hz; q), 163.7 (d, J_{CP} = 5.7 Hz; s). Anal. Calcd for $C_6H_{14}NO_4P$: C, 36.93; H, 7.23; N, 7.18; P, 15.87. Found: C, 36.72; H, 7.18; N, 7.02; P, 15.72.

Dimethyl [Diazo[(dimethylamino)sulfonyl]methyl]phosphonate (1b). A 26-mmol sample of a suspension of potassium hydride in oil was washed with hexane and suspended in 70 mL of dry THF containing 4.46 g (22.6 mmol) of *p*-toluenesulfonyl azide. This mixture was stirred at 0 °C under nitrogen, and a solution of 5.33 g (20.6 mmol) of the sulfonamide **1a** in 35 mL of THF was added slowly. After hydrogen evolution ceased, the mixture was brought to 21 °C, where it set to an orange gel. After 30 min, the mixture was diluted with ether, washed three times with dilute NaOH and twice with brine, dried ($MgSO_4$), and evaporated to a wet oil. After the residue was redissolved in CCl_4 and the mixture dried ($MgSO_4$) and reevaporated, 4.55 g (78% yield) of diazo compound **1b** was obtained as an ochre oil, pure by ^1H NMR. This material could be purified by chromatography or bulb-to-bulb distillation [200 °C (0.03 torr)]: IR 2950, 2100, 1340, 1260, 1140, 1020 cm^{-1}; ^1H NMR δ 1.24 (t, 6), 3.3 (q, 4), 3.87 (d, 6, J_{PH} = 12 Hz); ^{13}C NMR δ 13.8 (q), 42.6 (t), 53.1 (d, J_{CP} = 5.7 Hz; q), 59.4 (d, J_{CP} = 216 Hz; s). Anal. Calcd for $C_7H_{16}N_3O_5PS$: C, 29.47; H, 5.65; N, 14.73. Found: C, 29.00; H, 5.70; N, 14.39.

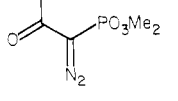
This material (408 mg, 1.43 mmol) was further characterized by its reaction with 375 mg (1.43 mmol) of triphenylphosphine in 3 mL of isopropyl ether at 21 °C. The oily precipitate was purified by chromatography (1:1:2 ethyl acetate/CH_2Cl_2/ether, silica gel) to give 260 mg of hydrazone **9**, mp 83–84 °C (after recrystallization from isopropyl ether). Anal. Calcd for $C_7H_{18}N_3O_5PS$: C, 29.27; H, 6.32; N, 14.63; P, 10.78; S, 11.16. Found: C, 29.38; H, 6.32; N, 14.59; P, 10.83; S, 10.97.

Dimethyl [[Bis(1-methylethoxy)phosphinyl]diazomethyl]phosphonate (2b). In a similar manner, 2.96 g (10.3 mmol) of methylenediphosphonate **2a** was converted to 2.63 g (82% yield) of diazo compound **2b** after column chromatography (10% ethanol–CH_2Cl_2/silica gel): bp 90 °C (0.03 Torr, bulb-to-bulb distillation); IR 3000, 2110, 1260, 1000 cm^{-1}; ^1H NMR δ 1.4 (d, 12), 3.8 (d, 6, J_{PH} = 12 Hz), 4.8 (d of septets, 2); ^{13}C NMR δ 22.4, 22.6 (d, J_{CP} = 5.3 Hz, diastereotopic $(CH_3)_2CH$; q), 37.6 (t, J_{CP} = 204 Hz, s), 52.3 (d, J_{CP} = 5.4 Hz; q), 71.3 (d, J_{CP} = 6.0 Hz; d); mass spectrum *m/z* (relative intensity) 314 (0.7, M^+), 213 (14), 187 (12), 173 (11), 155 (10), 142 (26), 127 (11), 110 (100); exact mass, calcd for $C_9H_{20}N_2O_6P_2$ *m/z* 314.0796, found 314.0791.

Dimethyl [1-Diazo-2-(dimethylamino)-2-oxoethyl]phosphonate (3b). In a similar manner, 5.52 g (28.3 mmol) of phosphonoacetamide **3a** was subjected to the diazo transfer reaction, giving 4.4 g (70% yield) of the diazo derivative **3b** after column chromatography (1:1 ethyl acetate/ethanol, silica gel): IR 2950, 2105, 1610, 1500, 1420, 1400, 1275, 1180, 1130, 1030, 850, 720 cm^{-1}; ^1H NMR 3.07 (s, 6), 3.9 (d, 6, J_{PH} = 12 Hz); ^{13}C NMR 35.5 (q), 49.7 (d, J_{CP} = 220 Hz; s), 52.0 (d, J_{CP} = 5.6 Hz; q).

