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Synthesis and Properties of Carbamate Derivatives of Tetrakis(hydroxymethyl)phosphonium Chloride

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Tetrakis(hydroxymethyl)phosphonium chloride (**1**) condenses with primary or secondary alkyl carbamates, forming stable quaternary phosphonium salts having the structure $(RO_2CNHCH_2)_4PCl$ (**3**) or $[EtO_2CN(R)CH_2]_4PCl$ (**6**). The alkyl carbamates are too feebly basic to cause the displacement of formaldehyde and HCl that characterizes the reaction of **1** with primary or secondary amines. The quaternary phosphonium salt **3a** (R = Me) undergoes halogen exchange, either by metathesis or by passage over an ion-exchange column, giving the corresponding iodide **9a** or bromide **11a**. Acid hydrolysis of **3a** unexpectedly regenerates **1**—a rare case of alkyl–nitrogen fission in a carbamate. The reaction of **3a** with sodium hydroxide is complicated by interaction of the product $(RO_2CNHCH_2)_3P$ (**13**) with the by-product $RO_2CN{=}CH_2$ (**16**), resulting in a different tertiary phosphine **15**, but this can be avoided by replacing the base by a reagent capable of reacting with the by-product, such as ammonium hydroxide, morpholine, or sodium sulfite. Oxide and sulfide derivatives of **13** are described.

The development of durable flame-retardant finishes for cotton based on the reaction of tetrakis(hydroxymethyl)phosphonium chloride (**1**) with trimethylolmelamine and urea[2] has led to the investigation of many other nitrogen compounds as resin-forming substrates.[3] The alkyl carbamates are particularly appealing in this respect, for they are the substrates of another important set of cotton finishes, the durable-press finishes.[4] Some attempts have been made to combine these properties in a single finish, without notable success.[5–7] In this paper, we report our investigation of the reaction of **1** with alkyl carbamates, leading to a series of novel nitrogen-containing quaternary phosphonium salts and their tertiary phosphine, phosphine oxide, and phosphine sulfide derivatives.

Quaternary Phosphonium Salts. Condensation of the phosphonium salt **1** with the alkyl carbamates **2a–e** took place in refluxing toluene (bp 110 °C) with azeotropic removal of the water, giving tetrakis(*N*-carbalkoxylaminomethyl)phosphonium chlorides (**3a–e**) in moderate to good yield (eq 1).[8,9]

$$\underset{\mathbf{1}}{(HOCH_2)_4PCl} + 4\underset{\mathbf{2}}{RO_2CNH_2} \rightarrow \underset{\mathbf{3}}{(RO_2CNHCH_2)_4PCl} + 4H_2O \quad (1)$$

a, R = Me; b, R = Et; c, R = *i*-Pr; d, R = *n*-Bu; e, R = $MeOCH_2CH_2$–

The methyl (**3a**), ethyl (**3b**), and isopropyl (**3c**) esters crystallized and were purified by recrystallization, giving yields of 86, 60, and 45%, respectively. The others were purified by adsorption on a cation-exchange resin, followed by displacement with hydrogen chloride, adopting a procedure developed for the analysis of tetramethylphosphonium chloride.[10,11] The 2-methoxyethyl ester **3e**, which is water soluble, was isolated in 53% yield as a viscous colorless oil. The *n*-butyl ester **3d**, which is not water soluble, was isolated in 38% yield as a viscous colorless oil, together with 21% of unreacted carbamate (**2d**) and 14% of di-*n*-butyl *N,N'*-methylenedicarbamate (**4d**).[12]

The products **3a–e** are air-stable, odorless compounds that, unlike **1**, are only mildly acidic in aqueous solution. Their infrared spectra are dominated by intense absorption bands at 1715 ± 10 (C=O, amide I) and 1525 ± 15 (NH, amide II) cm^{-1}, regions characteristic of secondary carbamates.[13] In the solid phosphonium salts **3a–c**, the amide I band appears as a sharp doublet in Nujol but as a singlet in solution. In KBr disks, the amide I band appears as a doublet in strong spectra and a singlet in weak spectra. This concentration dependence is ascribed to self-association (NH···OC) in the solid phase. Deuteration of **3b** with deuterium oxide shifts the free and hydrogen-bonded NH stretching bands and, to a lesser degree, the amide II band to lower frequencies in the expected manner.[14]

The ^1H NMR spectra of the phosphonium salts **3a–e** show that the four phosphorus substituents in each product are identical. Owing to coupling with NH, the PCH_2 protons appear as a triplet, which, upon shaking with D_2O, collapses to a doublet. The ^{31}P NMR spectra of **3a,b,d,e** all show a single peak at −30.5 ± 0.5 ppm, a region characteristic of phosphonium salts.[15] Molecular weight measurements on **3a** in water by vapor-phase osmometry give values that are just over half of the calculated value. These data are all consistent with the formulation of the compounds as phosphonium salts.

The condensation of **1** with **2b** also occurred in xylene (bp 139 °C), but not in benzene (bp 80 °C). Upon further investigation, it was found that removal of the water by azeotropic distillation was unnecessary. The phosphonium salt **3a** was prepared in 41% yield by heating **1** with **2a** in *n*-butyl alcohol (bp 117.5 °C), and in 80% yield by heating technical 80% **1** with **2a** to 110 °C in the absence of any solvent other than the water in the reagent.

Condensation of **1** with ethyl *N*-methylcarbamate (**5a**), a secondary carbamate, also took place in refluxing toluene with azeotropic removal of the water, giving tetrakis(*N*-carbethoxy-*N*-methylaminomethyl)phosphonium chloride (**6a**) in 31% yield (eq 2).

$$\underset{\mathbf{5}}{1} + 4EtO_2CNHR \rightarrow \underset{\mathbf{6}}{(EtO_2CN[R]CH_2)_4PCl} + 4H_2O \quad (2)$$

a, R = Me f, R ≠ Ph

The product, a mobile liquid, showed an unchanging PCH_2 doublet in the ^1H NMR, and no NH stretching or amide II absorption bands in the IR. The C=O, amide I bond at 1690 cm^{-1} was within the limits assigned to tertiary carbamates.[13] The ^{31}P NMR spectrum showed a single peak at −31.0 ppm, in the same region as **3**.

