New Syntheses of Phosphorylaminoethanols

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A new convenient synthesis of phosphoryl-2-methylaminoethanol from 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine has been developed, and another method for the preparation of alkylphosphorylcholines from the same starting agent has been studied.

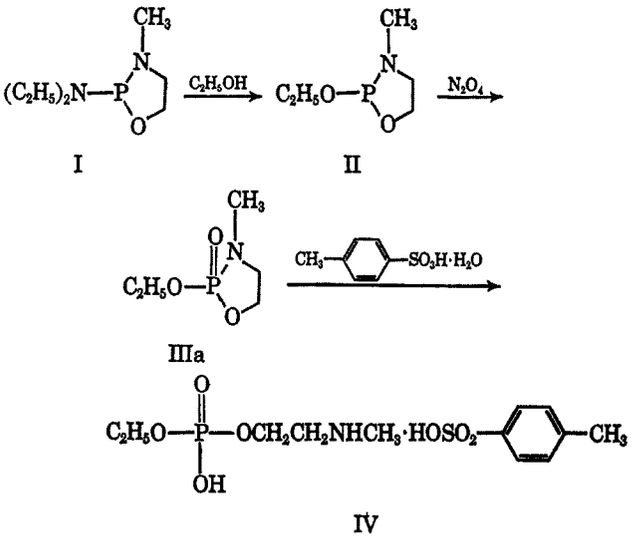
Syntheses of glycerylphosphorylaminoethanols, such as lecithins and cephalins, by the use of phenyl phosphorodichloridate as a phosphorylating agent, have been described in a number of reports.[1-5]

The preceding paper[6] described a convenient method for the synthesis of the *p*-toluenesulfonium salt of ethyl 2-methylaminoethyl phosphate (IV) starting from 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine (I) by a three-step procedure (Scheme I).

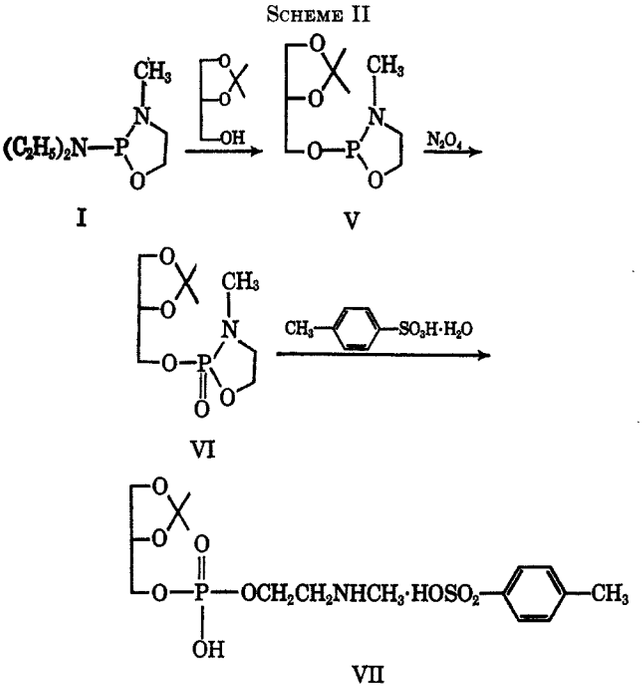
In the present study, the above-mentioned procedure was further extended to the preparation of some glycerylphosphorylaminoethanols by the use of 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine. 2-Acetoneglycerino-3-methyl-1,3,2-oxazaphospholidine (V) was synthesized in 75% yield from acetoneglycerine and 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine which was obtained by the reaction of 2-methylaminoethanol with tris(diethylamino) phosphite.[6] The oxidation of V by means of nitrogen tetroxide[7] in dichloromethane at −78° resulted in the formation of an undistillable, colorless, viscous, oily product. The product showed one spot at the R_f 0.77 in its paper chromatograph (*n*-PrOH:NH_4OH:H_2O = 6:3:1) and the infrared spectrum exhibited an absorption at 1250 cm^{-1} indicative of the P=O bond. Chemical analysis indicated formula $C_9H_{18}O_5NP$ and suggested 2-acetoneglycerino-3-methyl-1,3,2-oxazaphospholidin-2-one (VI) as the structure (96% yield). The subsequent hydrolysis of VI with *p*-toluenesulfonic acid monohydrate in benzene gave a colorless oil which showed one spot at R_f 0.22 in its paper chromatograph and the infrared spectrum exhibited absorptions at 1250 and 1050 cm^{-1} indicative of the P=O and P—O—C bonds. Chemical analysis indicated formula $C_{16}H_{26}O_9NP$ and suggested that we were dealing with the *p*-toluenesulfonium salt of acetoneglycerylphosphoryl-2-methylaminoethanol (VII, 91% yield). (See Scheme II.)

