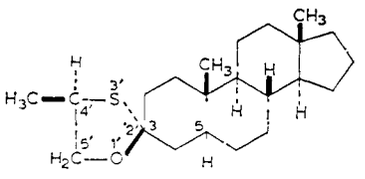
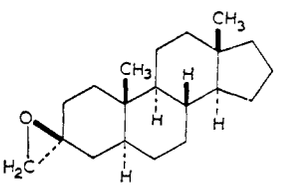
5. Spiro Derivatives. Spiro derivatives of steroids are named n accordance with the principles laid down in IUPAC Rules A-41, A-42, B-10, and B-11. Additional stereochemistry due to the spiro junction and substituents in the nonsteroid ring is designated by the sequence-rule procedure. Alternative names permitted by IUPAC rules are illustrated for (122) and (123).



(122)

4′*R*-Methyl-(*R*)-spiro[5α-androstane-3,2′-(1′,3′-oxathiolane)] or 5α-androstane-3(*R*)-spiro-2′-(4′*R*-methyl-1′,3′-oxathiolane)



(123)

(3*S*)-Spiro[5α-androstane-3,2′-oxiran] or (3*S*)-5α-androstane-3-spiro-2′-oxiran

Acknowledgment

We are indebted to the editors and publishers (Elsevier Publishing Company) of *Biochimica et Biophysica Acta* for permission to reproduce photographically the chemical structures that appeared in their publication of these tentative rules.

Phosphonic Acids and Esters. XX.[1] Preparation and Ring-Opening Reactions of α,β- and β,γ-Epoxyalkylphosphonates. The Proton Magnetic Resonance Spectra of Vicinally Substituted Ethyl- and Propylphosphonates

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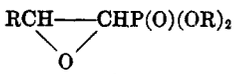
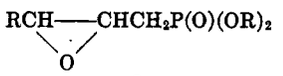
Diethyl (**3a**) and dimethyl (**3b**) α,β-epoxyethylphosphonates have been prepared by the epoxidation of the corresponding vinylphosphonates with *t*-butyl hydroperoxide in the presence of a basic catalyst. These epoxides fail to undergo thermal or acid-catalyzed rearrangements in contrast to the behavior of their β-substituted analogs. Both **3** and diethyl β,γ-epoxypropylphosphonate (**4**) undergo conventional hydrations, alcoholyses, and aminolyses to give α,β-disubstituted ethyl- and β,γ-disubstituted propylphosphonates, respectively. In every case, the products are formed by attack of nucleophile at the terminal carbon of the epoxide and isomerically pure products are formed. Attempted sodium borohydride reductions and Grignard reactions with **3** and **4** failed. The structures of **3** and **4** and their transformation products were established by proton magnetic resonance spectroscopy. Certain aspects of these spectra, namely, geminal β-proton nonequivalence in XCH_2–CHY–P systems and three- (P–C–O–H) and four- (P–O–C–C–H, P–C–C–C–H) bond spin–spin couplings, are discussed.

Despite their obvious potential as synthetic intermediates, relatively little attention has been directed to the preparation and reactions of dialkyl alkylphosphonates possessing an epoxide function in either the α,β (**1**) or β,γ (**2**) positions. Although the synthesis of

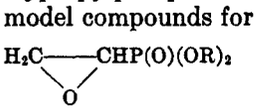


1

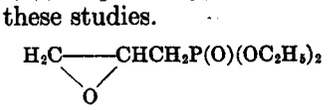


2

2 can be achieved by standard methods, *e.g.*, the Arbuzov reaction of epiiodohydrin with trialkyl phosphites,[2] the synthesis of **1** is more difficult. The formation of α-substituted **1** as by-products in the reactions of sodium dialkyl phosphonates with halomethyl ketones has been reported,[3,4] but the yields are low and a complex mixture of products (enol phosphate, β-ketoalkylphosphonate, and **1**) is formed. Similarly, α-substituted **1** may be prepared by alkaline treatment of the halohydrins formed by the addition of dialkyl phosphonates to halomethyl ketones,[4] but the slow rate of reaction and low yields limit the utilization of the reaction. To date, the most effective method for the preparation of **1** and its β,β-disubstituted analogs is the Darzens condensation of aromatic aldehydes and aryl and alkyl ketones with dialkyl chloromethylphosphonates.[5–7] The reaction is, however, ineffective for the preparation of β-alkyl and α-alkyl or aryl substituted **1**.[7] Because of our interest in the skeletal rearrangements of **1**[6,7] and the possible utilization of **1** and **2** as starting materials for the preparation of α,β- and β,γ-difunctionalized alkylphosphonates as substrates for neighboring-group participation studies,[8] we have examined alternative routes for the synthesis of **1** and certain ring-opening reactions of both **1** and **2**. The simplest examples of **1** and **2**, diethyl and dimethyl α,β-epoxyethylphosphonates (**3**), and diethyl β,γ-epoxypropylphosphonate (**4**),[2] respectively, were chosen as model compounds for these studies.



3a, R = C_2H_5
b, R = CH_3



4

(1) Part XIX: R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).

(2) B. A. Arbuzov and V. P. Lugovkin, *Zh. Obshch. Khim.*, **22**, 1193 (1952); *Chem. Abstr.*, **47**, 4872a (1953). However, the corresponding reaction with epichlorohydrin follows a different course, namely, formation of dialkyl methylphosphonate and dialkyl vinyl phosphate [V. S. Abramov and R. N. Savintseva, *J. Gen. Chem. USSR*, **37**, 2650 (1967)].

(3) G. Sturtz, *Bull. Soc. Chim. Fr.*, 2333 (1964); A. Meisters and J. M. Swan, *Aust. J. Chem.*, **18**, 159 (1956).

(4) B. A. Arbuzov, "Phosphoric Esters and Related Compounds," Chem. Soc. Special Publ. No. 8, The Chemical Society, London, 1957, pp 47–59.

(5) V. F. Martynov and V. E. Timofeev, *J. Gen. Chem. USSR*, **34**, 3383, 3950 (1964).

(6) R. H. Churi and C. E. Griffin, *J. Amer. Chem. Soc.*, **88**, 1824 (1966).

(7) R. H. Churi, Ph.D. Thesis, University of Pittsburgh, 1966.

(8) R. B. Davison, Ph.D. Thesis, University of Pittsburgh, 1965; M. Gordon, V. A. Notaro, and C. E. Griffin, *J. Amer. Chem. Soc.*, **86**, 1898 (1964).