Ethyl carbanilate (**5f**) failed to react with **1**, either in toluene or xylene.

Condensation of (hydroxymethyl)triphenylphosphonium chloride (**7**) with methyl carbamate (**2a**) took place under the same conditions as with **1**, giving (*N*-carbomethoxylaminomethyl)triphenylphosphonium chloride (**8a**) as a white, crystalline solid in 73.1% yield (eq 3).

$$\underset{\mathbf{7}}{[Ph_3PCH_2OH]Cl} + \mathbf{2a} \rightarrow \underset{\mathbf{8a}}{[Ph_3PCH_2NHCO_2Me]Cl} + H_2O \quad (3)$$

The ^1H NMR spectrum of **8a** exhibits long-range coupling (2.0 Hz) between the NH and aromatic protons.[16] Similar coupling (3.5 Hz) is observed between OH and aromatic protons in **7**, but not in urea derivatives which have no NH proton in this position.[17]

Efforts to characterize the phosphonium salts **3a**, **3e**, or **6a** as the picrates[18] yielded only uncrystallizable yellow oils. Metathesis of the phosphonium chloride **3a** with sodium iodide in ethanol, however, gave the corresponding iodide, tetrakis(*N*-carbomethoxylaminomethyl)phosphonium iodide (**9a**), in 49.1% yield. Attempts to prepare **9a** directly from tetrakis(hydroxymethyl)phosphonium iodide (**10**) and **2a** were unsuccessful.

The corresponding bromide, tetrakis(*N*-carbomethoxylaminomethyl)phosphonium bromide (**11a**), was prepared from **3a** by adsorption on the ion-exchange column followed by displacement with hydrogen bromide instead of hydrogen chloride. The yield was 70.2%.

The foregoing experiments established beyond doubt that the products **3a–e**, **6a**, **8a**, **9a**, and **11a** are all quaternary phosphonium salts. The alkyl carbamates are too feebly basic to cause the characteristic displacement of formaldehyde and HCl that occurs when hydroxymethylphosphonium salts such as **1** or **7** react with primary, secondary, or tertiary amines.[19]

Acid Hydrolysis. Hydrolysis of the phosphonium salt **3a** with 6 N HCl at 110 °C gave, unexpectedly, a 68.0% yield of **1**, together with 92.0% of ammonium chloride (eq 4).

$$\mathbf{3a} + 8HCl + 4H_2O \rightarrow 1 + 4CO_2 + 4RCl + 4NH_4Cl \quad (4)$$

Carbamates, like amides, decompose by acyl– rather than alkyl–nitrogen fission, except when the alkyl substituent possesses unusual carbonium ion stability, as, for example, *t*-Bu.[20,21] We suggest that protonation of a nitrogen in **3a** renders the methylene group, flanked by positive charges on both sides, highly electron deficient and susceptible to nucleophilic attack by water:

$$\mathbf{3a} \overset{H^+}{\rightleftharpoons} RO_2\overset{+}{C}—\underset{H_2O}{\overset{\curvearrowleft}{NH_2}}—CH_2\overset{+}{P}— \rightleftharpoons RO_2CNH_2$$

$$+ H_2\overset{+}{O}—CH_2\overset{+}{P}— \overset{-H^+}{\rightleftharpoons} HOCH_2\overset{+}{P}—$$

The alkyl carbamate displaced in this reaction is subsequently hydrolyzed to RCl, CO_2, and ammonium chloride;[21] the other product, through successive reactions, ultimately yields **1**.[22]

The hydrolysis of **3a** also yielded a small amount (7.3%) of bis(hydroxymethyl)methylphosphine oxide (**12**), a by-product of the acid degradation of **1**.[23]

Alkaline Hydrolysis. Hydrolysis of the phosphonium salt **3a** with aqueous sodium hydroxide was expected to give tris(*N*-carbomethoxylaminomethyl)phosphine (**13a**), together with methyl (hydroxymethyl)carbamate (**14a**) (eq 5).

$$\mathbf{3} + NaOH \rightarrow \underset{\mathbf{13}}{(RO_2CNHCH_2)_3P} + \underset{\mathbf{14}}{RO_2CNHCH_2OH} + NaCl \quad (5)$$

Some **13a** separated from the reaction mixture as a white, crystalline solid, but the major product was a water-soluble tertiary phosphine **15a** which could not be induced to yield any **13a** after workup.[24] The yield of **13a** varied from 0 to 29%, depending on the reaction conditions. Barium hydroxide, the preferred catalyst for condensing carbamates with formaldehyde,[25,26] gave a 21% yield of **13a**. Other moderately strong bases, such as sodium bicarbonate, disodium phosphate, trisodium phosphate, or triethylamine, gave yields in the 40 to 60% range. Sodium hydroxide buffered with borax or phosphate also gave yields in this range. Yields of 87 to 92%, approaching the quantitative, were only attained with reagents that were capable of reacting with the by-product **14a**, viz., ammonium hydroxide,[19] morpholine, or sodium sulfite (Table I).[27]

The (hydroxymethyl)carbamate **14a**, which is prone to undergo self-condensation[25] or reaction with formaldehyde[28] in the presence of alkaline catalysts such as sodium hydroxide, did not react with **13a** at room temperature but did upon

