Total Dealkylation of Esters of Trivalent Phosphorus and Promotion of Anhydride Formation by *N,N,N′,N′*-Tetramethylchloroformamidinium Chloride

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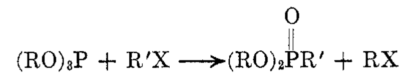
N,N,N′,N′-Tetramethylchloroformamidinium chloride (1) exhibits two unusual reactions with esters of trivalent phosphorus acids. (1) It fully dealkylates the esters, in most cases, giving tetramethylformamidinium phosphorus(V) compounds. (2) It extracts oxygen from the resulting acid anions, causing condensation to anhydrides, an effect that 1 may have on acid anions in general. The reaction of 1 with trialkyl phosphites at ordinary temperatures results in the formation of the double inner salt (*N,N,N′,N′*-tetramethylformamidinium)phosphonic anhydride, $[(Me_2N)_2C^+PO_2^-]_2O$, along with tetramethylurea and alkyl chloride; presumably, the esters $(Me_2N)_2C^+P(O)(OR)_2Cl^-$ and $(Me_2N)_2C^+P(OR)O_2^-$ are intermediates. Basic hydrolysis of the anhydride gives disodium dimethylcarbamylphosphonate. Acid hydrolysis converts it to (*N,N,N′,N′*-tetramethylformamidinium)phosphonic acid. Diethyl phenylphosphonite, $PhP(OEt)_2$, and 1 give *N,N,N′,N′*-tetramethyl(ethoxyphenylphosphinyl)formamidinium chloride, which readily loses ethyl chloride, forming the inner salt (*N,N,N′,N′*-tetramethylformamidinium)phenylphosphinate, $(Me_2N)_2C^+P(Ph)O_2^-$. Ethyl diphenylphosphinite, Ph_2POEt, undergoes a normal Michaelis–Arbuzov reaction with 1, giving *N,N,N′,N′*-tetramethyl(diphenylphosphinyl)formamidinium chloride, $Ph_2P(O)C^+(NMe_2)_2Cl^-$. Structural identifications were made principally by nmr (^{31}P and ^1H) spectroscopy and X-ray crystallography.

In the normal course of the reaction of a trialkyl phosphite ester with an alkyl halide, a carbon–phosphorus bond is formed, a carbon–oxygen bond is cleaved, and phosphorus is converted from trivalency to pentavalency. This is the classical Michaelis–Arbuzov reaction.[1-3]



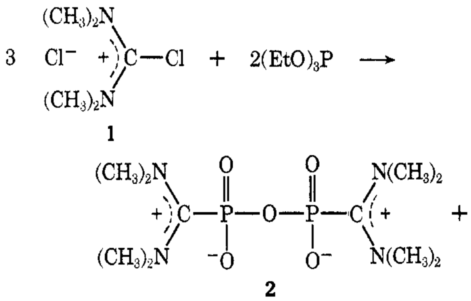
$$(RO)_3P + R'X \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}R' + RX$$

The resulting phosphonate ester is relatively unreactive compared to the phosphite precursor, and further structural changes do not ordinarily occur readily. Alkyl exchange reactions with phosphonates and phosphinates have been shown to take place as side effects in certain Michaelis–Arbuzov reactions at high temperatures. For example, Harwood and Grisley found that, when dimethyl phenylphosphonite and β-bromoethylacetate were warmed at 160–175° for 5 hr, β-acetoxyethyl phenyl(methyl)phosphinate was the major product rather than the expected methyl phenyl(β-acetoxyethyl)phosphinate;[4] and Laughlin found that 40% of the product obtained when trimethyl phosphite and dodecyl bromide were warmed at 180–200° for 20 hr was the alkyl exchange product, methyl dodecyl methylphosphonate.[5] Chlorides required even higher temperatures (200–250°) for exchange.[6]

This paper describes a new multistep reaction in which all three alkyl groups of trialkyl phosphites are rapidly cleaved at ordinary temperatures by *N,N,N′,N′*-tetramethylchloroformamidinium chloride (1).[7] Besides causing the displacement of the alkyl groups, 1 extracts oxygen from phosphorus, resulting in the formation of a dizwitterionic phosphonic anhydride. Related transformations of phosphonite and phosphinite esters are also described.