The most attractive and potentially most general route for the synthesis of **3** and its various α- and β-substituted analogs appeared to be the direct epoxidation[9] of the corresponding dialkyl vinylphosphonates, $R_2C{=}CRP(O)(OR')_2$ (**5**). The syntheses of **5** with essentially any desired combination of α and β substituents can be achieved readily by a number of procedures.[10] In view of the relative electrophilicity of the double bond of **5** and the tendencies of these compounds to undergo nucleophilic addition,[11a] *e.g.*, the Michael reaction, epoxidations with either strongly electrophilic peracids or nucleophilic oxidants (alkaline hydrogen peroxide and *t*-butyl hydroperoxide) were deemed most feasible. Attempted reaction of diethyl vinylphosphonate,[12] $H_2C{=}CHP(O)(OC_2H_5)_2$ (**6**), with buffered pertrifluoroacetic acid in methylene chloride[13] and with peracetic acid in ethyl acetate[14] under a variety of conditions failed to provide any evidence for oxidation of the double bond.[15] These reagents have been shown to be effective in the epoxidation of α,β-unsaturated carboxylic esters.[13,14]

However, reaction of **6** with the nucleophilic oxidants known[9] to be effective in the epoxidation of α,β-unsaturated ketones was successful. Treatment of **6** with methanolic hydrogen peroxide at pH 9.5–10.0[17] resulted in the formation of **3a** (10%). The structure of **3a** was established by elemental analysis and infrared (ir) and proton magnetic resonance (pmr) spectra. The ir spectrum of **3a** showed typical diethylphosphono group absorptions at 1256, 1162, and 1020 cm^{-1} and oxirane ring absorptions at 877 and 828 cm^{-1}.[18,19] The pmr spectrum of neat **3a** showed a triplet (6 H, CH_3CH_2O–, J_{HH} = 7.4 Hz) at τ 8.70, a doublet of quartets (4 H, CH_3CH_2O–, J_{PH} = 8.9 Hz[20]) at 5.90, a quartet (0.5 H, J = 3.2, 4.7 Hz) at 6.68, and a complex multiplet (2.5 H) centered at 7.08 ppm. The signals at τ 6.68 and 7.08 ppm are assigned to the oxirane ring protons; the chemical shifts of these protons are quite similar to those observed in substituted **1**[7] and simple substituted oxiranes, such as glycidonitrile.[21] It is probable that the downfield quartet represents the low field portion of the methine proton resonance; this resonance would consist of the A part of an ABCX spectrum and the observed multiplicity is correct. Additionally, the observed ^1H–^1H coupling constants (3.2, 4.7 Hz) are of the correct order for *trans*- and *cis*-vicinal coupling constants in substituted oxiranes.[7,21] However, the complexity of the 7.08-ppm multiplet precluded a trivial analysis of the spectrum.[22] The absence of vinylic groups in **3a** was established by both pmr and ir spectra.

Although repetitions of the hydrogen peroxide oxidation of **6** failed to improve the yields of **3a** to any significant extent, an acceptable yield (62%) of **3a** was obtained by the epoxidation of **6** with *t*-butyl hydroperoxide in benzene[23] using Triton B as a catalyst. In addition to **3a**, a significant amount of diethyl β-*t*-butoxyethylphosphonate (**7a**) was also formed in this

$$(CH_3)_3COCH_2CH_2P(O)(OR)_2$$

7a, R = C_2H_5
b, R = CH_3

reaction. Presumably, **7a** is formed by the Michael addition[11a] of *t*-butoxide ion, a by-product of the epoxidation reaction, to **6**, although attempts to prepare **7a** by the reactions of potassium *t*-butoxide with **6** or *t*-butyl alcohol with **6** in the presence of Triton B failed.[24] Dimethyl α,β-epoxyethylphosphonate (**3b**) was also successfully prepared from dimethyl vinylphosphonate (**8**)[26] by this route. The structure of **3b** was established by the similarity of its ir and pmr spectra to those of **3a**. As in the case of **3a**, the formation of **3b** was accompanied by the addition of *t*-butoxide ion to **8** to yield **7b**. In neither the hydrogen peroxide nor the *t*-butyl hydroperoxide preparations was any evidence obtained for the formation of products resulting from the attack of nucleophiles on the oxiranes **3a** and **3b**.

Diethyl β,γ-epoxypropylphosphonate (**4**)[2] was readily prepared by the Arbuzov reaction of epibromohydrin and triethyl phosphite. Although the reactions of trialkyl phosphites with oxiranes to yield β-alkoxyalkylphosphonates have been reported,[11b] no products from analogous reactions were observed in the formation of **4**.

Two types of reactions of these epoxyalkylphosphonates, namely, the rearrangement of **3** to oxoalkylphosphonates and the reactions of **3** and **4** with nucleophiles to produce α,β- and β,γ-difunctionalized alkylphosphonates, were of potential interest. It has been shown[6,7] that β-mono- and β,β-disubstituted α,β-epoxyethylphosphonates (**1**) undergo both thermal (170–300°) and acid- (boron trifluoride etherate in benzene) catalyzed rearrangements to yield, as a result of dialkoxyphosphono-group migration, substituted α-formylmethylphosphonates (**9**). The phosphono group migration is apparently specific in these

(9) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 109–123; M. S. Malinovskii, "Epoxides and Their Derivatives," D. Davey, New York, N. Y., 1965, pp 39–68.

(10) E. L. Gefter, "Organophosphorus Monomers and Polymers," Associated Technical Services, Inc., Glen Ridge, N. J., 1962, pp 3–21; W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961); T. Hullar, *Tetrahedron Lett.*, 4921 (1967); D. C. Wysocki, Ph.D. Thesis, University of Pittsburgh, 1967.

(11) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., New York, N. Y., 1967: (a) pp 220–221; (b) p 190.

(12) (a) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947); (b) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **70**, 1971 (1948).

(13) W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 89 (1955).

(14) D. L. MacPeek, P. S. Starcher and B. Phillips, *ibid.*, **81**, 680 (1959).

(15) However, since the completion of this work, Hunger[16] has reported the formation of **3a** and certain of its methyl substitution products in good yield by reaction of the vinylphosphonates with unbuffered pertrifluoroacetic acid. Hunger also achieved the formation of **3a** (10%) by epoxidation of **6** with permaleic acid, but found that reaction with buffered pertrifluoroacetic acid gave only trace amounts (0.8%) of **3a**.

(16) K. Hunger, *Chem. Ber.*, **101**, 3530 (1968).

(17) R. L. Wasson and H. O. House, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., p 552.

(18) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963.

(19) Hunger[16] reports a strong oxirane absorption for **3a** at 860–870 cm^{-1}.

(20) For typical coupling constants and chemical shifts in diethyl alkylphosphonates, see M. P. Williamson and C. E. Griffin, *J. Phys. Chem.*, **72**, 4043 (1968).

(21) C. A. Reilly and J. Swalen, *ibid.*, **32**, 1378 (1960).

(22) On irradiation of the ^{31}P nucleus at 24.3 MHz, the pmr spectrum of **3a** collapsed, as expected, giving a tightly coupled ABC spectrum, typical of substituted oxiranes,[18] for the ring protons. A complete analysis of the spectrum of **3a** is in progress.

(23) N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958).

(24) In previous studies of epoxidations of α,β-unsaturated ketones with *t*-butyl hydroperoxide,[23] no products corresponding to the Michael addition of *t*-butoxide ion to the substrate have been reported, although the analogous addition of *t*-butyl peroxide ion to yield *t*-butyl alkyl peroxides has been observed.[23,25]

(25) D. Harman, U. S. Patent 2,508,256 (May 16, 1950); *Chem. Abstr.*, **44**, 7341*i* (1950).