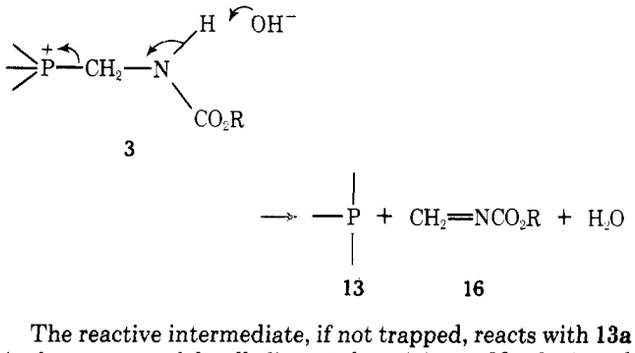
Table I. Hydrolysis of 3a with Various Bases

Base	Conditions	13a (% yield)
NaOH	100 °C, 15 min	29.1[a]
NaOH (borax)	100 °C, 15 min	42.7
NaOH (Na_2HPO_4)	100 °C, 15 min	43.7
NaOH (Na_2HPO_4)	60 °C, 90 min[b]	45.0
$Ba(OH)_2$[c]	100 °C, 1 h	21.0
$NaHCO_3$	100 °C, 1 h	60.1[d]
Na_2HPO_4	100 °C, 1 h	60.3
Na_3PO_4[c]	100 °C, 30 min	48.2
Et_3N	100 °C, 30 min	53.4
Et_3N	25 °C, 3 h	54.1[e]
Morpholine	100 °C, 1 h	46.7
Morpholine	25 °C, 2 h	90.6[f]
NH_4OH	25 °C, 2 h	87.0
Na_2SO_3	100 °C, 1 h	92.5

[a] Yield raised to 51.3% by subsequent treatment with ammonium hydroxide. [b] Sodium hydroxide solution added dropwise to the buffered **3a** solution during the first 45 min. [c] Mixture yellowed when the amount of base was doubled. [d] Subsequent treatment with 6 N HCl regenerated only 24.4% of the **3a**. [e] Yield unaffected by subsequent treatment with ammonium hydroxide or sodium bisulfite. [f] Together with 93.5% of morpholine hydrochloride, mp 175–176 °C (lit.[31] mp 175–176 °C).

heating to 100 °C, giving a colorless, neutral oil having the same properties (IR, solubility) as those of **15a**.

We suggest that the reactive species in these reactions is not **14a** but its anhydro precursor, methyl *N*-methylenecarbamate (**16a**), which is formed from **3a** by β-elimination of **13a**.



3

13 **16**

The reactive intermediate, if not trapped, reacts with **13a** in the presence of the alkaline catalyst giving an N-substituted tertiary phosphine **15a** from which no **13a** can be recovered.[29,30]

The tertiary phosphine **13a** is an air-sensitive white, crystalline solid. It dissolves readily in 6 N HCl, and precipitates unchanged upon neutralization. Oxidation of **13a** with hydrogen peroxide in acetone gave tris(*N*-carbomethoxylaminomethyl)phosphine oxide (**17a**) in 81.0% yield, and reaction with sulfur in benzene gave tris(*N*-carbomethoxylaminomethyl)phosphine sulfide (**18a**) in 73.4% yield. Both derivatives were crystalline. Their structures were confirmed by IR, NMR, and elemental analysis.

None of the carbamate derivatives described in this paper exhibited the sensitivity to base that is characteristic of the hydroxymethyl compounds 1,[32-34] tris(hydroxymethyl)-phosphine,[35,36] or tris(hydroxymethyl)phosphine oxide.[33,36] No hydrogen evolution was observed even when the carbamate derivatives were heated to boiling with concentrated sodium hydroxide solution. This could be used to advantage to detect and destroy any $HOCH_2P$-containing impurities that might be present in these substances.

Other Reactions. Several attempts were made to develop independent synthetic routes toward the carbamate derivatives **3**, **13**, or **17**. No reaction occurred between methyl (hydroxymethyl)carbamate (**14a**) and phosphine in the presence of hydrochloric acid[37] (to give **3a**), or cadmium chloride catalyst[38] (to give **13a**), nor between **14a** or **14b** and white phosphorus[39] (to give **17a** or **17b**).

Experimental Section[40,41]

Reagents. Tetrakis(hydroxymethyl)phosphonium chloride (**1**) was dried by azeotropic distillation with benzene and recrystallized from 2-propanol, mp 149–149.5 °C. (Hydroxymethyl)triphenylphosphonium chloride (**7**), mp 190–192 °C, was prepared from triphenylphosphine:[42] ^1H NMR (Me_2SO-d_6) δ 5.76 (s, 2 H, CH_2), 6.25 (s, ~1 H, OH), and 7.9 (m, 15 H, C_6H_5; doublet at δ 7.95, J = 3.5 Hz collapsing with D_2O to a singlet, δ 7.96). In $CDCl_3$: ^1H NMR δ 5.52 (lit.[43] δ 5.51), 6.62, and 7.8, respectively; same behavior in the aromatic region. Other reagents were used as obtained, except for **5a** and triethylamine, which were redistilled.

Tetrakis(*N*-carbomethoxylaminomethyl)phosphonium Chloride (3a). (A) From Crystalline 1. A mixture of **1** (47.64 g, 0.25 mol), **2a** (75.07 g, 1.00 mol), and toluene (200 mL) was heated to reflux in an apparatus fitted with a Dean–Stark trap for azeotropic removal of the water. The mixture was held at reflux until the evolution of water ceased; after 2.5 h, 18.5 mL (1.03 mol) had been collected. The product crystallized on standing to a hard mass and was broken up, triturated under ethyl acetate, filtered, and dried, giving 90.67 g (86.5%) of **3a**, mp 177 °C (dec). Two recrystallizations from ethanol afforded pure **3a** as a white, crystalline solid: mp 189 °C (dec); IR (Nujol) 1540 (vs; NH, amide II), 1700 and 1740 [s and vs; C=O, amide I; doublet in Nujol, but a singlet, 1730 (vs), in Me_2SO], 3220 (m; NH, bonded), and 3300 (m; NH, free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.63 (s, 12 H, CH_3), 4.32 (t, 8 H, CH_2, J = 5.0 Hz, collapsing with D_2O to d, J = 4.0 Hz), and 8.05 (m, ~4 H, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO), δ −30.7.