This material (104 mg, 0.47 mmol) was further characterized by its reaction with 123 mg (0.47 mmol) of triphenylphosphine in 1 mL of 1:1 isopropyl/ethyl ether. The solid precipitate was recrystallized from ethanol/ispropyl ether to give 110 mg of the phosphazene **8** as large prisms, mp 115–157 °C dec. Anal. Calcd for $C_{24}H_{27}N_3O_4P_2$: C, 59.63; H, 5.63; N, 8.69; P, 12.81. Found: C, 59.65; H, 5.73; N, 8.67; P, 12.72.

In the chromatographic purification of **3b**, a less polar component (190 mg) was isolated. Except for slight differences in the ^1H NMR chemical shifts and in the fingerprint region of the IR spectrum (and R_f on TLC), this material appeared to be identical with the major product **3b**. Although we did not pursue this further, we tentatively assign the structure of the minor component to a conformational isomer, e.g., **25**: IR 2950, 2105, 1630, 1500, 1395, 1275, 1195, 1040, 880, 840, 800, 780, 730; ^1H NMR δ 2.9 (s, 6), 3.8 (d, 6, J_{PH} = 11 Hz).



25

Dimethyl [1-Diazo-2-[(phenylmethyl)amino]-2-oxo-

ethyl]phosphonate (6b). A mixture of 3.3 g (14.5 mmol) of *N*-benzylbromoacetamide and 10 mL of trimethyl phosphite was stirred at 90–95 °C for 1 h, evaporated at 0.1 torr, and distilled [bulb-to-bulb, 200 °C (0.02 torr)] to give 3.2 g (86% yield) of the phosphonoacetamide **6a** as an oil: IR 3300, 3100, 1680, 1460, 1250, 1040 cm^{-1}; ^1H NMR δ 2.9 (d, 2, J_{PH} = 21 Hz), 3.7 (d, 6, J_{PH} = 11 Hz), 4.4 (d, 2, J = 6 Hz), 7.3 (s, 5), 7.6 (br s, 1).

A 264-mg (1.03 mmol) portion of this material was added to a suspension of 1.3 mmol of potassium hydride in 2 mL of THF. When hydrogen evolution ceased, the solution was cooled to 0 °C, and 214 mg (1.09 mmol) of *p*-toluenesulfonyl azide was added, leading to an immediate precipitate. After 1 h, the mixture was partitioned between ether and water, and the aqueous layer was washed with ether, saturated with NaCl, acidified with 2 N H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to give 318 mg of an oil, consisting of starting material, *p*-toluenesulfonamide, and hydroxytriazole **7** (R′ = $PhCH_2$) in a ratio of 2:3:6. The product was purified by dissolving it in ether, extracting twice with saturated $NaHCO_3$, and washing the aqueous layer twice with CH_2Cl_2 before acidification and reisolation. The yield of purified product **7** (R′ = $PhCH_2$) was 156 mg (54%): IR 3500–2300, 1580, 1200, 1040 cm^{-1}; ^1H NMR δ 3.8 (d, 6, J_{PH} = 12 Hz), 5.4 (s, 2), 7.4 (s, 2), 10.8 (br s, 1); UV (MeOH) λ_{max} 256 nm (log ϵ 3.43), λ_{max} (alkaline MeOH) 253 (3.85).

A portion of this material was distilled [bulb-to-bulb, 200 °C (0.025 torr)], resulting in quantitative isomerization to the diazoamide **6b**: IR 3300, 3025, 2950, 2850, 2120, 1650, 1530, 1280, 1030 cm^{-1}; ^1H NMR 3.8 (d, 6, J_{PH} = 12 Hz), 4.6 (d, 2, J = 5 Hz), 7.4 (s, 5), 7.8 (br, 1). Anal. Calcd for $C_{11}H_{14}N_3O_4P$: C, 46.65; H, 4.98; N, 14.84; P, 10.94. Found: C, 46.45; H, 4.99; N, 14.61; P, 10.75.

Diazoacetamides 4b and Hydroxytriazoles 7 (R = *i*-Pr and c-C_6H_{11}). In a similar manner, *N*-isopropylbromoacetamide and *N*-cyclohexylbromoacetamide were converted to the respective hydroxytriazoles **7** and the diazoamides **4b** and **5b**. These compounds were only characterized spectroscopically.