(26) A. Ya. Yakubovich, L. Z. Soborovskii, L. I. Muler, and V. A. Faermark, *J. Gen. Chem. USSR*, **28**, 313 (1958).

reactions, since no evidence for the formation of the isomeric hydrogen migration products (**10**) was obtained.[6,7] Rearrangement of **3a** would correspondingly yield either diethyl formylmethylphosphonate, $OHCCH_2P(O)(OC_2H_5)_2$ (**11**), by phosphono-group migration or diethyl acetylphosphonate, $CH_3COP(O)(OC_2H_5)_2$ (**12**), by hydrogen migration. However, **3a** failed to undergo thermal rearrangement at either 210° (15 min) or 240–270° (45 min) under nitrogen.[27] In neither reaction was any evidence obtained for the formation of carbonyl compounds, although at the higher temperature some decomposition of **3a** to a polymeric material was observed. Similarly, treatment of **3a** with boron trifluoride etherate in benzene and other acidic catalysts failed to result in rearrangement; products of ring opening were isolated in all cases (*vida infra*).[28]

$R_2CP(O)(OR)_2$ (CHO) — **9**

$R_2CHCOP(O)(OR)_2$ — **10**

Evidence for a possible rearrangement of **3a** was obtained in only one instance. In the formation of **3a** by the hydrogen peroxide epoxidation of **6**, a small amount of a carbonyl-containing (ν_{CO} 1728 cm^{-1}) fraction was isolated. This material is apparently the formylmethylphosphonate **11** and not the acetylphosphonate **12** since the carbonyl frequency lies in the region typical of aldehydes;[18] ν_{CO} for **11** is reported[29] as 1726–1728 cm^{-1} and for **12**[30] as 1695 cm^{-1}. The pmr spectrum of this material was also in accord with structure **11**, showing typical $POCH_2CH_3$ resonances and a methylene doublet (J_{PH} = 21 Hz) at τ 7.03.[31,33] The formation of **11** in this reaction may be the result of rearrangement with phosphono migration of **3a** during isolation of the product or may be the result of some nonepoxidative reaction of hydrogen peroxide with **6**. The available evidence does not allow a choice between the two possibilities.

The formation of α,β- and β,γ-difunctionalized alkylphosphonates from **3** and **4**, respectively, was achieved readily by both acid-catalyzed and noncatalyzed openings of the oxirane rings. Treatment of **3a** with aqueous sulfuric acid led to the formation of the glycol **13**, while the glycol monoethers **14** and **15** were obtained by reaction of **3a** with methanolic and ethanolic sulfuric acid. Similar acid-catalyzed ethanolysis of **3b** gave the glycol monoether **18**. Treatment of **3a** and **3b** with boron trifluoride etherate in benzene also resulted in ethanolysis to yield **15** and **18**. Products **13–15** were formed in acceptable yields (50–62%) and in no case was any evidence obtained for the formation of the rearrangement products **11** or **12**.[35] Treatment of **3a** with aniline at 120° also resulted in ring opening with the formation of the amino alcohol **16** (90%). Attempted reaction of **3a** with aqueous ammonia under identical conditions resulted in the formation of black oils and the expected product (**17**) could not be isolated. However, **17** was obtained by reaction of **3a** with an excess of aqueous ammonia at room temperature; **17** decomposed on attempted distillation, but was successfully acetylated to give **19**.

$CH_2CHP(O)(OCH_2CH_3)_2$ (X, OH)

13, X = OH
14, X = OCH_3
15, X = OCH_2CH_3
16, X = NHC_6H_5
17, X = NH_2

$CH_3CH_2OCH_2CHP(O)(OCH_3)_2$ (OH) — **18**

$CH_3CONHCH_2CHP(O)(OCH_2CH_3)_2$ ($OCOCH_3$) — **19**

The openings of the oxirane rings of **3a** and **3b** to give **13–18** were apparently directionally specific; in no instance was evidence obtained for the formation of the isomeric products resulting from attack of nucleophile at the α carbon.[36]

Diethyl β,γ-epoxypropylphosphonate (**4**) underwent a similar series of ring-opening reactions. Acid-catalyzed hydration gave the glycol **20**,[37] while the glycol monoethers **21** and **22** were formed by acid-catalyzed alcoholyses. The ethoxy compound **22** was also produced by the action of boron trifluoride etherate in benzene. The amino alcohol **23** was formed by reaction of **4** with aniline at 120°, while **24** was produced by reaction with aqueous ammonia at room temperature.

$CH_2CHCH_2P(O)(OC_2H_5)_2$ (X, OH)

20, X = OH
21, X = OCH_3
22, X = OCH_2CH_3
23, X = NHC_6H_5
24, X = NH_2

(27) Similarily, Hunger[16] obtained no evidence for thermal rearrangements of **3a** and its α-methyl and α,β-dimethyl analogs. However, the α,β,β-trimethyl analog readily underwent rearrangement during distillation to yield diethyl α,α-dimethylacetonylphosphonate.

(28) The failure to detect the formation of **11** in these acid-catalyzed reactions may not bar the possibility of its formation since it has been shown[25] that **11** readily undergoes an aldol trimerization followed by dehydration to yield 1,3,5-trisdiethoxyphosphonobenzene.

(29) A. I. Razumov and V. V. Moskva, *J. Gen. Chem. USSR.*, **34**, 2612 (1964).

(30) K. D. Berlin, D. M. Hellwege, and M. Nagabhushanam, *J. Org. Chem.*, **30**, 1265 (1965).

(31) The methylene resonance of a suitable model compound, $CH_3COCH_2P(O)(OC_2H_5)_2$, is observed at τ 7.03 ppm (J_{PH} = 23.0 Hz).[32] Berlin and coworkers have reported τ 7.57 ppm (J_{PH} = 5 Hz) for the methyl resonance of **12**.[30]

(32) M. Gordon, Ph.D. Thesis, University of Pittsburgh, 1965.

(33) Infrared[34] and nmr[7] studies indicate that the α-phenyl analog of **11** is totally enolic in character. However, neither the ir nor nmr spectrum of **11** provided evidence for any detectable enol content. Apparently, the stabilizing effect of the phenyl substituent is a requisite for enolization.

(34) L. E. Tammelin and L. Fagerlind, *Acta Chem. Scand.*, **14**, 1353 (1960).

(35) Churi[7] also found acid-catalyzed methanolysis of β-substituted α,β-epoxyethylphosphonates to be unaccompanied by rearrangement, but attempted acid-catalyzed hydrations resulted only in rearrangement with phosphono-group migration.

(36) The reaction products from the alcoholyses of **3a**, **3b**, and **4** were subjected to careful chromatographic separations which failed to show evidence for the presence of the isomeric glycol monoethers.

(37) Arbuzov and Lugovkin[2] have reported the isolation of the barium salt of β,γ-dihydroxypropylphosphonic acid from the hydrolysis of **4** with aqueous sodium hydroxide. To the best of our knowledge, this reaction represents the only reported transformation of the oxirane ring of either **3** or **4**.

As in the case of **17**, attempted distillation of **24** resulted in decomposition, but the compound was characterized by acetylation to give **25**. Compounds

$$CH_3CONHCH_2\underset{\displaystyle OCOCH_3}{\underset{|}{C}}HCH_2P(O)(OC_2H_5)_2$$

25

20–25 were formed in 42–88% yield. As in the reactions with **3a** and **3b**, the opening of the oxirane ring of **4** is apparently directionally specific; no evidence was obtained for the formation of the isomeric products resulting from attack of nucleophiles at the β position.