Results and Discussion

When triethyl phosphite was mixed with 1 in acetonitrile, a moderate temperature rise was observed, followed a short time later by separation of a white, crystalline product, mp 272–274° dec. This product exhibited only a single line in both its ^1H and ^{31}P nmr spectra. The proton resonance occurred at δ 3.45, a position typical of amidinium *N*-methyl groups (*e.g.*, 1 has a singlet at δ 3.43). These results, along with mass spectra, elemental analyses, molecular weight measurement, and identification of by-products (*cf.* Experimental Section), suggested the phosphonic anhydride–inner salt, structure 2, formed according to the following equation.



$(CH_3)_2NCON(CH_3)_2 + 6EtCl$

Based on this equation, the yield of 2 was 61%. Trimethyl and tris(2-chloroethyl) phosphites gave 82 and 29% yields of 2, respectively. Tetramethylurea and the appropriate chlorides (ethyl and methyl chloride and ethylene dichloride) were formed in approximately the amounts called for by the above equation. In one case tetramethylurea was isolated and identified by its nmr and mass spectra and glc retention time.

The presence of the anhydride linkage in 2 was supported by changes that occurred during hydrolysis and methanolysis. After hydrolysis with aqueous acid, the ^{31}P nmr spectrum consisted of a single line 8.9 ppm downfield from the line assigned to 2 (14.2 ppm in H_2O); however, after methanolysis (dry HCl in methanol), two signals of equal area were present, a singlet 8.3 ppm downfield from that of 2 and a quartet (J_{POCH_3} = 12 Hz) 10 ppm downfield. The proton

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(1) A. Michaelis and R. Kaehne, *Ber.*, **31**, 1048 (1898).

(2) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).

(3) R. G. Harvey and E. R. DeSombre "Topics in Phosphorus Chemistry," Vol. 1, Interscience, New York, N. Y., 1964.

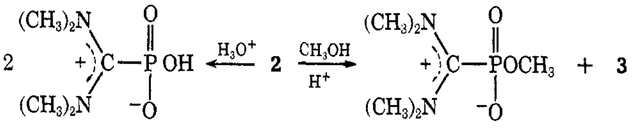
(4) H. J. Harwood and D. W. Grisley, *J. Amer. Chem. Soc.*, **82**, 423 (1960).

(5) R. G. Laughlin, *J. Org. Chem.*, **27**, 1005 (1962).

(6) V. V. Korshak, I. A. Gribova, and V. K. Shitikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 210 (1958); *Chem. Abstr.*, **52**, 12804 (1958).

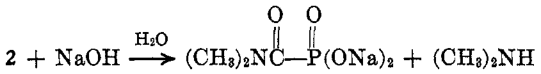
(7) H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, **97**, 1232 (1964).

nmr spectrum of the methanol solution contained a doublet at δ 3.73 (J_{CH_3OP} = 12 Hz). The patterns and positions of these resonances are consistent with the formation of acid **3** and methyl ester **4** from **2**, changes that only an anhydride could undergo.



3 **4**

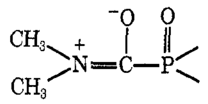
The presence of P–C bonds in **2** was demonstrated by hydrolysis with aqueous NaOH to disodium *N*,*N*-dimethylcarbamylphosphonate (**5**).



$$2 + \text{NaOH} \xrightarrow{\text{H}_2\text{O}} (CH_3)_2N\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{P}}(ONa)_2 + (CH_3)_2NH$$

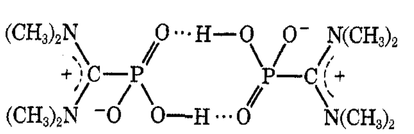
5

The ¹H nmr spectrum of **5** contained doublets of equal areas at δ 3.23 (*J* = 1.2 Hz) and 2.84 (*J* = 1.2 Hz), reflecting dissimilar environments for the methyl groups and the coupling of each with phosphorus. Diethyl *N*,*N*-dimethylcarbamylphosphonate has a similar pair of ¹H nmr doublets for the nitrogen-bonded methyl groups. This nonequivalence of the methyl groups, characteristic also of *N*,*N*-dimethylcarboxamides, results, presumably, from existence of the carbamyl phosphonates to some degree in the charge-separated state