In the next place, it was established that 2-alkoxy-3-methyl-1,3,2-oxazaphospholidin-2-ones are conveniently prepared by the phosphorylation[8] of alcohols by means of 2-allyloxy-3-methyl-1,3,2-oxazaphospholidine (VIII) and monobromocyanoacetamide (Scheme III). 2-Allyloxy-3-methyl-1,3,2-oxazaphospholidine was prepared in excellent yield by the exchange reaction between 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine and allyl alcohol in refluxing benzene. When 2-allyloxy-3-methyl-1,3,2-oxazaphospholidine was added to a solution of an equimolar amount of monobromocyanoacetamide and a three-molar amount of ethyl alcohol in tetrahydrofuran at room temperature, 2-ethoxy-3-methyl-1,3,2-oxazaphospholidin-2-one was obtained in 64% yield. Similarly, *n*-propyl and *n*-butyl alcohols were phoshorylated to give 2-*n*-propoxy- and 2-*n*-butoxy-3-methyl-1,3,2-oxazaphospholidin-2-ones in 55 and 52% yields, respectively. However, when the phosphorylation of isopropyl alcohol was attempted in

SCHEME I



SCHEME II



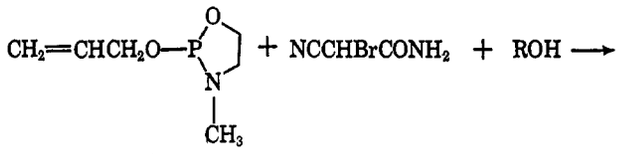
(1) W. G. Rose, *J. Am. Chem. Soc.*, **69**, 1384 (1947).
(2) I. R. Hunter, R. I. Roberts, and E. B. Kester, *ibid.*, **70**, 3244 (1948).
(3) E. Baer and M. Kates, *ibid.*, **70**, 1394 (1948); **72**, 942 (1950).
(4) E. Baer and J. Maurukas, *ibid.*, **74**, 152 (1952); 158 (1952).
(5) E. Baer, D. Buchenea, and A. G. Newcombe, *ibid.*, **78**, 232 (1956).
(6) T. Mukaiyama and Y. Kodaira, *Bull. Chem. Soc. Japan*, in press.
(7) Cox and Westheimer, *J. Am. Chem. Soc.*, **80**, 5441 (1958).
(8) T. Mukaiyama, O. Mitsunobu, and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).

TABLE I

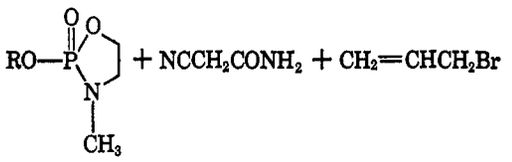
REACTION OF 2-ALLYLOXY-3-METHYL-1,3,2-OXAZAPHOSPHOLIDINE WITH MONOBROMOCYANOACETAMIDE AND ALCOHOLS

ROH	Yield of $NCCN_2CONH_2$, %	2-Alkoxy-3-methyl-1,3,2-oxazaphospholidin-2-one: Yield, %	Bp, °C (mm)	$n^{15}D$	Calcd, % N	Found, % N
C_2H_5OH	64	64	79–94 (0.14)	1.4547	8.48	8.52
n-C_3H_7OH	67	55	91–99 (0.16)	1.4715	7.82	7.65
i-C_3H_7OH	57	28	98–102 (0.18)	1.4562	7.82	7.95
n-C_4H_9OH	66	52	117–123 (0.13)	1.4706	7.25	7.59
$C_6H_{11}OH$	63					

SCHEME III



VIII



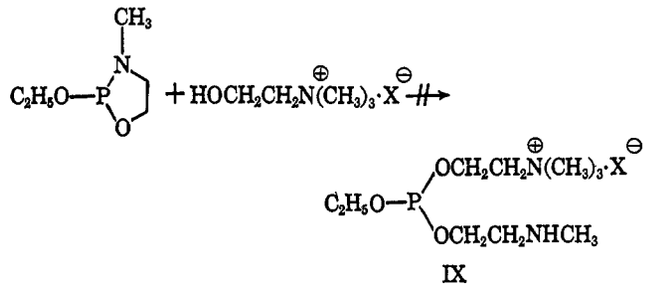
III

the same manner, 2-isopropoxy-3-methyl-1,3,2-oxazaphospholidin-2-one was formed in only 28% yield, and, in the case of cyclohexyl alcohol, the expected product could not be isolated by distillation at all, although cyanoacetamide was obtained in 63% yield. These results are summarized in Table I.