Two types of attempted reactions of **3a** and **4** failed to give the expected products. Treatment of **3a** with ethylmagnesium bromide and **4** with both methyl- and ethylmagnesium bromides resulted in the formation of the glycols **13** (50%) and **20** (42–55%), respectively No evidence for the formation of the expected monohydroxy alkylphosphonates was obtained. Apparently, the oxirane rings of **3a** and **4** are opened by reaction with magnesium bromide to yield the halohydrins,[38] which undergo hydrolysis to the glycols during product isolation. Attempted reactions of **3a** and **4** with sodium borohydride led to recovery of the starting materials.

The structures of the ring-opening products **13–25** were established by studies of their ir and prm spectra. The hydroxyl (3170–3300) and phosphoryl (1220–1230 cm^{-1}) stretching frequencies of those compounds possessing free hydroxyl groups in either the α or β positions were in the normal ranges for intra- or intermolecularly hydrogen-bonded hydroxyalkylphosphonates.[18] For example, the ranges ν_{OH} 3180–3285 cm^{-1} and ν_{PO} 1230–1232 cm^{-1} have been cited for α-hydroxyalkylphosphonates.[39] Normal[18] $POCH_2CH_3$ signals were observed at 1150–1170 and 1020–1022 cm^{-1}. The acetylated derivatives **19** and **25** showed typical[18] ester (1735–1745) and amide (1660–1682 cm^{-1}) carbonyl absorptions; the low ν_{PO} (1217–1220 cm^{-1}) values observed for these compounds indicate a probable hydrogen bonding with the amide proton.

The pmr spectra of **13–25** were in full accord with the postulated structures; parameters for selected compounds and certain of their derivatives are listed in Tables I and II. In all cases, the observed chemical shifts, peak multiplicities, coupling constants, and integrated intensities were consistent with the postulated structures. However, the extensive occurrence of overlap between the α and β proton resonances of **13–18** and the β and γ proton resonances of **20–24** with the ester (OCH_2) resonances did not allow a consistent and unequivocal confirmation of the secondary nature of the hydroxyl groups in these compounds. Confirmation was obtained by the use of either DMSO-d_6 [40] as solvent or by conversion of the alcohols into urethan derivatives (**26–30**) by reaction with trichloroacetyl isocyanate (TAI).[41] The hydroxyl resonances of all the alcohols examined were either sharp or broadened singlets in $CDCl_3$. However, in DMSO-d_6, the hydroxyl resonances of **21** and **22** were observed as doublets (J_{HCOH} = 5.4–5.5 Hz), confirming the secondary nature of the hydroxyl group.[40] A similar confirmation was obtained for **18** (*vida infra*). Corresponding hydroxyl–carbinol ^1H–^1H couplings were not observed in the spectra of the other hydroxylic compounds in DMSO-d_6; in all cases, the hydroxyl resonances were broadened, but no resolution of the multiplets was achieved.[42] The secondary nature of the alcoholic function in the latter compounds, as well as **21** and **22**, was established by examination of the spectra of their TAI derivatives.[41] For example, conversion of **14** into its TAI derivative **27** resulted in a 1.30-ppm downfield shift of the methine multiplet; the remaining resonances of **27** were shifted only slightly from the corresponding resonances of **14**. It has been shown that conversion of secondary alcohols into their urethan derivatives results in a deshielding of the carbinol proton by 1.0–1.5 ppm; a smaller deshielding (0.5–0.9 ppm) is observed for primary alcohols.[41,43] Except for the glycols **13** and **20**, no evidence for the presence of primary alcoholic functions was obtained.

Two additional aspects of the pmr spectra of these compounds merit comment. The α-proton resonances of the urethans **27** and **28** and the acetyl derivative **19** are sufficiently well resolved to permit analysis. The multiplets comprise the M parts of ABMX (X = phosphorus) spectra, indicating the geminal β protons to be nonequivalent. In similar fashion, the β protons of **18** (in DMSO-d_6) were also found to be nonequivalent. Presumably, the β protons are also nonequivalent in the remaining α,β-disubstituted ethylphosphonate derivatives (**13–17** and **26**), but the α-proton resonances of these compounds were not sufficiently well resolved to allow analysis. The geminal proton nonequivalence observed in **18, 19, 27,** and **28** may be the result of either restricted rotation about the C_α–C_β bond or the presence of an asymmetric center in the molecule.[44] The latter origin appears to be more likely since it was found that the spectra of both **18** and **28** were temperature independent over the range 35–145°. The appearance of the spectrum of dimethyl β-*t*-butoxyethylphosphonate (**7b**) was also indicative of geminal (in this case, α) proton nonequivalence. The α-proton multiplet of **7b** consisted of a doublet of triplets arising from coupling with the phosphorus nucleus and the two equivalent β protons; further additional small and incompletely resolved splittings consistent with different chemical shifts for the two α protons were present.[45] No comparable nonequivalence was observed in the spectrum of the corresponding

(38) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(39) C. D. Miller, R. C. Miller, and W. Rogers, Jr., *J. Amer. Chem. Soc.*, **80**, 1562 (1958).

(40) (a) O. L. Chapman and R. W. King, *ibid.*, **86**, 1256 (1964); (b) J. G. Traynham and G. A. Knesel, *ibid.*, **87**, 4220 (1965).

(41) V. Goodlett, *Anal. Chem.*, **37**, 431 (1965); I. R. Trehan, C. Monder, and A. K. Bose, *Tetrahedron Lett.*, 67 (1968).

(42) Traynham and Knesel[40b] have previously noted the lack of such couplings in the spectra of alcohols possessing adjacent strong electron acceptors.

(43) Both primary (0.32 ppm) and secondary (1.67 ppm) deshieldings were observed in the spectrum of the TAI derivative (**26**) of glycol **13**.

(44) The same structural features are present in the β,γ-disubstituted propyl compounds **20–25, 29,** and **30** and, consequently, both α- and γ-proton nonequivalence might be expected. However, no evidence for nonequivalence was obtained from the spectra of these compounds. In general, neither the β- nor γ-proton resonances were sufficiently well resolved to permit analysis. In two instances (**20** and **29**), the γ-proton resonance was resolved, consisting of a doublet of doublets, indicative of either geminal proton equivalence or a neglible chemical-shift difference between the two protons. The α-proton resonances in all cases indicated geminal proton equivalence.

(45) Double-irradiation experiments (β-proton and phosphorus irradiation) showed these small splittings to originate with the α protons.