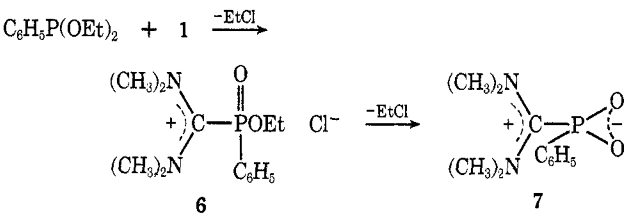
Final confirmation of structure **2** was provided by an X-ray crystal structure study carried out by J. J. Daly.[8] This study showed that the P–O–P angle is bent at 126°, the P–O bond lengths in this group being 1.617 Å. The remaining P–O bond lengths average 1.469 Å. The P–C bond length is 1.878 Å, slightly longer than found in other phosphonates. The C–N bond lengths (average 1.330 Å) at the central carbon atom are close to the conjugated heterocyclic value (1.339 Å) and are characteristic of formamidinium compounds.[8]

For an anhydride, **2** is surprisingly resistant to hydrolysis. In one experiment a sample was recovered unchanged after having been in neutral aqueous solution for 24 hr at room temperature. As mentioned, **2** hydrolyzes in dilute aqueous acids to the acid **3**. Crystals of **3** (³¹P nmr 5.8 ppm in CH₃OH) were inadvertently obtained when **2** was recrystallized from moist chloroform. A crystal structure study showed that **3** forms hydrogen-bonded dimers (**3a**) across centers of symmetry (O···O = 2.57 Å across the hydrogen bond). Its P–C and C–N bond lengths are close to those of the anhydride **2**.[8]



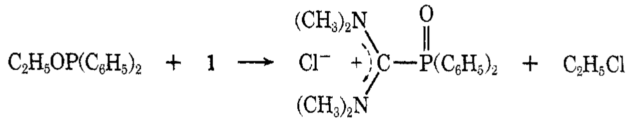
3a

While an attempt to isolate an intermediate in the formation of **2** was unsuccessful even when an excess of trimethyl phosphite was used, the addition of **1** to an excess of diethyl phenylphosphonite gave *N*,*N*,*N'*,*N'*-tetramethyl(ethoxyphenylphosphinyl)formamidinium chloride (**6**), an isolable product which could be converted to the stable inner salt, (*N*,*N*,*N'*,*N'*-tetramethylformamidinium) phenylphosphinate (**7**), by gentle warming. The phenyl group evidently has a stabilizing effect on **6**.



6 **7**

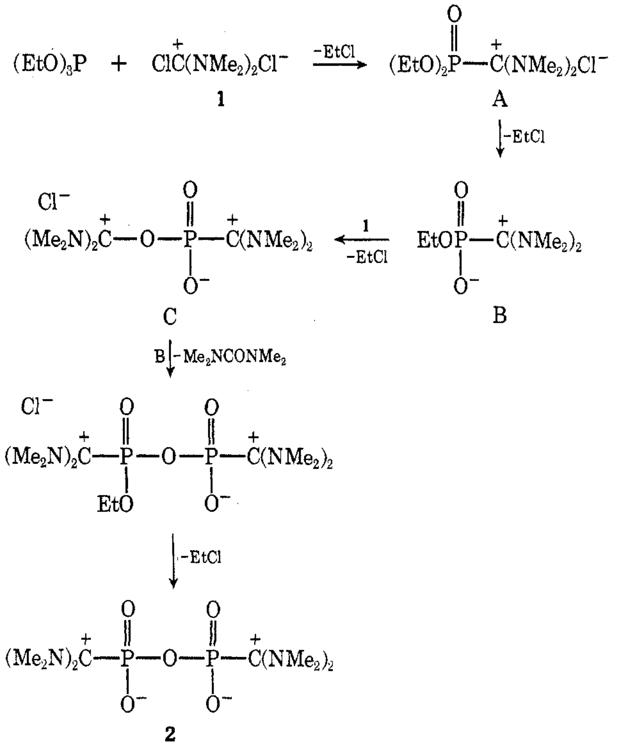
Ethyl diphenylphosphinite, having only one displaceable alkyl group, was limited to a normal Michaelis–Arbuzov reaction with **1**, giving the outer salt, *N*,*N*,*N'*,*N'*-tetramethyl(diphenylphosphinyl)formamidinium chloride (**8**).