Anal. Calcd for $C_{12}H_{24}ClN_4O_8P$: C, 34.41; H, 5.78; Cl, 8.47; N, 13.38; P, 7.40; mol wt, 419. Found: C, 34.64; H, 5.66; Cl, 8.71; N, 13.24; P, 7.53; mol wt (osmometric in H_2O), 249, 259.

The phosphonium salt **3a** is partially soluble in water, Me_2SO (7 mL/g), and methanol, and insoluble in other common organic solvents. Its aqueous solution is mildly acidic (pH 4.5). It can be recrystallized from ethanol (20 mL/g) or 2-propanol (75 mL/g), and is air stable, nonhygroscopic, and odorless.

(B) From Technical 1. For large-scale preparation, it is more convenient to use the commercially available 80% aqueous **1** solution (THPC)[44] and omit the azeotropic distillation. A large flask was charged with 80% THPC (1191 g, 5 mol) and half of the **2a** (1501 g, 20 mol) was heated briefly to 100 °C, allowed to cool to 65 °C, charged with the remainder of the **2a**, and heated at gentle reflux (110 °C) for 3 h. The next day the crystalline mass was broken up, triturated in portions with ethanol, filtered, and allowed to air-dry in evaporating dishes. The product **3a**, 1472 g, was a white, crystalline solid, mp 189 °C (dec) (70.3%). Workup of the mother liquor raised the yield to 80.1%.

Tetrakis(*N*-carbethoxylaminomethyl)phosphonium Chloride (3b). Reaction of **1** (47.64 g, 0.25 mol) with **2b** [Caution: carcinogenic[45]] (89.10 g, 1.00 mol), following procedure A, gave 71.53 g (60.2%) of **3b** as a white, crystalline solid, mp 112–13 °C, after two recrystallizations from ethyl acetate: IR (Nujol) 1515 and 1535 (vs and s, NH, amide II), 1680 and 1730 (both s, C=O, amide I; doublet in Nujol or concentrated KBr changing to singlet in $CHCl_3$ or dilute KBr), 3230 (m, NH bonded), and 3360 (w, NH free) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 12 H, CH_3, J = 7.0 Hz), 4.17 (q, CH_2C, J = 7.0 Hz), 4.42 (m, PCH_2, collapsing with D_2O to d, δ 4.46, J = 3.0 Hz; total CH_2, 16 H), and 7.43 (m, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO) δ −31.2.

Anal. Calcd for $C_{16}H_{32}ClN_4O_8P$: C, 40.46; H, 6.79; Cl, 7.47; N, 11.80; P, 6.52. Found: C, 40.49; H, 6.80; Cl, 7.59; N, 11.60; P, 6.61.

The phosphonium salt **3b** is soluble in water, ethanol, chloroform, benzene, Me_2SO (1.5 mL/g), and acetone, and insoluble in ether, carbon tetrachloride, and cyclohexane. Its aqueous solution is mildly acidic. It is readily recrystallized from ethyl acetate (5 mL/g), but tends to oil out from hot carbon tetrachloride or toluene.

Upon deuteration, the free and H-bonded NH bands in the IR spectrum of **3b** were shifted from 3360 and 3230 cm^{-1} to 2500 and 2370 cm^{-1}, respectively, and the amide II doublet was shifted from 1515 and 1535 cm^{-1} to (Nujol-masked) and 1425 cm^{-1}. The hydrogens were exchanged by dissolving **3b** in D_2O, stripping in a rotary evaporator, and drying in a vacuum desiccator. This sequence was repeated twice.

Tetrakis(*N*-carbisopropoxylaminomethyl)phosphonium Chloride (3c). Reaction of **1** (9.53 g, 0.05 mol) with **2c** (20.62 g, 0.20 mol), following procedure A but using ether instead of ethyl acetate,

gave 9.32 g (45.6%) of **3c** as a white, crystalline solid, mp 140–41 °C, after two recrystallizations from water: IR (Nujol), 1510 (s, NH, amide II), 1720 and 1730 (s and vs, C=O, amide I), 3220 (m, NH bonded), and 3320 (m, NH free) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 24 H, CH_3, J = 6.0 Hz), 4.44 (br s, CH_2, resolved with D_2O to d, δ 4.46, J = 3.0 Hz), 4.94 (m, CH, J = 6.0 Hz; combined CH_2 and CH, 12 H), and 7.31 (m, 4 H, NH, vanishing with D_2O).

Anal. Calcd for $C_{20}H_{40}ClN_4O_8P$: C, 45.24; H, 7.59; Cl, 6.68; N, 10.55; P, 5.83. Found: C, 45.11; H, 7.37; Cl, 6.63; N, 10.74; P, 5.94.

The phosphonium salt **3c** is soluble in ethanol, chloroform, carbon tetrachloride, and benzene, and insoluble in ether. It can be recrystallized from ethyl acetate (10 mL/g) or water (3 mL/g).

Ion-Exchange Method. Fifty grams of the resin (Bio-Rad AG 50W-X4), a high porosity nuclear sulfonic acid cation-exchange resin suitable for organic ions of mol wt 300–400 or over,[46] was charged into a 19 × 600 mm chromatographic column with a sealed-in coarse-fritted disk, backwashed thoroughly with water, and rinsed with water until the effluent was neutral and chloride free.