7 (R = *i*-Pr): ^1H NMR δ 1.6 (d, 6), 3.8 (d, 6, J_{PH} = 12 Hz), 4.7 (septet, 1), 10.6 (br s, 1).

4b: ^1H NMR δ 1.2 (d, 6), 3.8 (d, 6, J_{PH} = 12 Hz), 4.1 (d septet, 1), 7.2 (br, 1); ^{13}C NMR δ 21.7 (q), 41.3 (d), 50.5 (d, J_{CP} = 209 Hz; s), 52.5 (d, J_{CP} = 5.9 Hz; q), 159.5 (d, J_{CP} = 13.8 Hz; s).

7 (R = c-C_6H_{11}): ^1H NMR δ 1.2–2.2 (m, 10), 3.8 (d, 6, J_{PH} = 12 Hz), 4.3 (m, 1), 10.4 (br s, 1); ^{13}C NMR δ 25.2 (t), 25.9 (t), 31.6 (t), 53.6 (d, J_{CP} = 5.6 Hz; q), 56.3 (d), 112.0 (d, J_{CP} = 247 Hz; s), 155.7 (d, J_{CP} = 31 Hz; s).

5b: ^1H NMR δ 1.0–2.1 (m, 10), 3.8 (d, 6, J_{PH} = 12 Hz), 3.8 (m, 1), 7.3 (br d, 1); ^{13}C NMR δ 24.4 (t), 25.4 (t), 32.8 (t), 48.7 (d), 53.4 (d, J_{CP} = 5.4 Hz; q), 160.4 (d, J_{CP} = 14.5 Hz; s), diazo carbon obscured by overlap).

Sodium [Diazo[(diethylamino)sulfonyl]methyl]-phosphonate (1d). A 351-mg (1.23 mmol) sample of diazo sulfonamide **1b** was frozen at −75 °C, and 0.8 mL (6 mmol) of trimethylsilyl bromide was added. The frozen mixture was brought to 21 °C for 1.3 h and finally to 40 °C for 10 min. After removal of all volatiles under vacuum, ^1H NMR analysis of a solution in CCl_4 indicated complete absence of resonances due to the methyl esters. The CCl_4 solution of the crude disilyl ester was cooled to 0 °C and mixed vigorously with an ice-cold solution of 280 mg (1.3 mmol) of K_3PO_4 in 1 mL of D_2O. The aqueous layer was made strongly alkaline by the addition of 1 drop of 1 N NaOD/D_2O and clarified by centrifugation: ^1H NMR (D_2O) δ 1.2 (t, 6), 3.3 (q, 4), 5.0 (HOD); ^{13}C NMR (D_2O) δ 14.0 (q), 42.5 (t), 60.9 (d, J_{CP} = 152 Hz; s). From a similar experiment starting with 0.45 mmol of **1b**, the aqueous mixture was diluted to 10.0 mL, giving a 4.5×10^{-2} M solution of the phosphonate anion **1d**, assuming quantitative reaction and extraction. With this solution, the UV extinction coefficients listed in Table II were determined.

Alternatively, addition of a solution of the bis(trimethylsilyl)ester in CH_2Cl_2 to 2 equiv of NaOH in methanol at 0 °C and evaporation gave a quantitative yield of the sodium salt as a yellow powder: IR (KBr) 3400 (br, OH), 2150, 1140 cm^{-1}; ^1H and ^{13}C NMR as above.

Sodium [[Bis(1-methylethoxy)phosphinyl]diazomethyl]phosphonate (2d). In a similar manner, 289 mg (0.92 mmol) of diazomethylenediphosphonate **2b** and 0.6 mL (4.6 mmol) of trimethylsilyl bromide were combined at −75 °C and then brought to 21 °C for 1 h. After removal of all volatile material, 400 mg of syrup was obtained (theoretical = 396 mg), and ^1H NMR indicated the absence of CH_3O resonances. The disilyl ester was extracted from CCl_4 into D_2O as described above to give a solution of the diazophosphonate anion **2d**: ^1H NMR (D_2O) δ 1.8 (d), 5.2 (HOD), methine resonance obscured by HOD; ^{13}C NMR (D_2O) δ 23.2 (three resonances, diastereotopic doublets, J_{CP} = 5.0 Hz; q), 37.9 (dd, J_{CP} = 147, 200 Hz; s), 72.7 (d, J_{CP} = 5.9 Hz); UV, see Table II.