8

The reaction of **1** with trialkyl phosphites presumably proceeds according to Scheme I. The covalently bonded chlorine on **1** is displaced by phosphorus *via* a typical Michaelis–Arbuzov reaction, giving ethyl chloride and intermediate A. The presence of the cationic center adjacent to phosphorus apparently weakens the remaining alkyl–oxygen bonds to the extent that

SCHEME I



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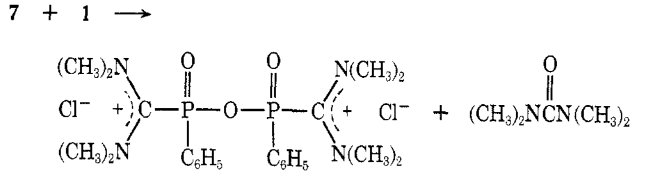
[8] J. J. Daly, submitted for publication in *J. Chem. Soc.*

another molecule of ethyl chloride is lost, giving a second intermediate, B, which can react with more **1** to form uronium salt C. Displacement of tetramethylurea from C by a molecule of B and then cleavage of the remaining *O*-ethyl group leads to the final product, **2**.

The effectiveness of **1** in converting an intermediate of **2** to the anhydride suggested that it might be possible to similarly convert **7** to its anhydride by treatment with **1**. The product from this reaction was a viscous liquid that could not be induced to crystallize, possibly because of the presence of two asymmetric centers. Formation of the required amount of tetramethylurea and a ^{31}P nmr change from −9.0 ppm for **7** to −19.0 ppm for the product (related structure **6** has −20.6 ppm) indicated that the anhydride **9** may have been formed.



9

Preliminary results suggest that **1** may also convert other acid anions, *e.g.*, acetate, to their corresponding anhydrides.

Experimental Section

Melting points were obtained in a Thomas-Hoover Unimelt instrument. Infrared spectra were determined in potassium bromide disks on a Beckman IR-4 spectrophotometer. Proton nuclear magnetic resonance (nmr) spectra were obtained at 60.0 or 100.0 MHz on Varian T-60 or HR-100 spectrometers with tetramethylsilane as an internal standard. Phosphorus nmr spectra were determined at 24.3 or 40.5 MHz on Varian HR-60 or HR-100 instruments and are reported with respect to 85% H_3PO_4 contained in a capillary. The nmr measurements were generally made on saturated solutions. Mass spectra were obtained on a Consolidated Engineering Corp. Type 21-104 spectrometer fitted with a probe for direct introduction of solids. Elemental analyses and molecular weights were determined by Galbraith Laboratories, Knoxville, Tenn.

(*N,N,N',N'*-Tetramethylformamidinium)phosphonic Anhydride (2).—A 20.5-g (0.12 mol) portion of *N,N,N',N'*-tetramethylchloroformamidinium chloride (**1**)[7] (^1H nmr δ 3.43 ppm) was stirred with 40 g of dry acetonitrile under N_2 in a drybox as 13.3 g (0.08 mol) of freshly distilled triethyl phosphite was added dropwise in 5 min. The temperature of the uncooled reaction mixture increased to 40°, and all of the solid **1** dissolved to give a clear, colorless solution from which a white solid began separating after about 35 min. Stirring at room temperature was continued overnight. The reaction mixture was then filtered under N_2, and the solid was washed with CH_3CN and dried to give 7.9 g (58% yield), mp 272–274° dec; 7.4 g with the melting point unchanged was recovered after the product was stirred in 40 ml of boiling CH_3CN and filtered hot. The white solid had a ^{31}P nmr singlet at 13.0 ppm ($CDCl_3$); ^1H nmr δ 3.45 ppm (s); mass spectrum (70 eV) *m/e* 342 (molecular ion), 298, 270, 227, 163; ir (KBr) 3.43 (m), 6.60 (s), 7.16 (s), 7.8 (vs), 8.28 (m), 8.53 (m), 9.22 (s), 11.1 (vs), 11.46 (s), 13.66 μ (s); mol wt ($CHCl_3$) 340 (calcd 342).

Anal. Calcd for $C_{10}H_{24}N_4O_5P_2$: C, 35.08; H, 7.07; Cl, 0.00; N, 16.37; P, 18.10. Found: C, 34.94; H, 7.21; Cl, 0.12; N, 16.28; P, 18.35.

The filtrate contained a ^1H nmr singlet at δ 2.75 for tetramethylurea as well as a quartet at δ 3.63 and a triplet at δ 1.45 for ethyl chloride. In another preparation of **2** carried out under similar conditions (yield 61%), a sample of the liquid phase was removed before the filtration step and found by gas chromatography to contain 27.6% ethyl chloride (theory 30.8%) and 10.7% tetramethylurea (theory 9.2%).