Next, a synthesis of phosphorylcholine was attempted in the expectation that 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine could be converted to IX by the reaction with choline halide and that subsequent oxidation of IX would give dimethylpiperazinium dihydrohalide and ethylphosphorylcholine similar to the thermal decomposition of the diethyl 2-diethylaminoethyl phosphate[9-10] or thiophosphate (Aminton)[11] to yield the corresponding tetraethylpiperazinium salt (Scheme IV).

Unfortunately, IX could not be obtained by the

SCHEME IV

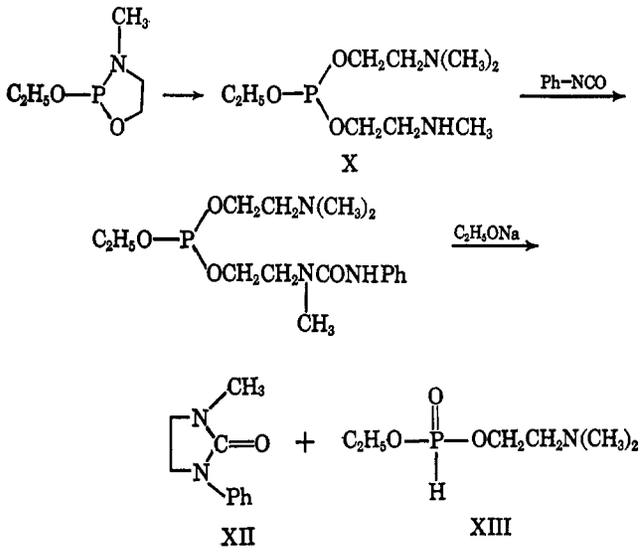


IX

above-mentioned procedure, because of the very limited solubility of choline halides in organic solvents, such as benzene, ether, tetrahydrofuran, and acetonitrile.

In the second synthesis, ethyl 2-methylaminoethyl 2-dimethylaminoethyl phosphite (X, prepared by the reaction of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine and 2-dimethylaminoethanol) was treated with phenyl isocyanate, affording N-methyl-N′-phenyl-2-imidazolidone (XII) in 50% yield and ethyl 2-dimethylaminoethyl phosphite (XIII), presumably through the intermediate XI (Scheme V). Unfortunately, pure XIII could not be isolated, and the expected thiophosphorylcholine could not be obtained by the subsequent oxidation of XIII with sulfur.