Sodium [1-Diazo-2-(dimethylamino)-2-oxoethyl]-phosphonate (3d). Application of the same procedure to diazoacetamide **3b** gave a solution of the dianion **3d**: ^1H NMR (D_2O) δ 3.2 (s), 5.2 (HOD); ^{13}C NMR (D_2O) δ 37.6 (q), 54.3 (d, J_{CP} = 166 Hz), 169.2 (d, J_{CP} = 7.9 Hz); UV, see Table II. This compound proved to be quite unstable, and quantitative formation of the salt was not possible. The concentration of an aliquot was determined by following its conversion to *N,N*-dimethyldiazoacetamide **15** to completion and extrapolating from the known extinction coefficient for this compound.

Sodium [1-diazo-2-[(1-methylethyl)amino]-2-oxoethyl]-phosphonate (4d): ^1H NMR (D_2O) δ 1.2 (d, 6), 4.0 (m, 2), 5.2 (HOD); ^{13}C NMR (D_2O) δ 22.1 (q), 41.9 (d), 55.3 (d, J_{CP} = 163 Hz; s), 167.8 (d, J_{CP} = 9.9 Hz; s).

Sodium [5-hydroxy-1-[(1-methylethyl)amino]-1,2,3-triazolyl]phosphonate (10) was prepared from the dimethyl ester by the same procedure: ^1H NMR (D_2O) δ 1.35 (d, 6), 4.7 (m, 2), 5.2 (HOD); ^{13}C NMR (D_2O) δ 21.7 (q), 45.4 (d), 126.9 (d, J_{CP} = 211 Hz; s), 157.6 (d, J_{CP} = 26 Hz; s). When the mixture was allowed to stand for 2 days, an orange oil separated from the aqueous solution; it was identified as 5-hydroxy-1-isopropyl-1,2,3-triazole on the basis of its ^{13}C NMR spectrum: (D_2O) δ 21.5 (q), 45.9 (q), 115.7 (d), 156.4 (s).

Determination of Rates of Decomposition of α-Diazophosphonates. From a stock solution of the α-diazophosphonate in aqueous base, prepared as described above, were prepared solutions of appropriate concentration (2.5×10^{-4} M) in 0.2 M phosphate buffer (0.01 M for **3d** at pH 7.5), and these were kept in a water bath at room temperature (21–22 °C). Aliquots were removed at time intervals, and the progress of the decomposition sequence was followed at 225 nm (for the sulfonamide **1d** and phosphonate **2d**) or 254 nm (for carboxamide **3d**). The rate constants were determined from a graph of log ($A_t - A_\infty$) vs. t. For the dephosphorylation of **2d** at pH 7.5 and of **3d** at pH 7.5 and 9.0, A_∞ was that due to the neutral diazo intermediate **14** or **15**, since there was essentially no decomposition of this material over the course of the dephosphorylation. For the decomposition of **1d** and **2d** at pH 6.0, the two-step sequence was followed to completion, and the rate constants of both reactions were determined. Because the rate of decomposition of sulfonamide **1d** is so slow at pH 7.5, the initial slopes of graphs of log $(A_{235} - A_{240})/A_{230}$ (a value independent of total concentration but dependent on the ratio of **1d** to **13** and, therefore, the progress of the dephosphorylation step) vs. t were compared for the decompositions at pH 6.0 and 7.5 (UV spectra of aliquots recorded at pH 7.5 in both cases). This procedure indicated that at pH 7.5, the sulfonamide is dephosphorylated at approximately $^1/_{40}$ the rate at pH 6.0.

***N,N*-Dimethyldiazoacetamide (15).** A solution of 9.7 g (75 mmol) of *N,N*-dimethylacetoacetamide,[29] 14.4 g (75 mmol) of tosyl azide, and 10.4 mL (75 mmol) of triethylamine in 90 mL of acetonitrile was kept at 21 °C for 24 h and then stirred vigorously with 75 mL of 2 N KOH. The product was partitioned between ether/methylene chloride and 2.5 N KOH saturated with NaCl, and the organic layer was dried ($MgSO_4$), concentrated, and distilled [45 °C (0.06 torr)] to give 3.4 g (50% yield) of the diazoacetamide **15**. An analytical sample was obtained by low-temperature recrystallization from ether: mp 22–26 °C; IR ($CHCl_3$) 3025, 2125, 1615, 1410 cm^{-1}; ^1H NMR δ 2.9 (s, 6), 5.0 (s, 1); UV (0.2 M phosphate buffer, pH 9.0) λ_{max} 254 nm (log ϵ 4.34), 376 (1.36). Anal. Calcd for $C_4H_7N_3O$: C, 42.47; H, 6.24; N, 37.15. Found: C, 42.73; H, 6.20; N, 36.96.