TABLE I

PMR PARAMETERS (τ, PARTS PER MILLION) FOR DIETHYL α,β-DISUBSTITUTED ETHYLPHOSPHONATES[a]

$$\begin{matrix} CH_2CHP(O)(OCH_2CH_3)_2 \\ \quad | \quad | \\ \quad X \quad OY \end{matrix}$$

Compound	13	26	14	27	15	28	19[b]	18[c]	
X =	OH	OCONHCOCCl$_3$	OCH$_3$	OCH$_3$	OCH$_2$CH$_3$	OCH$_2$CH$_3$	NHCOCH$_3$	OCH$_2$CH$_3$	
Y =	H	CONHCOCCl$_3$	H	CONHCOCCl$_3$	H	CONHCOCCl$_3$	COCH$_3$	H	
CH_3COP	8.67	8.62	8.68 (7.5)	8.63[d] (7.4) [1.2]	8.68	8.67[d] (7.4) [1.4]	8.63		t[e]
XCH_2–	6.05	5.73	6.32	6.40	6.37	6.17	6.33	6.48	m
–OCHP–	6.05	4.38	5.82	4.52[f] (5.0, 5.9) [11.0]	5.80	4.53[f] (6.2, 6.1) [11.5]	4.63[f] (4.8, 7.5) [10.3]	5.83	m
$-POCH_2-$	5.72	5.73	5.82	5.77	5.80	5.77	5.80 (7.6) [7.6]		dq
HO–	5.02		4.82		4.92			5.17	s
–NH–		0.12, −0.42		−0.53		−0.60	3.00		s
CH_3O–			6.60	6.62				6.39[g]	s
CH_3COC					8.78	8.85		8.80	t
CCH_2OC					6.37	6.17[h]		6.48	m

[a] All spectra were recorded in $CDCl_3$ solution. For procedural details, see Experimental Section. ^1H–^1H coupling constants are given in parentheses and ^{31}P–^1H coupling constants are given in brackets (both in hertz). [b] τ_{COCH_3} 7.87 (s), 8.03 (s) ppm. [c] Dimethyl ester. [d] Doublet of triplets. [e] Multiplicities, unless otherwise noted: s, singlet, t, triplet; dq, doublet of quartets, m, unresolved multiplet. [f] M portion of ABMX spectrum. [g] $POCH_3$ doublet. [h] Quartet.

TABLE II

PMR PARAMETERS (τ, PARTS PER MILLION) FOR DIETHYL β,γ-DISUBSTITUTED PROPYLPHOSPHONATES[a]

$$\begin{matrix} CH_2CHCH_2P(O)(OCH_2CH_3)_2 \\ \quad | \quad | \\ \quad X \quad OY \end{matrix}$$

Compound	20	21[b]	29[c]	22[d]	30[e]	23[f]	24	25[g]	
X =	OH	OCH$_3$	OCH$_3$	OCH$_2$CH$_3$	OCH$_2$CH$_3$	NHC$_6$H$_5$	NH$_2$	NHCOCH$_3$	
Y =	H	H	CONHCOCCl$_3$	H	CONHCOCCl$_3$	H	H	COCH$_3$	
CH_3COP	8.75	8.68	8.68	8.68	8.68	8.80	8.72	8.67	t[h]
$-CH_2P-$	8.05 (6.4) [18.7]	8.00 (6.7) [18.3]	7.75 (6.2) [19.6]	7.97 (6.3) [18.2]	7.77 (6.8) [18.7]	7.98[i] [~16]	8.03 (6.9) [18.2]	7.95[j]	dd
XCH_2–	6.64[k] (5.2) [1.2]	6.57	6.40[k] (3.6) [1.1]	6.57[i] (5.5)	6.35	6.58	7.28	5.95	m
–CCHC–	5.98	6.25	4.65[l]	5.87	4.63[m]	6.58	5.65	4.75	m
$-POCH_2-$	5.98	5.88	5.87	5.87	5.87	6.03	5.95	5.95	dq
HO–	5.32	5.55[n]		5.67[n]		3.22	5.65[j]		s
–NH–			−0.40		−0.25	2.70[j]	5.65[j]	2.53	s
Solvent	DMSO-d_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	DMSO-d_6	DMSO-d_6	$CDCl_3$	

[a] For procedural details, see Experimental Section. ^1H–^1H coupling constants are given in parentheses and ^{31}P–^1H coupling constants are given in brackets (both in hertz). [b] τ_{OCH_3} 6.63 (s) ppm. [c] τ_{OCH_3} 6.62 (s) ppm. [d] τ_{CH_3COC} 8.82 (t), τ_{CCH_2OC} 6.46 (q) ppm. [e] τ_{CH_3COC} 8.82 (t) ppm (7.0), τ_{CCH_2OC} 6.40 (q) ppm. [f] $\tau_{C_6H_5}$ 2.70 (m) ppm. [g] τ_{COCH_3} 7.62 (s), 7.98 (s) ppm. [h] Multiplicities, unless otherwise noted: s, singlet; dd, doublet of doublets; t, triplet; q quartet; dq doublet of quartets; m, unresolved multiplet. [i] Broad doublet. [j] Multiplet. [k] Doublet of doublets. [l] Poorly resolved six-line multiplet. [m] Poorly resolved eight-line multiplet. [n] In DMSO-d_6, τ_{OH} 5.11–5.12 (d) ppm (5.4–5.5).

TABLE III
ELEMENTAL ANALYSES

Compound	Formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
3a	$C_6H_{13}O_4P$	40.00	7.22	17.22	39.78	7.44	17.46
3b	$C_4H_9O_4P$	31.58	5.92	20.52	31.39	6.09	20.51
7a	$C_{10}H_{23}O_4P$	50.42	9.66	13.02	50.60	9.51	12.91
7b	$C_8H_{19}O_4P$	45.71	9.05	14.76	45.88	8.89	15.01
13	$C_6H_{15}O_5P$	36.41	7.58	15.65	36.20	7.50	15.44
14	$C_7H_{17}O_5P$	39.70	8.02	14.63	39.83	7.94	14.78
15	$C_8H_{19}O_5P$	42.47	8.40	13.71	42.64	8.31	13.79
16	$C_{12}H_{20}NO_4P$	53.28	7.66	11.31	53.40	7.90	11.49
18	$C_6H_{15}O_5P$	36.41	7.58	15.65	36.49	7.73	15.80
19	$C_{10}H_{20}NO_6P$	42.70	7.12	11.03	42.94	7.31	10.87
20	$C_7H_{15}O_5P$	39.70	8.02	14.63	39.81	7.80	14.53
21	$C_8H_{19}O_5P$	42.50	8.40	13.71	42.54	8.34	13.90
22	$C_9H_{21}O_5P$	44.99	8.75	12.92	44.85	9.01	13.08
23	$C_{13}H_{22}NO_4P$	54.20	7.98	10.78	53.95	7.69	10.48
25	$C_{11}H_{22}NO_6P$	46.31	7.72	10.88	46.16	7.77	11.15

ethyl ester **7a**. Since **7b** possesses no formally asymmetric center, the α-proton nonequivalence must be the result of either restricted rotation about the C_α–C_β bond or the intrinsic asymmetry of the α carbon.[20] The former explanation is apparently correct, since in the temperature range 60–85° the additional splittings in the α-proton resonance of **7b** disappeared and at temperatures above 90° this resonance consisted of a simple doublet of triplets.

Two types of long-range ^{31}P–^1H spin–spin couplings were observed in the spectra of these compounds. The $POCH_2CH_3$ resonances of **27** and **28** consisted of triplets of doublets. The triplet splitting arises from coupling with the methylene protons, while the smaller splitting (1.2–1.4 Hz) is the result of a long-range ($^4J_{PH}$) interaction with the phosphorus nucleus. Somewhat smaller (0.3–1.2 Hz) couplings of this type have been observed previously in the spectra of ethyl esters of phosphorus acids.[20] In the spectra of **20** and **29**, the γ protons were observed to be coupled ($^4J_{PH}$ = 1.1–1.2 Hz) to the phosphorus nucleus. Although long-range ^{31}P–^1H couplings have been observed commonly in systems containing π bonds,[46] *e.g.*, HCC=CP, and hetero atoms,[20] *e.g.*, HCCOP, couplings through three sp^3-hybrid carbons (HCCCP) are rare. To the best of our knowledge, the only previous example of such a coupling was reported by Ross and Martz,[47] who observed coupling ($^4J_{PH} \leq 0.8$ Hz) between C_{19} protons and phosphorus in some 5α-phosphonocholestane derivatives.