The use of trimethyl phosphite with **1** at a 2:3 molar ratio gave a 74% yield of **2**. In another run, excess trimethyl phosphite was used in an attempt to limit the reaction to an intermediate stage. In this run 8.6 g (0.05 mol) of **1** was added in portions over a period of 1 hr to a stirred solution of 24.8 g (0.2 mol) of freshly distilled trimethyl phosphite and 25 g of dry CH_3CN under N_2 at room temperature. After this mixture was stirred overnight, an 82% yield of **2** was isolated.

Tris(2-chloroethyl) phosphite and **1** at a 2:3 molar ratio gave a 29% yield of **2**.

Hydrolysis of 2 with Sodium Hydroxide.—A solution of 1.7 g (0.005 mol) of **2** in 5 g of distilled H_2O was stirred as 0.025 mol of NaOH (10% aqueous solution) was added dropwise. Most of the water was allowed to evaporate, and the salt was washed twice with warm ethanol and dried to give 1.6 g of disodium *N,N*-dimethylcarbamylphosphonate, ^{31}P nmr 1.1 ppm (D_2O). Recrystallization of a portion from ethanol–water gave a white solid: ^{31}P nmr 1.1 ppm (D_2O); ^1H nmr δ 3.23 (d, 3, J = 1.2 Hz), 2.84 (d, 3, J = 1.2 Hz).

Anal. Calcd for $C_3H_6NNa_2O_4P$: C, 18.28; H, 3.07; N, 7.11; P, 15.72. Found: C, 18.48; H, 3.15; N, 7.26; P, 15.69.

Hydrolysis and Methanolysis of 2 in Acidic Solutions.—A solution of **2** in distilled H_2O had a ^{31}P nmr singlet at 14.2 ppm and a ^1H nmr singlet at δ 3.35. After standing for 24 hr at room temperature, the H_2O was removed at 0.2 mm over $CaSO_4$ to give a white solid having a melting point and ir and nmr spectra identical with those of **2**.

When a catalytic amount of hydrochloric acid was added to a solution of **2** in distilled H_2O, a new ^1H nmr peak began forming at δ 3.32. This new peak represented ~60% of the total peak area after 2 hr and 100% after 24 hr. A new ^{31}P nmr peak formed at 5.3 ppm.

A solution of **2** in anhydrous trifluoroacetic acid showed a ^{31}P nmr peak at 15.4 ppm and a ^1H nmr peak at δ 3.47. When H_2O was slowly added to this solution, the ^{31}P peak gradually decreased and was finally completely converted to a new peak at 4.8 ppm; at the same time the ^1H peak at δ 3.47 disappeared and a new peak formed at δ 3.43.

A solution of **2** in methanol showed a ^{31}P nmr peak at 14.6 ppm. As trifluoroacetic acid was slowly added, this peak disappeared and peaks of about equal areas formed at 4.6 (q, J = 12 Hz, $POCH_3$) and 6.3 (s); the ^1H nmr spectrum had a doublet at δ 3.73 (J = 12 Hz, $POCH_3$) as well as a singlet at δ 3.46 for NCH_3.

***N,N,N',N'*-Tetramethyl(ethoxyphenylphosphinyl)formamidinium Chloride (6).**—An 8.6-g (0.05 mol) portion of **1** was added in about 1-g portions to 29.7-g (0.15 mol) of diethyl phenylphosphonite which was stirred under N_2. Stirring was continued overnight at room temperature, giving a thick, white slurry. Benzene was added to aid stirring, the reaction mixture was filtered, and the solid was washed with benzene and ether and dried at room temperature to give 11.5 g (96% yield) of white solid (**6**): mp 94–95° (with foaming); ^{31}P nmr ($CDCl_3$) −20.6 ppm (on fresh solution); ^1H nmr δ 1.51 (t, 3, J = 7 Hz, CH_2CH_3), 3.60 (s, 12, NCH_3), 4.55 (m, 2, $J \cong 7$ Hz, CH_2CH_3), 7.5–8.2 (m, 5, C_6H_5). When nmr measurements were not made immediately on a freshly prepared solution, new ^1H peaks and a new ^{31}P peak developed; after 2 days the ^{31}P peak at −20.6 ppm was replaced by a peak at −9.6 and the ^1H peak at δ 3.60 was replaced by a peak at 3.36.