A solution of **3a** (4.19 g, 10.0 mmol) in warm water (30 mL) was transferred to the column and eluted with water, collecting the effluent in 50-mL fractions at a flow rate of 30 drops/min. The top 2 in. of the resin lightened noticeably. Titration of the first five effluent fractions with 0.1 N NaOH gave 2.42, 7.32, 0.04, 0.02 and 0.01 mmol of HCl for a total of 9.82 mmol (98.2%). The resin was then eluted with 6 N HCl at the same flow rate, causing the resin to contract from 12 to 8.5 in., and restoring its original color. The effluent, collected in 50-mL fractions and stripped carefully in a rotary evaporator at 50 °C/3 mm, yielded 0, 2.26, 1.31, 0.57, and 0.31 g of crystalline **3a**, totaling 4.45 g (106.2%) with melting points decreasing progressively from 177.5 (dec) to 165 °C (dec). The four fractions, combined and recrystallized from ethanol, yielded 3.25 g (77.5%) of pure **3a**, mp 189 °C (dec).

Tetrakis(*N*-carbo-*n*-butoxylaminomethyl)phosphonium Chloride (3d). Reaction of 1 (9.53 g, 0.05 mol) with **2d** (29.29 g, 0.25 mol), following procedure A, gave 37.67 g of a colorless oil that partly crystallized on standing. Attempts to separate the excess **2d** from the product by extraction with hot ligroin,[47] ether, or carbon tetrachloride were unsuccessful, for the two substances exhibit the same solubility behavior. Half of the mixture was therefore dissolved in ethanol (25 mL) and percolated through the ion-exchange resin described above, using ethanol as the eluent. The neutral fractions yielded 17.6 mmol (70.4%) of HCl, 3.10 g (21.2%) of **2d**, and 2.24 g (14.6%) of di-*n*-butyl *N,N'*-methylenedicarbamate (**4d**), mp 93–95 °C; the latter, a by-product of the original condensation, was identified by comparison of its IR, NMR, and mp with the authentic sample described below. The phosphonium salt fractions, eluted with ethanolic HCl, yielded 7.83 g of a viscous, colorless oil, n^{20}_D 1.4839, whose composition, determined by NMR and elemental analysis, comprised some unreacted 1 (11.2%) in addition to the product **3d** (38.4%). To remove the unreacted **1**, the oil was taken up in chloroform (50 mL), extracted twice with water, filtered, stripped, and dried, giving 4.71 g (30.1%) of **3d** as a viscous, colorless oil: n^{20}_D 1.4951; IR (Nujol) 1515 (vs, NH, amide II), 1710 (vs, C=O, amide I), and 3230 (s, NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 12 H, CH_3, J = 6.0 Hz), 1.1–2.0 (m, 16 H, CH_2C), 4.13 (t, 8 H, OCH_2, J = 6.0 Hz), 4.43 (m, 8 H, PCH_2), and 7.37 (m, ~4 H, NH, vanishing slowly with D_2O); ^{31}P NMR ($CHCl_3$) δ −30.0.

The phosphonium salt **3d** is soluble in all of the common organic solvents, including toluene and hot ligroin, and insoluble in water.

Di-*n*-butyl *N,N'*-Methylenedicarbamate (4d). This compound has been described as a crystalline solid, mp 97–98 °C,[48] and as a liquid.[49] A mixture of **2d** (5.86 g, 0.05 mol), paraformaldehyde (0.80 g, 0.025 mol of CH_2O), and 2-propanol (15 mL) was heated to reflux in an oil bath. When the solids had all dissolved, the solution was treated with 3 drops of concentrated HCl, refluxed for 30 min, allowed to cool, and stripped under reduced pressure. The residue (7.01 g) was recrystallized twice from hexane, giving 2.85 g (46.3%) of **4d** as a white, crystalline solid: mp 97–98 °C; IR (Nujol) 1530 (s, NH, amide II), 1690 (vs, C=O, amide I), and 3350 (s, NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 6 H, CH_3, J = 7.0 Hz), 1.1–1.8 (m, 8 H, CH_2C), 4.10 (t, 4 H, OCH_2, J = 6.5 Hz), 4.52 (t, 2 H, NCH_2, J = 6.5 Hz, collapsing with D_2O to s), and 6.05 (br s, ~2 H, NH, vanishing very slowly with D_2O).

Anal. Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.38. Found: C, 53.33; H, 9.18; N, 11.10.

The dicarbamate **4d** is soluble in ethanol, acetone, chloroform, carbon tetrachloride, ether, and benzene, and insoluble in water. It can be recrystallized from 2-propanol (6 mL/g, with water added to incipient turbidity) or from hexane (50 mL/g), in which it dissolves slowly and clumps out like cotton.

Tetrakis[*N*-carbo(2-methoxyethoxyl)aminomethyl]phosphonium Chloride (3e). Reaction of 1 (9.53 g, 0.05 mol) with **2e** (35.74 g, 0.30 mol), following procedure A, gave 40.71 g of a viscous, almost colorless oil that resisted efforts at crystallization or conversion to a crystalline oxalate or picrate. Half of the oil was therefore dissolved in water (10 mL) and percolated through the ion-exchange resin described above, using water as the eluent. The neutral fractions yielded 16.9 mmol (67.6%) of HCl. The phosphonium salt fractions yielded 11.10 g of oil which was taken up in chloroform, filtered, stripped and dried [omitting the extraction with water, since the partition is unfavorable], giving 9.05 g (53.7%) of **3e** as a viscous, colorless oil: n^{20}_D 1.5094; IR (neat), 1515 (s, NH, amide II), 1720 (vs, C=O, amide I), and 3240 (m, NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.38 (s, 12 H, CH_3), 3.61 (m, 8 H, 2-CH_2), 4.29 (m, 8 H, 1-CH_2), 4.53 (m, 8 H, PCH_2), and 7.42 (m, ~4 H, NH, vanishing slowly with D_2O); ^{31}P NMR ($CHCl_3$) δ −31.0.

The phosphonium salt **3e** is soluble in water, ethanol, acetone, chloroform, ethyl acetate, and hot toluene.