Certain aspects of the spectrum of **18** in DMSO-d_6 were also of interest. The hydroxyl resonance appeared as a doublet of doublets as a result of coupling with the carbinol proton (J_{HCOH} = 6.9 Hz) and the phosphorus nucleus (J_{PCOH} = 10.0 Hz). Although the latter coupling is only through three bonds, to the best of our knowledge, such couplings have not been observed previously. The phenomenon is not general, since no comparable couplings were observed in the other α-hydroxy compounds examined in this study.[48] Both the nonequivalence of the β protons and J_{HCOH} were obvious in the α-proton multiplet, which comprised the M portion of an ABMXY (X = phosphorus; Y = OH) system. The resolution of this multiplet only allowed an approximate analysis, but double-resonance (X and Y decoupling) experiments permitted analysis; the couplings J_{MX}, J_{AX}, and J_{BX} were of the same order as those observed in **19**, **27**, and **28**.

The results of this study indicate that the epoxyalkylphosphonates **3** and **4** possess essentially normal oxirane reactivity and that they may be employed as synthetic intermediates for the preparation of more complex organophosphorus compounds.

Experimental Section

Pmr spectra were determined at ambient probe temperature (37°) with a Varian Associates A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Coupling constants were taken from 50-Hz sweep width spectra and are accurate to ±0.2 Hz. Unless otherwise noted, satisfactory integrated intensities were obtained for all compounds. Variable-temperature 60-MHz studies employed a V6040 variable-temperature controller. Heteronuclear decoupling experiments were performed with an NMR Specialties SD-60B heteronuclear spin decoupler with an irradiation frequency of 24.3 MHz. Homonuclear decoupling experiments were performed on a Varian Associates HA-100 spectrometer which was frequency swept in the HA mode, the field frequency being locked to the internal TMS; the irradiating frequency was provided by a Hewlett-Packard 201CR audiooscillator. Ir spectra were recorded as films or Nujol mulls on a Beckman IR-8 spectrophotometer using polystyrene calibration. Melting and boiling points are uncorrected. Results of elemental analyses are given in Table III.

Diethyl vinylphosphonate (**6**) was prepared in 67% over-all yield by reaction of ethylene bromide with triethyl phosphite,[12] followed by dehydrobromination with triethylamine in benzene.[12b] Dimethyl vinylphosphonate (**8**) [bp 45° (0.65 mm), lit.[26] bp 82–84° (3.5 mm)] was prepared in 40% over-all yield by the same sequence using trimethyl phosphite.[49,50] Triton B and *t*-butyl hydroperoxide were obtained from K and K Laboratories.

Hydrogen Peroxide Epoxidation of Diethyl Vinylphosphonate (6).—A solution of 24.6 g (0.15 mol) of **6** in 150 ml of methanol was treated with 60 ml of 30% hydrogen peroxide at room temperature. The solution was cooled in an ice bath and 75 ml

(46) For a summary of long-range ^{31}P–^1H coupling phenomena in systems of this type, see C. E. Griffin and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4427 (1967).

(47) J. A. Ross and M. D. Martz, *J. Org. Chem.*, **34**, 399 (1969).

(48) The spectra of three simple hydroxymethylphosphorus compounds [$HOCH_2P(O)RR'$, R = R' = CH_2Cl; R = CH_3, R' = CH_2Cl; R = CH_2OH, R' = OH] in DMSO-d_6 were also examined, but no evidence for the existence of J_{PCOH} was obtained. The hydroxyl resonances were broadened singlets in all cases.

(49) The previously reported[26] preparation of **8** utilized the dehydrochlorination of dimethyl β-chloroethylphosphonate.

(50) The structure of **8** was established by its pmr spectrum: τ 6.34 (d, J_{PH} = 11.1 Hz, $POCH_3$), 3.2–4.3 ppm (m, $-CH=CH_2$). The appearance of the vinylic multiplet is identical with that reported for **6**.[51]

(51) M. P. Williamson, S. Castellano, and C. E. Griffin, *J. Phys. Chem.*, **72**, 175 (1968).

of 1 *N* sodium hydroxide was added dropwise at a rate sufficient to maintain the pH at 9.5–10.0. After the addition was completed, the reaction mixture was stirred at room temperature for 3 hr to give a solution of pH 8.0. An additional 50 ml of 30% hydrogen peroxide was added and the pH was readjusted to 9.5 by the addition of 1 *N* sodium hydroxide. The reaction mixture was then stirred for an additional 20 hr at room temperature to give a solution of pH 7.0. This solution was poured into 100 ml of water, then saturated with sodium chloride, and extracted thoroughly with chloroform. The combined chloroform extracts were dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a 14-g residue which was fractionally distilled through a 5-in. Vigreux column to give 8 g of **6**, 1.89 g (10.4%) of **diethyl α,β-epoxyethylphosphonate (3a)** [bp 66–68° (0.2 mm), lit.[16] bp 124° (5 mm)], and 1.4 g (7.7%) of **diethyl formylmethylphosphonate (11)** [bp 89–90° (0.35 mm), lit.[52] bp 104–105° (3 mm); ir (film) 1728 (C=O), 1250 (P=O), 1162 (POC_2H_5), 1030 cm^{-1} (P–O-alkyl); pmr ($CDCl_3$) τ 8.65 (t, CH_3), 7.03 (d, J_{PH} = 21 Hz, PCH_2–), 5.87 ppm (dq, OCH_2–)].[53]

***t*-Butyl Hydroperoxide Epoxidation of Diethyl (6) and Dimethyl (8) Vinylphosphonates.**—A solution of 40% Triton B in methanol (0.84 g, 1 mmol) was added over a period of 2 hr to a mixture of 65.6 g (0.4 mol) of **6** and 20 ml (0.18 mol) of 90% *t*-butyl hydroperoxide in 200 ml of benzene at ice-bath temperatures. The reaction mixture was then allowed to warm to room temperature and stirred continuously overnight. The benzene solution was washed twice with 50-ml portions of water; the aqueous layer was saturated with sodium chloride and extracted thoroughly with chloroform. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure to give a 70-g residue which was fractionally distilled to yield 35 g of a mixture of **6** and *t*-butyl alcohol, 20 g (61.7%) of **3a**, and 10 g (23.4%) of **diethyl β-*t*-butoxyethylphosphonate (7a)** {bp 82° (0.2 mm); ir (film) 1250 (P=O), 1165 (POC_2H_5), 1020 (PO–alkyl), 880 cm^{-1} (*t*-C_4H_9O); pmr (neat) τ 8.78 [s, $(CH_3)_3CO$–], 8.72 (t, J_{HH} = 7.4 Hz, CH_3COP), 7.95 (dt, J_{HH} = 7.0, J_{PH} = 19.5 Hz, PCH_2–), 5.95 (m, CH_2OC), 5.95 ppm (dq, J_{PH} = 8.8 Hz, $POCH_2$–)}.