General Photolysis Procedure. All photolyses were carried out in a water-cooled apparatus with continuous nitrogen purging

(29) H. Bredereck, R. Gompper, K. Klemm, and B. Föhlisch, *Chem. Ber.*, **94**, 3119 (1961).

of the solution, using a 450-W Hanovia medium-pressure Hg lamp equipped with a Pyrex filter.

Dimethyl [[(Diethylamino)sulfonyl]methoxymethyl]phosphonate (1f). Photolysis of 1b in Methanol. A solution of 452 mg (1.6 mmol) of diazo sulfonamide **1b** in 330 mL of methanol was irradiated for 15 min. After evaporation, the crude product was purified by HPLC (2:3 ether/ethyl acetate, silica gel) to give 55 mg (12% recovery) of starting material **1b**, 126 mg (31% yield, based on unrecovered starting material) of the methanol insertion product **1f**, and 63 mg (17%) of photoreduction product **1a**. Longer irradiation times, while ensuring consumption of starting material, resulted in the production of secondary photoproducts. For methyl ether **1f**: IR 2950, 1340, 1260, 1030 cm^{-1}; ^1H NMR δ 1.2 (t, 6), 3.30 and 3.35 (each q, 2, diastereotopic $N(CH_2CH_3)_2$), 3.66 (s, 3), 3.8 (d, 6, J_{PH} = 10 Hz), 4.35 (d, 1, J_{PH} = 12 Hz); ^{13}C NMR δ 14.6 (q), 42.6 (t), 54.1 (d, J_{CP} = 7.1 Hz; q), 62.5 (d, J_{CP} = 6.2 Hz; q), 91.3 (d, J_{CP} = 167.6 Hz; d). Anal. Calcd for $C_8H_{20}NO_6PS$: C, 33.22; H, 6.97; N, 4.84; P, 10.70. Found: C, 33.32; H, 6.84; N, 4.99; P, 10.80.

Dimethyl [[(Diethylamino)sulfonyl]ethoxymethyl]phosphonate (1g). Photolysis of 1b in Ethanol. In a similar manner, irradiation of 2.02 g (7.1 mmol) of **1b** in 330 mL of absolute ethanol for 50 min and chromatography of the resulting product on silica gel (0–10% ethanol/ethyl acetate) afforded 144 mg (7% recovery) of starting material, 481 mg (24% yield) of ethyl ether **1g**, and 384 mg (23%) of photoreduction product **1b**. For ethyl ether **1g**: IR 2980, 1330, 1260, 1020 cm^{-1}; ^1H NMR δ 1.23 (t, 6), 1.26 (t, 3), 3.29 and 3.37 (each q, 2), 3.8 (d, 6, J_{PH} = 13 Hz), 3.82 (q, 2); ^{13}C NMR δ 14.6 (q), 14.9 (q), 42.7 (t), 54.4 (d, J_{CP} = 7.2 Hz; q), 71.1 (d, J_{CP} = 13.6 Hz; t), 89.7 (d, J_{CP} = 168.5 Hz; d). Anal. Calcd for $C_9H_{22}NO_6PS$: C, 35.6; H, 7.3; N, 4.6; P, 10.2. Found: C, 35.1; H, 7.3; N, 5.1; P. 10.2.

Dimethyl [[(Diethylamino)sulfonyl]hydroxymethyl]phosphonate (20). Irradiation of 1b in Water. A solution of 416 mg (1.46 mmol) of **1b** in 330 mL of H_2O was irradiated for 1 h and evaporated under reduced pressure to give a yellow oil. TLC analysis indicated almost complete consumption of starting material and formation of a single new product, to which we assign the structure **20** on the basis of its spectral properties: IR 3150, 2980, 1450, 1200, 1020 cm^{-1}; ^1H NMR 1.35 (t, 6), 3.0 (q, 4), 3.8 (d, 6, J_{PH} = 11 Hz), 4.8 (d, 1, J_{PH} = 10 Hz), 7.3 (br s, 1); ^{13}C NMR 10.49 (q), 41.9 (t), 53.85 (d, J_{CP} = 6.1 Hz) and 54.04 (d, J_{CP} = 7.0 Hz, diastereotopic CH_3O; q), 79.8 (d, J_{CP} = 161.4 Hz; d). Attempts to purify the crude product led to decomposition.