Tetrakis[*N*-carbethoxy-*N*-methylaminomethyl]phosphonium Chloride (6a). Reaction of **1** (9.53 g, 0.05 mol) with **5a** (20.62 g, 0.20 mol), following procedure A, gave 29.86 g of a mobile, colorless oil that, unlike the products of the primary carbamates, was not at all viscous. The oil was dissolved in ethanol (25 mL) and percolated through the ion-exchange resin described above, using ethanol as the eluent. The neutral fractions yielded 35.1 mmol (70.2%) of HCl. The phosphonium salt fractions, eluted with ethanolic HCl, yielded 12.42 g of a colorless oil, n^{20}_D 1.4985, which, from the elemental analysis and NMR, was calculated to contain some unreacted 1 (3.8%) in addition to the product **6a** (31%): IR (neat), 1690 (vs, C=O, amide I), and 3000 (m) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.42 (t, 12 H, CH_3C, J = 7.0 Hz), 3.22 (d, 12 H, NCH_3, J = 1.0 Hz), 4.33 (q, 8 H, CH_2C, J = 7.0 Hz), and 4.61 (d, 8 H, PCH_2, J = 4.0 Hz); ^{31}P NMR ($CHCl_3$) δ −31.3.

The phosphonium salt **6a** is soluble in ethanol, acetone, chloroform, and hot toluene, and insoluble in water.

(*N*-Carbomethoxylaminomethyl)triphenylphosphonium Chloride (8a). Reaction of **7** (3.29 g, 0.01 mol) with **2a** (0.75 g, 0.01 mol), following procedure A but using benzene instead of ethyl acetate, gave 2.82 g (73.1%) of **8a** as a white, crystalline solid, mp 198.5–199 °C (dec), after recrystallization from 2-propanol: IR (Nujol) 994 (w, P-C_6H_5), 1430 (s, P-C_6H_5), 1540 (m, NH, amide II), 1580 (w, C=C), 1720 (vs, C=O, amide I), and 3170 (m, sh, NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.36 (s, 3 H, CH_3), 4.39 (d pair, 2 H, CH_2, J = 3.0 Hz, collapsing with D_2O to d, δ 4.31, J_{PCH} = 3.0 Hz), 6.87 (m, 15 H, C_6H_5; doublet at δ 6.92, J = 2.0 Hz collapsing with D_2O to s, δ 6.90), and 7.67 (m, 1 H, NH, vanishing with D_2O); ^{31}P NMR ($CHCl_3$) δ −20.0.

Anal. Calcd for $C_{21}H_{21}ClNO_2P$: C, 65.37; H, 5.49; Cl, 9.19; N, 3.63; P, 8.03. Found: C, 65.04; H, 5.67; Cl, 9.35; N, 3.47; P, 8.07.

The phosphonium salt **8a** is soluble in water, ethanol, and chloroform, and insoluble in ether, carbon tetrachloride, acetone, and ethyl acetate. It can be recrystallized from 2-propanol (5 mL/g).

Tetrakis(*N*-carbomethoxylaminomethyl)phosphonium Iodide (9a). **3a** (8.38 g, 0.02 mol) was added to a solution of sodium iodide (3.00 g, 0.02 mol) in ethanol (30 mL), heated at reflux for 1 h, cooled, and filtered, giving 3.23 g of granular solid consisting of sodium chloride and unreacted **3a**. The latter was removed by stirring with dimethyl sulfoxide, leaving 0.67 g (57.3%) of sodium chloride. The ethanol filtrate was stripped, taken up in hot chloroform, filtered to remove unreacted sodium iodide (0.22 g, giving a positive test with acidified iodate), and stripped again. The residue (8.45 g) was recrystallized from ethanol, giving 5.01 g (49.1%) of **9a** as a white, crystalline solid: mp 142.5–143 °C; IR (Nujol) 1535 (vs, NH, amide II), 1690 and 1730 (s and vs, C=O, amide I), 3230 (m, NH bonded), and 3300 (m, sh, NH free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.67 (s, 12 H, CH_3), 4.33 (t, 8 H, CH_2, J = 5.0 Hz, collapsing with D_2O to d, J = 4.0 Hz), and 7.67 (m, 4 H, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO) δ −30.3.

Anal. Calcd for $C_{12}H_{24}IN_4O_8P$: I, 24.87; P, 6.07. Found: I, 24.50 (gravimetric), 25.05 (by iodometric titration[50]); P, 6.12.

Tetrakis(*N*-carbomethoxylaminomethyl)phosphonium Bromide (11a). A solution of **3a** (8.38 g, 0.02 mol) in methanol (200 mL) was percolated through the ion-exchange resin described above, giving 18.6 mmol (93.0%) of hydrogen chloride. It was necessary to wrap the column in heating tape and warm it to 40–50 °C to prevent the salts from crystallizing. The column was then eluted with hydrogen bromide in methanol, yielding four liquid fractions (6.79 g) followed by eight solid fractions (19.19 g). The solids were combined, shaken with ethanol, and filtered, giving 6.50 g (70.2%) of **11a**, mp 180–184.5 °C (dec). One recrystallization from ethanol (75 mL/g) afforded pure **11a** as a white, crystalline solid: mp 185–186 °C (dec); IR (Nujol) 1550 (vs, NH, amide II), 1700 and 1730 (s and vs, C=O, amide I), 3220 (s, NH bonded), and 3320 (m, NH free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.65 (s, 12 H, CH_3), 4.35 (t, 8 H, CH_2, J = 5.0 Hz, col-

lapsing with D_2O to d, J = 4.0 Hz), and 7.75 (br t, 4 H, NH, vanishing with D_2O); ^{31}P NMR (Me_2SO) δ −30.0.

Anal. Calcd for $C_{12}H_{24}BrN_4O_8P$: Br, 17.25; P, 6.69. Found: Br, 17.71; P, 6.93.

The product suffered no loss in weight when heated in a drying pistol for 2 h at 100 °C/0.5 mm.