(*N,N,N',N'*-Tetramethylformamidinium)phenylphosphinate (Inner Salt) (7).—Diethyl phenylphosphonite, 6.0 g (0.03 mol), was added rapidly to a stirred mixture of 5.1 g (0.03 mol) of **1** in 10 g of dry CH_3CN under N_2. The heat of reaction raised the temperature to 52°, and all of the solid dissolved. Stirring was continued at room temperature for 20 hr, and then the clear solution was diluted with ether, which caused 4.7 g of white solid to separate. Recrystallization twice from diglyme–CH_3CN gave 3.6 g (50% yield) of **7**: mp 186–188°; ^{31}P nmr ($CDCl_3$) −9.0 ppm; ^1H nmr δ 3.30 (s, 12, CH_3), 7.2–7.9 (m, 5, C_6H_5); ir (KBr) 2.9 (m), 6.32 (s), 7.17 (m), 7.97 (s), 8.80 (s), 9.40 μ (s).

Anal. Calcd for $C_{11}H_{17}N_2O_2P$: C, 54.99, H, 7.13, N, 11.66; P, 12.89. Found: C, 55.08; H, 7.08, N, 11.76; P, 12.77.

In another preparation of **7** a 5.0-g portion of **6** in 25 ml of diglyme was stirred and warmed at 115–120° as enough CH_3CN was added to give a clear solution. After 5 min at this temperature, the reaction mixture was cooled and filtered. The solid obtained was recrystallized from diglyme–CH_3CN to give 2.3 g of **7**, mp 186–188°, and having nmr and ir spectra essentially identical with those of the product obtained by the first method.

Treatment of (*N,N,N',N'*-Tetramethylformamidinium)-phenylphosphinate (7) with *N,N,N'N'*-Tetramethylchloroformamidinium Chloride (1).—A mixture of 4.1 g (0.017 mol) of **7** and 1.45 g (0.0085 mol) of **1** in 10 g of dry CH_3CN was stirred under N_2 at room temperature for 22 hr. Nmr measurements on the resulting clear, slightly yellow solution showed a ^{31}P signal at −19.0 ppm and ^1H signals at δ 2.73 (s, 12), 3.43 (s, 24), and 7.6–8.4 (m, 10). The ^1H signal at δ 2.73 was enhanced by addition of tetramethylurea. Stripping of the reaction mixture at reduced pressure and extraction of the residue with ether left a gum having a ^{31}P nmr signal at −19.0 ppm and ^1H nmr signals at δ 3.45 (s, 24) and 7.6–8.4 (m, 10). It could not be induced to crystallize. Tetramethylurea was isolated from the ether extract and identified by mass spectra.

***N,N,N',N'*-Tetramethyl(diphenylphosphinyl)formamidinium Chloride (8).**—Ethyl diphenylphosphinite, 6.9 g (0.03 mol), was added dropwise to a stirred mixture of 5.1 g (0.03 mol) of **1** in 20 g of CH_3CN under N_2. All of **1** dissolved during the addition, and then another solid separated. The reaction mixture was stirred at room temperature overnight and then filtered to give 9.6 g (94% yield) of **8**, mp 137–138.5°. Recrystallization from acetonitrile gave a white solid: mp 137.5–138.5°; ^{31}P nmr −28.8 ppm; ^1H nmr δ 3.46 (s, 12, CH_3), 7.5–8.3 (m, 10, C_6H_5); ir (KBr) 2.9 (m), 6.3 (s), 6.95 (m), 7.15 (m), 8.3–8.4 (s), 8.95 (s).

Anal. Calcd for $C_{17}H_{22}ClN_2OP$: C, 60.62; H, 6.58; Cl, 10.53; N, 8.32; P, 9.20. Found: C, 60.33; H, 6.65; Cl, 10.54; N, 8.20; P, 9.07.

Registry No.—**1**, 13829-06-6; **2**, 34959-65-4; **5**, 34959-66-5; **6**, 34982-10-0; **7**, 34959-67-6; **8**, 34982-11-1.