The epoxidation of **8** was carried out by the same procedure using the same molar quantities of reactants. Distillation of the crude reaction product (58 g) gave 30 g of a mixture of **8** and *t*-butyl alcohol, 5 g (18%) of **dimethyl α,β-epoxyethylphosphonate (3b)** [bp 58° (0.4 mm); ir (film) 1250 (P=O), 1180 ($POCH_3$), 1020 (PO–alkyl), 872 and 830 cm^{-1} (oxirane); pmr ($CDCl_3$) τ 7.03 (m, 2.5, oxirane), 6.65 (m, 0.5, oxirane), 6.33 ppm (d, J_{PH} = 11 Hz, $POCH_3$)], and 20 g (53%) of **dimethyl β-*t*-butoxyethylphosphonate (7b)** {bp 85° (0.5 mm); ir (film) 1250 (P=O), 1185 ($POCH_3$), 1030 (PO–alkyl), 875 cm^{-1} (*t*-C_4H_9O); pmr (neat) τ 8.80 [s, $(CH_3)_3CO$–], 7.87 (dt, J_{HH} = 6.9, J_{PH} = 19.4 Hz, PCH_2–), 6.32 (d, J_{PH} = 11.2 Hz, $POCH_3$), 5.95 ppm (m, CH_2OC)}.

Preparation of Diethyl β,γ-Epoxypropylphosphonate (4).—A mixture of 137 g (1 mol) of epibromohydrin and 166 g (1 mol) of triethyl phosphite was heated under a nitrogen atmosphere. Ethyl bromide distilled from the reaction mixture when the temperature reached 120°. The reaction mixture was held at 130° for 4 hr and then at 155° until the evolution of ethyl bromide ceased. Distillation of the reaction mixture through a 14-in. Vigreux column gave 120 g (61.9%) of **4**: bp 98° (0.6 mm) [lit.[2] bp 130–132° (11 mm)]; ir (film) 1250 (P=O), 1158 (POC_2H_5), 1020 (PO–alkyl), 868 and 838 cm^{-1} (oxirane); pmr (neat) τ 8.72 (t, CH_3COP), 7.7–8.3 (m, PCH_2–), 6.7–7.6 (m, oxirane), 6.10 ppm (dq, $POCH_2$–).

Hydration of Epoxides 3a and 4.—A solution of 3 g of the epoxide in 25 ml of water containing 6 drops of concentrated sulfuric acid was refluxed for 2.5 hr, allowed to cool to room temperature, and adjusted to pH 7.0 by the addition of aqueous sodium bicarbonate. The solution was concentrated under reduced pressure to yield a thick liquid which was extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and concentrated to give a residue which was distilled to yield the product. **Diethyl α,β-dihydroxyethylphosphonate (13)** [bp 140° (0.3 mm)] was obtained in 55% yield from **3a**. **Diethyl β,γ-dihydroxypropylphosphonate (20)** [bp 142° (0.25 mm)] was obtained in 52% yield from **4**.

Alcoholysis of Epoxides 3a, 3b, and 4.—A solution of 3 g of the epoxide in 45 ml of ethanol or methanol containing 6 drops of concentrated sulfuric acid was refluxed for 1.5 hr, allowed to cool to room temperature, and adjusted to pH 7.0 by the addition of aqueous sodium bicarbonate. The mixture was then concentrated under reduced pressure to yield a thick oil (*ca.* 3.4 g) which was chromatographed on a 2 × 60 cm column of silicic acid (50 g, J. T. Baker) using *ca.* 250 ml of benzene followed by 400–500 ml of chloroform as eluents. The chloroform eluents were concentrated and distilled to yield the glycol monoethers. **Diethyl α-hydroxy-β-methoxyethylphosphonate (14)** [bp 108° (0.25 mm)] and **diethyl α-hydroxy-β-ethoxyethylphosphonate (15)** [bp 110° (0.25 mm)] were obtained from **3a**. **Dimethyl α-hydroxy-β-ethoxyethylphosphonate (18)**[54] [bp 105° (0.30 mm)] was obtained from **3b**. **Diethyl β-hydroxy-γ-methoxypropylphosphonate (21)** [bp 105° (0.16 mm)] and **diethyl β-hydroxy-γ-ethoxypropylphosphonate (22)** [bp 105° (0.2 mm)] were obtained from **4**. Compounds **14, 15, 18, 21,** and **22** were produced in 55–62% yield.

The glycol monoethyl ethers **15, 18,** and **22** were also obtained in 46–55% yield by refluxing a solution of 0.1 mol of the epoxide in 100 ml of benzene containing 0.2 mol of boron trifluoride etherate for 20 min. The reaction was washed with two 50-ml portions of water; the aqueous washings were saturated with sodium chloride and extracted with ether. The combined organic solutions were dried ($MgSO_4$) and reduced in volume to give a viscous liquid. Products were isolated by chromatography and distillation as in the preceeding experiment.

Reaction of Epoxides 3a and 4 with Aniline.—A mixture of 0.1 mol of the epoxide and 0.1 mol of freshly distilled aniline was heated in a sealed tube at 125° for 24 hr. The tube was cooled to −78° and opened, and the highly viscous reaction mixture was extracted repeatedly with hot absolute alcohol. The alcoholic extracts were then concentrated under reduced pressure to yield a pasty solid which was crystallized and recrystallized from a mixture of chloroform and ether. The products were dried under vacuum and the crystallization operations were carried out under an atmosphere of dry nitrogen because of the hygroscopic nature of the products. **Diethyl α-hydroxy-β-phenylaminoethylphosphonate (16)** [mp 95–97°; ir (Nujol) 3340–3160 (NH, OH), 1220 (P=O), 1170 (POC_2H_5), 1020 (PO–alkyl), 1600, 752, 695 cm^{-1} (C_6H_5); pmr (DMSO-d_6), τ 8.67 (t, CH_3COP), 5.4–7.1 (m, $-CH_2CH-$, $POCH_2$–, OH), 2.1–4.0 ppm (m, C_6H_5NH–)] was prepared from **3a** in 90% yield. **Diethyl β-hydroxy-γ-phenylaminopropylphosphonate (23)** [mp 91–92°; ir (Nujol) 3370–3150 (NH, OH), 1220 (P=O), 1150 (POC_2H_5), 1020 (PO–alkyl), 1598, 742, 690 cm^{-1} (C_6H_5)] was obtained from **4** in 88% yield.

Reaction of Epoxides 3a and 4 with Ammonia.—A mixture of 0.04 mol of the epoxide and 100 ml of aqueous ammonia (specific gravity 0.90) was allowed to stand at room temperature for 60 hr. The reaction mixture was concentrated under reduced pressure using a rotary evaporator to give a viscous residue. This residue was extracted with chloroform and the chloroform extracts were dried over magnesium sulfate. The products, **diethyl α-hydroxy-β-aminoethylphosphonate (17)** from **3a** and **diethyl β-hydroxy-γ-aminopropylphosphonate (24)** from **4**, were isolated as thick colorless to yellow oils by concentration of the chloroform solutions: ir (**17** and **24**, films) 3480–3160 (NH, OH), 1200 (P=O), 1158 (POC_2H_5), 1025 cm^{-1} (PO–alkyl). Both **17** and **24** decomposed on attempted vacuum distillation.