Acid Hydrolysis of 3a. A solution of **3a** (8.38 g, 0.02 mol) in 6 N HCl (100 mL) was heated to reflux under argon in an oil bath, held at 110 °C for 17 h, and then stripped under vacuum. The residue (7.51 g) was extracted with boiling ethanol, giving 3.94 g (92.0%) of ammonium chloride, identified by IR, by a positive Beilstein test, and by the liberation of ammonia upon treatment with 10% NaOH solution. The ethanol extract yielded 3.23 g of a colorless oil, $n^{20}D$ 1.5514, which was separated by passage over the ion-exchange resin into a neutral fraction (0.18 g, 7.3%), consisting solely of bis(hydroxymethyl)-methylphosphine oxide, **12**, ^1H NMR (D_2O) δ 1.59 (d, 3 H, CH_3, J = 13.0 Hz) and 4.08 (d, 4 H, CH_2, J = 3.5 Hz), and a phosphonium salt fraction containing 2.59 g (68.0%) of **1**, ^1H NMR (D_2O) δ 4.73 (d, 8 H, CH_2, J = 1.5 Hz), together with other impurities. The phosphonium salt fraction showed residual amide I and II bands in the IR.

Alkaline Hydrolysis of 3a. A slurry of **3a** (20.94 g, 0.05 mol) in water (50 mL) was treated dropwise under argon with a solution of sodium hydroxide (2.00 g, 0.05 mol) in water (25 mL).

During the addition, which took 15 min, the mixture cleared, turned milky, and then cleared again. After heating to 100 °C to complete the reaction, the solution, which had a pH of 8.4 and gave a strongly positive iodine test, abruptly crystallized, giving 4.30 g (29.1%) of the tertiary phosphine **13a**, identical to the product of the ammonium hydroxide reaction (mp, IR). The filtrate was extracted with chloroform, leaving an iodine-negative aqueous solution which, on workup, yielded 2.90 g (99.3%) of sodium chloride. The chloroform extract, which gave a strongly positive iodine test, was filtered under argon and concentrated, giving 16.49 g (65.7%) of the tertiary phosphine **15a** as a colorless oil: $n^{20}D$ 1.5011; IR (neat) 750 (m, $CHCl_3$), 1530 (vs, NH, amide II), 1710 (vs. C=O, amide I), and 3350 (m, br) cm^{-1}. The phosphine **15a** is soluble in acetone, chloroform, and water, and its aqueous solution is neutral.

The other alkaline hydrolyses listed in Table I were performed in the same manner, using 0.05 mol of **3a** and 0.05 mol of the base for each experiment, except for the experiments with barium hydroxide (0.025 mol), triethylamine (0.10 mol), morpholine (0.10 mol), and ammonium hydroxide (excess, described in detail below). The buffer experiments were each performed with 0.05 mol of base and 0.01 mol of buffer.

Tris(*N*-carbomethoxylaminomethyl)phosphine (13a). Concentrated ammonium hydroxide (10 mL) was added to a well-stirred slurry of **3a** (20.94 g, 0.05 mol) in water (50 mL) in an apparatus previously purged with argon. There was no exotherm nor gassing, but the mixture gradually thickened. After 30 min, more water (50 mL) was added to facilitate stirring. The mixture was then stirred for 2 h and filtered, and the filter cake was washed with water and dried in a vacuum desiccator, giving 12.85 g (87.0%) of **13a** as a white, crystalline powder, mp 100–125 °C. All of these operations were performed under argon, for the product becomes hot and sticky when exposed to air. One recrystallization from 2-propanol raised the melting point (sealed tube) to 137–140 °C: IR (Nujol) 1535 (vs, br, NH, amide II), 1700 and 1735 (vs and s, C=O, amide I), and 3350 (m, NH) cm^{-1}.

The phosphine **13a** is soluble in ethanol, chloroform, and acetone, and insoluble in water, ether, carbon tetrachloride, and benzene. It can be recrystallized from water (8 mL/g) or 2-propanol (7 mL/g).

Tris(*N*-carbomethoxylaminomethyl)phosphine Oxide (17a). Thirty percent hydrogen peroxide (57.0 g, 0.5 mol) was added dropwise to a vigorously stirred slurry of **13a** (147.6 g, 0.5 mol) in 500 mL of acetone under an argon atmosphere. Ice-bath cooling was applied as necessary to counter the strongly exothermic reaction. The **13a** gradually dissolved, and was all in solution when two-thirds of the peroxide had been added. About 10 min after the addition was completed, the product started to crystallize. The next day the solid was collected on a filter, washed with acetone, and dried, giving 98.9 g (63.5%) of **17a**, mp 179–180 °C. Workup of the filtrate raised the yield to 126.0 g (81.0%). Two recrystallizations from ethanol afforded pure **17a** as a white, crystalline solid: mp 189–190 °C; IR (Nujol) 1540 (s, NH, amide II), 1710 (vs, br, C=O, amide I), 3250 (w, NH bonded), and 3400 (w, NH free) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.60 (s, CH_3), 3.47 (t, CH_2, J = 9.0 Hz, blending into the CH_3 peak with D_2O; combined CH_3 and CH_2, 15 H), and 7.34 (m, 3 H, NH, vanishing with D_2O).

Anal. Calcd for $C_9H_{18}N_3O_7P$: C, 34.73; H, 5.83; N, 13.50; P, 9.95. Found: C, 34.69; H, 5.70; N, 13.48; P, 10.00.

The phosphine oxide **17a** is soluble in chloroform and insoluble in water, acetone, and the common organic solvents. It can be recrystallized from ethanol (25 mL/g) or water. When heated above its melting point, **17a** gasses without discoloration at 200 °C and froths to a tan-colored resin at 260 °C.