Dimethyl [[Bis(1-methylethoxy)phosphinyl]methoxymethyl]phosphonate (2f). Photolysis of 2b in Methanol. Irradiation of a solution of 314 mg (1 mmol) of the diazomethylenephosphonate **3b** in 250 mL of methanol for 20 min and chromatographic purification of the products (1:4 ethanol/ethyl acetate) gave 138 mg (44% yield) of the methyl ether **2f** and 119 mg (41 mmol) of photoreduction product **2a**. For **2f**: ^1H NMR δ 1.40 (d, 12), 3.6 (s, 3), 3.78 (t, 1, J_{PH} = 18 Hz), 3.9 (d, 6, J_{PH} = 11 Hz), 4.85 (d of septets, 2); ^{13}C NMR δ 23.5–24.0 (four peaks, q), 53.4 (d, J_{CP} = 6.3 Hz, 9), 62.2 (t, J_{CP} = 5.0 Hz; q), 75.2 (dd, J_{CP} = 156.3, 159.9 Hz; d); exact mass calcd for $C_{10}H_{24}O_7P_2$ m/z 318.1017, found m/z 318.1007.

Irradiation of Diazomethylenediphosphonate 2b in Ethanol. Irradiation of 314 mg (1 mmol) of **2b** in 250 mL of absolute ethanol for 10 min and evaporation gave a crude product which was shown by ^1H NMR to consist entirely of photoreduction product **2a**.

Sodium Methyl [[(Diethylamino)sulfonyl]hydroxymethyl]phosphonate (21). Photolysis of 1d in Methanol. A 4 mM solution of α-diazophosphonate **1d** in methanol was irradiated for 10 min, concentrated under reduced pressure, dissolved in 20 mL of water, and reevaporated to a yellowish solid consisting primarily of the monoester **21**: ^1H NMR (D_2O) δ 1.4 (t, 6), 3.5 (q, 4), 3.8 (d, 3, J_{PH} = 10 Hz), 4.7 (d, 2), 4.8 (HOD); ^{13}C NMR (D_2O) 14.0 (q), 42.3(t), 52.8 (d, J_{CP} = 6.2 Hz; q), 80.3 (d, J_{CP} = 153 Hz).

Sodium Methyl [[Bis(1-methylethoxy)phosphinyl]hydroxymethyl]phosphonate (22). Irradiation of 2d in Methanol. A 2 mM solution of **2d** in methanol was irradiated for 15 min and evaporated to a colorless solid consisting primarily of **22**: ^1H NMR 1.4 (d, 12), 3.6 (d, 3, J_{PH} = 10 Hz), 4.6 (m, 2); ^{13}C NMR 23.7 (diastereotopic $(CH_3)_2C$; q), 52.4 (d, J_{CP} = 5 Hz; q), 72.5 (d, J_{CP} = 5.3 Hz; d). In neither spectrum were the resonances for the central CHOH group clearly resolved.

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Registry No. 1a, 62285-40-9; **1b**, 62285-42-1; **1c**, 62285-51-2; **1d**, 80721-51-3; **1f**, 80721-52-4; **1g**, 80721-53-5; **2a**, 62285-41-0; **2b**, 62285-43-2; **2d**, 80721-54-6; **2f**, 80721-55-7; **3a**, 62285-48-7; **3b**, 62285-44-3; **3d**, 80721-56-8; **4b**, 80721-57-9; **4d**, 80721-58-0; **5b**, 80721-59-1; **6a**, 80721-60-4; **6b**, 80721-61-5; **7** (R = $PhCH_2$), 80721-62-6; **7** (R = *i*-Pr), 80721-63-7; **7** (R = *c*-C_6H_{11}), 80721-64-8; **8**, 62285-50-1; **9**, 62285-49-8; **10**, 80721-65-9; **13**, 62285-45-4; **14**, 62285-46-5; **15**, 62285-47-6; **20**, 80721-66-0; **21**, 80721-67-1; **22**, 80721-68-2; *N,N*-diethylmethanesulfonamide, 2374-61-0; dimethyl phosphorochloridate, 813-77-4; diisopropyl methylphosphonate, 1445-75-6; bromoacetyl bromide, 598-21-0; *N,N*-dimethylbromoacetamide, 5468-77-9; *N*-benzylbromoacetamide, 2945-03-1; *N*-isopropylbromoacetamide, 75726-96-4; *N*-cyclohexylbromoacetamide, 63177-66-2.