The amino alcohols were characterized by conversion into their acetyl derivatives. A solution of 1.5 g of **17** or **24** in 30 ml of acetic anhydride was refluxed for 2.5 hr. Excess acetic anhydride was removed under vacuum using a rotary evaporator to give a thick residue which was allowed to stand with 10 ml of water for 2 hr and then adjusted to pH 8.0 by the addition of saturated aqueous sodium carbonate. Water was removed under reduced pressure and the residue was extracted with chloroform.

(52) I. F. Lutsenko, M. Kirilov, and G. B. Postnikova, *J. Gen. Chem. USSR*, **32**, 257 (1962).

(53) The relative integrated intensities of the $POCH_2CH_3$ and PCH_2– resonances indicated **11** to be slightly contaminated by a $POCH_2CH_3$ system, although the structure of the contaminant could not be determined from the spectrum.

(54) Pmr (DMSO-d_6) τ 8.98 (t, CH_3COC–), 6.58 (m, $-CH_2OCH_2$–), 6.32 (d, $POCH_3$), 5.95 (m, –CHP–), 4.37 ppm (dd, J_{HH} = 6.9, J_{PH} = 10.0 Hz, OH). Both homo- (irradiation of 4.37 multiplet) and hetero- (24.3 MHz) nuclear decouplings resulted in the resolution of the 5.95-ppm multiplet into an analyzable eight-line pattern: J_{HOCH} = 5.1, 6.3, J_{HCOH} = 6.9, J_{PCH} = 11.1 Hz.

After drying ($MgSO_4$), the chloroform solution was concentrated and the residue distilled to yield the products. **Diethyl α-acetoxy-β-acetamidoethylphosphonate** (**19**) [bp 160° (0.25 mm); ir (film) 3300, 3080 (NH), 1745 (ester C=O), 1660 (amide C=O), 1220 (P=O), 1158 (POC_2H_5), 1018 cm^{-1} (PO-alkyl)] was obtained from **17** (30% yield from **3a**) and **diethyl β-acetoxy-γ-acetamidopropylphosphonate** (**25**) [bp 162° (0.25 mm); ir (film) 3300, 3075 (NH), 1735 (ester C=O), 1682 (amide C=O), 1217 (P=O), 1170 (POC_2H_5), 1020 cm^{-1} (PO-alkyl)] was obtained from **24** (75% yield from **4**).

Registry No.—**3b**, 19462-37-4; **7a**, 19462-38-5; **7b**, 19462-39-6; **13**, 19462-40-9; **14**, 19462-41-0; **15**, 19462-42-1; **16**, 19462-43-2; **18**, 19462-44-3; **19**, 19462-45-4; **20**, 1866-28-0; **21**, 19462-47-6; **22**, 19462-48-7; **23**, 19462-49-8; **24**, 19462-50-1; **25**, 19462-51-2; **26**, 19462-52-3; **27**, 19462-53-4; **28**, 19462-54-5; **29**, 19462-45-4; **30**, 19462-56-7.

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The Action of Hydrogen Fluoride on Nucleotides and Other Esters of Phosphorus(V) Acids[1,2]

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The action of hydrogen fluoride, both liquid and aqueous, on a number of mono- and diesters of orthophosphoric acid, two cyclic phosphates, mono and diesters of polyphosphates, phosphorofluoridate esters, and inorganic phosphates was investigated. The particular reactions which take place are found to be a function of temperature (−50 to +25°), time (0.04–28 hr), and acid concentration. A comparison of the acid-catalyzed reactions of phosphate esters in aqueous solution with the behavior of such compounds toward 60% hydrofluoric acid brings out several interesting contrasts. First, the reactions in 60% hydrofluoric acid which are described here are fast compared with reactions observed with ordinary aqueous acids. Second, in the reactions with 60% hydrofluoric acid all of the evidence points toward the conclusion that phosphorus–oxygen, rather than carbon–oxygen, bond cleavage takes place exclusively. Third, this acid is a highly specific dephosphorylating agent compared with ordinary aqueous acids. These three features of the chemical properties of hydrogen fluoride in relation to phosphorus(V) esters are correlated with information concerning the characteristics of hydrogen fluoride both as an anhydrous liquid and in concentrated aqueous solution. Since extended exposure to 60% hydrofluoric acid causes no deamination of adenine, guanine, or cytosine, a method was devised for the base analysis of ribonucleic acid (RNA) by degradation with this reagent.

Hydrogen fluoride, either as anhydrous liquid or aqueous solution (hydrofluoric acid), has been used relatively little in nucleotide chemistry in comparison with other areas of organic chemistry.[3] The structure proofs of A-3′:5′-P[4,5] and of the diastereoisomeric 2′:3′-benzylidene ribonucleosides[6] were dependent, in part, on degradations carried out with liquid hydrogen fluoride and hydrofluoric acid, respectively. Furthermore, 5-iodouridine 5′-triphosphate has been degraded with 60% hydrofluoric acid to 5-iodouridine 5′-phosphate and then to 5-iodouridine.[7]

The principal objective of this study was to investigate, in detail, the action of hydrogen fluoride on ordinary mononucleotides. The study includes, however, a broader spectrum of phosphorus compounds. It covers a number of mono- and diesters of orthophosphoric acid, two cyclic phosphates, mono- and diesters of polyphosphates, phosphorofluoridate esters, and inorganic phosphates. That the present results are of rather general interest is attested to by the fact that they already have been utilized to obtain structural information concerning the teichoic acids.[8]

Results and Discussion

Various acid-catalyzed reactions have been observed for nucleoside monophosphates in aqueous solution.

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(2) For a brief summary of the results of this investigation, see D. Lipkin, J. W. Abrell, and B. E. Phillips, Abstracts, Seventh International Congress of Biochemistry, Tokyo, Aug 1967, No. B-57, p 631.

(3) K. Wiechert in "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, New York, N. Y., 1948, pp 315–368.

(4) The abbreviations used follow: A-2′ (3′)-P, adenosine 2′(3′)-phosphate; A-5′-P, adenosine 5′-phosphate; A-2′:3′-P, adenosine 2′:3′- (cyclic) phosphate; A-3′:5′-P, adenosine 3′:5′- (cyclic) phosphate; A-5′-PF, adenosine 5′-phosphorofluoridate; ADP, adenosine 5′-diphosphate; APPA, P^1,P^2-diadenosine 5′-pyrophosphate; ATP, adenosine 5′-triphosphate; C-2′(3′)-P, cytidine 2′(3′)-phosphate; dA-5′-P, 2′-deoxyadenosine 5′-phosphate; DCC, dicyclohexylcarbodiimide; DNA, deoxyribonucleic acid; DPN, diphosphopyridine nucleotide; 2-dR-5-P, 2-deoxyribose 5-phosphate; G-2′(3′)-P, guanosine 2′(3′)-phosphate; Me A-5′-P, methyl ester of adenosine 5′-phosphate; Nam, nicotinamide; NR, nicotinamide riboside; NR-5′-P, nicotinamide riboside 5′-phosphate; NR-5′-PF, nicotinamide riboside 5′-phosphorofluoridate; RNA, ribonucleic acid; T-3′-P, thymidine 3′-phosphate; T-5′-P, thymidine 5′-phosphate; Tris, tris(hydroxymethyl)aminomethane; U-2′(3′)-P, uridine 2′(3′)-phosphate.

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(8) L. Glaser and M. M. Burger, *ibid.*, **239**, 3187 (1964).