Tris(*N*-carbomethoxylaminomethyl)phosphine Sulfide (18a). A mixture of **13a** (2.95 g, 0.01 mol), sulfur (0.32 g, 0.01 g-atom), and benzene (25 mL) was heated to reflux under an argon atmosphere. After 1 h, most of the solids had dissolved. The mixture was cooled and stripped of benzene under reduced pressure. The residue was taken up in hot acetone, filtered hot to remove the unreacted sulfur (0.12 g), and stripped again under reduced pressure, leaving 2.40 g (73.4%) of **18a** as a white, crystalline solid. Two recrystallizations from ethanol afforded pure **18a**: mp 136.5–137 °C; IR (Nujol) 1520 (vs, br, NH, amide II), 1710 and 1740 (vs and s, C=O, amide I), and 3400 (s, NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.61 (s, CH_3), 3.72 (t, CH_2, J = 3.0 Hz, collapsing with D_2O to d, J = 3.0 Hz; combined CH_3 and CH_2, 15 H), and 7.39 (m, 3 H, NH, vanishing with D_2O).

Anal. Calcd for $C_9H_{18}N_3O_6PS$: C, 33.03; H, 5.54; N, 12.84; P, 9.46; S, 9.80. Found: C, 33.08; H, 5.49; N, 12.82; P, 9.60; S, 9.80.

The phosphine sulfide **18a** is soluble in chloroform, and insoluble in water or ethanol. It can be recrystallized from ethanol (6 mL/g), 2-propanol, or water.

Reaction of 13a with 14a. A mixture of **13a** (4.79 g, 0.01 mol), **14a**[29] (1.05 g, 0.01 mol), water (25 mL), and 50% sodium hydroxide (1 drop) was heated under argon for 15 min at 100 °C, cooled, and filtered, giving 1.55 g (32.4%) of recovered **13a**. The filtrate, extracted with chloroform and worked up as described above, yielded 1.68 g (44%) of a colorless, neutral oil, $n^{20}D$ 1.4788, identified by IR as **15a**. The presence of less chloroform in the product accounts for the lower refractive index.

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Registry No.—**1**, 124-64-1; **2a**, 598-55-0; **2b**, 51-79-6; **2c**, 1746-77-6; **2d**, 592-35-8; **2e**, 1616-88-2; **3a**, 63833-04-5; **3b**, 63833-05-6; **3c**, 63833-06-7; **3d**, 63833-07-8; **3e**, 63833-08-9; **4d**, 2533-21-3; **5a**, 105-40-8; **6a**, 63833-09-0; **7**, 5293-83-4; **8a**, 62779-17-3; **9a**, 63833-10-3; **11a**, 63833-11-4; **12**, 17919-49-2; **13a**, 63833-12-5; **14a**, 6092-56-4; **17a**, 63833-13-6; **18a**, 63833-14-7; paraformaldehyde, 30525-89-4.

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Derivatives of 6β-Methylpenicillanic Acid

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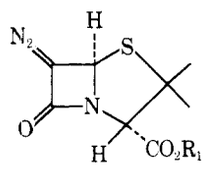
Diazo compounds **1** have been converted to intermediates **2** by two methods: reaction with aqueous *N*-bromosuccinimide, and treatment with triphenylphosphine and nitrous acid. Reaction of **2** with Wittig reagents gives a series of C_6 carbon analogues **6** and, after Curtius rearrangement, C_6 penicillin homologues **8**.

The C_6 carbon analogue of penicillin V has been synthesized and found to have interesting antibiotic activities.[1] The synthetic method for such analogues has therefore been improved and extended to make a series of carbon analogues available for further study.

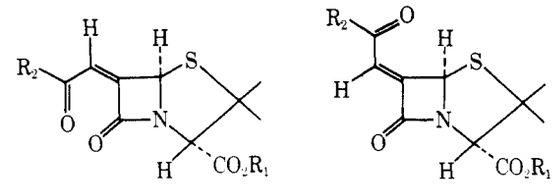
The starting intermediates for these syntheses are the 6-diazopenicillanates **1** (R_1 = CH_2CCl_3, CH_2Ph) which were synthesized according to a known method.[2] Compounds **1**



1

react with *N*-bromosuccinimide in aqueous solvents or Ph_3P followed by nitrous acid[3] to give keto compounds **2**.[4] Compounds **2** are relatively unstable and are not usually isolated, but used directly for further reactions.

For example, compound **2** (R_1 = CH_2CCl_3), as a crude oil derived from the treatment of **1** with aqueous NBS, reacted with $Ph_3P{=}CHCO_2CH_2Ph$ to give the syn and anti isomers **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph). These isomers were isolated in 32 and 3% yield [based on diazo compound **1** (R_1 = CH_2CCl_3)]. The major product was assigned the sterically less hindered anti structure. A major by-product of this series of reactions is the dibromide **4**, isolated in yields ranging from 13 to 32%. The triphenylphosphine–nitrous acid method of



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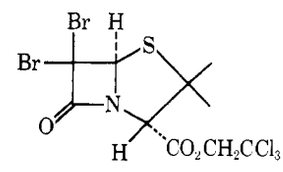
synthesizing compound **2** followed by reaction with the same Wittig reagent gave compounds **3** (R_1 = CH_2CCl_3; R_2 =



4

OCH_2Ph) in 60% yield. Similarly, ketone **2** (R_1 = CH_2CCl_3) reacted with $Ph_3P{=}CHCOCH(Ph)NH$-*tert*-Boc to give **3** (R_1 = CH_2CCl_3; R_2 = $CH(Ph)NH$-*tert*-Boc), mostly in the anti form. The yields, based on **1**, were 9% for the NBS method and 26% for the triphenylphosphine–nitrous acid method.

Addition of HCN to compound **2** (R_1 = CH_2Ph) gives a crystalline cyanohydrin **5** which can be used to regenerate the pure keto compound or react with other reagents.[5] For instance, cyanohydrin **5** (R_1 = CH_2Ph) reacts directly with an ylide such as $Ph_3P{=}CHCO_2$-*tert*-Bu or $Ph_3P{=}CHCOCH(Ph)NH$-*tert*-Boc to give compounds **3** (R_1 = CH_2Ph; R_2 = *O*-*tert*-Bu or $CH(Ph)NH$-*tert*-Boc) in 97 and