Degradation of Penicillin G Methyl Ester with Trifluoroacetic Acid[1]

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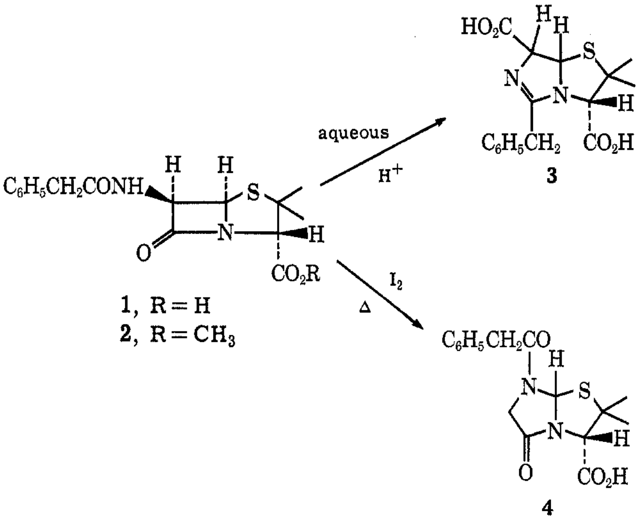
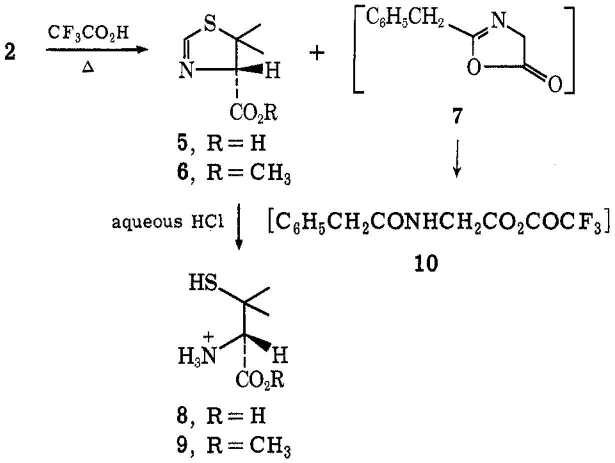
Penicillin G methyl ester (**2**) is degraded to methyl D-5,5-dimethyl-Δ^2-thiazoline-4-carboxylate (**6**) in trifluoroacetic acid. The *N*-phenylacetylglycyl fragment was isolated by conversion to its *N*-benzylamide. Methicillin and penillonic acid methyl esters were also degraded to **6**. A mechanism for the degradation is presented with special emphasis on the relationship to the penillic acid and penillonic acid rearrangements.

The penillic acid and the penillonic acid rearrangements are two well-known rearrangements of benzylpenicillin (**1**).[2] These rearrangements may be carried out by exposure of **1** to dilute aqueous mineral acid or by heating **1** in toluene with iodine, processes which respectively yield penillic acid (**3**) and penillonic acid (**4**).





We have discovered a new and potentially useful degradation of benzylpenicillin which we believe is closely related in mechanism to the penillic acid and penillonic acid rearrangements.

The nmr spectrum of a solution of either benzylpenicillin (**1**) or its methyl ester (**2**) in trifluoroacetic acid (TFAA) which had been briefly warmed exhibited the characteristic nmr signals of the thiazolines **5** or **6**. To facilitate isolation of the thiazoline, degradation was performed on the ester **2**. Optically active D-thiazoline ester could be obtained easily in 50–60% yield. That the configuration at C-4 has been retained was shown by comparison of its melting point with that reported in the literature[3] and by hydrolysis to D-penicillamine (**8**).[4]

The fate of the phenylacetylglycyl portion of **2** is not known with certainty. The fragment has clearly retained the capacity to acylate, since addition of the reaction mixture to an excess of benzylamine in pyridine led to the isolation of the benzylamide of *N*-phenylacetylglycine. As a result there appear to be at least three choices among monomeric species for the structure of the phenylacetylglycyl fragment: the oxazolone **7**, the mixed anhydride **10**, and the acylaminoketene **11**. An analogous ketene has been pro-

$C_6H_5CH_2CONHCH{=}C{=}O$

11

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(1) A preliminary communication has been published: M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Amer. Chem. Soc.*, **92**, 2177 (1970).

(2) (a) A. H. Cook in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 126; (b) R. L. Peck and K. Folkers, ref 2a, p 188.

(3) Merck Report No. 63, p 18, April 1945, cited by H. M. Crooks, Jr., in ref 2a, p 1057.

(4) "The Merck Index," P. G. Stecher, Ed., Merck and Co., Rahway, N. J., 1968, p 789.