SCHEME V



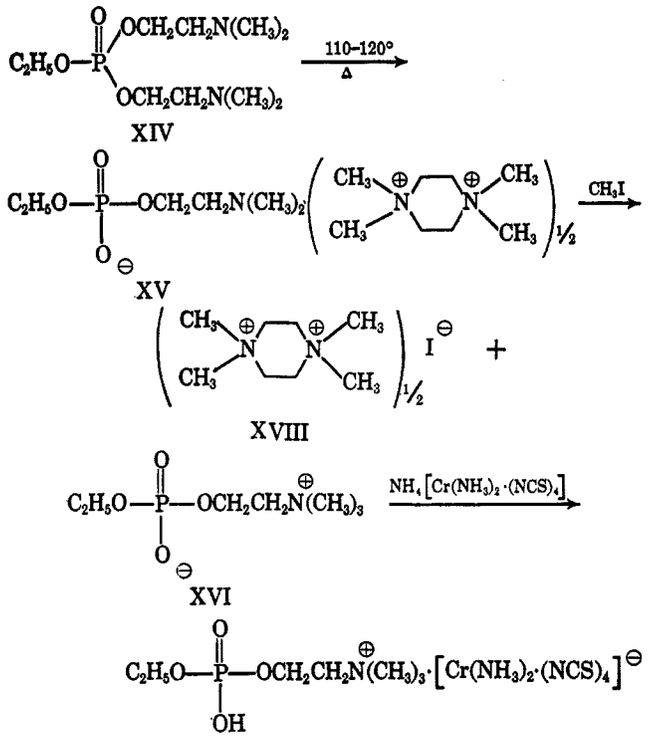
XII XIII

Finally, it was found that ethyl bis(2-dimethylaminoethyl) phosphate (XIV) was converted to ethylphosphorylcholine (XVI) and tetramethylpiperazinium diiodide in fairly good yields, as shown in Scheme VI. When ethyl bis(2-dimethylaminoethyl) phosphate (XIV), prepared in 75% yield from ethyl phosphorodichloridate and sodium 2-dimethylaminoethanol, was heated at 110–120° in a sealed tube, the tetramethylpiperazinium salt of ethyl 2-dimethylaminoethylphosphoric acid (XV) was obtained in 76% yield. The tetramethylpiperazinium diiodide (XVII) and ethylphosphorylcholine as Reinecke salt were obtained in 48 and 50% yields, respectively, when the piperazinium salt of ethyl 2-dimethylaminoethylphosphoric acid (XV) was treated with excess methyl iodide. Similarly, various alkyl bis(2-aminoethyl) thiophosphates, synthesized by the oxidation of the corresponding phosphites by means of sulfur, were converted to the piperazinium salts of alkyl 2-aminoethylthiophosphoric acids. These salts yielded the Reinecke salts of alkylthiophosphorylcholines and piperazinium diiodide on treatment with methyl iodide in fairly good yields (see Table II).

For the synthesis of the glycerylphosphorylcholine according to the above-mentioned procedure, a good preparation of glyceryl bis(2-aminoethyl) phosphate was needed. This was achieved by the use of 2-diethyl-

(9) D. M. Brown and G. O. Osborne, *J. Chem. Soc.*, 2950 (1957).
(10) J. G. Cadogan, *ibid.*, 4154 (1957).
(11) J. G. Cadogan and L. C. Thomas, *ibid.*, 2248 (1960).

SCHEME VI



XIV

XV

XVIII

XVI

TABLE II

PREPARATION OF ALKYLTHIOPHOSPHORYLCHOLINES FROM ALKYL BIS(2-AMINOETHYL) PHOSPHITE

Alkyl bis(2-aminoethyl) phosphite RO—P<OR′/OR″			Yields of Reinecke salt, %	Yields of piperazinium diiodide, %
R	R′	R″		
C_2H_5	$CH_2CH_2NHCH_3$	$CH_2CH_2NHCH_3$		65
C_2H_5	$CH_2CH_2N(C_2H_5)_2$	$CH_2CH_2N(C_2H_5)_2$	30[a]	38
C_2H_5	$CH_2CH_2N(CH_3)_2$	$CH_2CH_2N(CH_3)_2$	52[b]	53
C_2H_5	$CH_2CH_2NHCH_3$	$CH_2CH_2N(CH_3)_2$	53[a]	57
n-C_4H_9	$CH_2CH_2N(CH_3)_2$	$CH_2CH_2N(CH_3)_2$	35[c]	46

[a] Mp 168°. [b] Mp 182–183°. [c] Mp 153–156°.

amino-3-methyl-1,3,2-oxazaphospholidine as a starting material. Treatment of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine, prepared by the reaction of 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine and ethanol with 2-dimethylaminoethanol in refluxing benzene, gave ethyl 2-methylaminoethyl-2-dimethylaminoethyl phosphite (X) in 80% yield. The latter was oxidized smoothly by means of sulfur in benzene at room temperature. After the thiophosphate (XIX) was heated at 95–105° *in vacuo*, excess methyl iodide was added to the ethanolic solution of the product. Tetramethylpiperazinium diiodide and ethylthiophosphorylcholine as a Reinecke salt (XXII) were obtained in 57 and 53% yields, respectively (Scheme VII).

Experimental Section

Solvents and Reagents.—Benzene, ether, and tetrahydrofuran were dried and purified by ordinary procedure. 2-Diethylamino-3-methyl-1,3,2-oxazaphospholidine (bp 91–97° at 5 mm) was prepared by the reaction of equimolar amounts of tris(diethylamino) phosphite and 2-methylaminoethanol. 2-Ethoxy-3-methyl-1,3,2-oxazaphospholidine (bp 62–67° at 17 mm) and 2-allyloxy-3-methyl-1,3,2-oxazaphospholidine (bp 75–77° at 13 mm) were provided by the reaction of 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine and ethyl and allyl alcohols as described in the previous paper.[6]

Preparation of 2-Acetoneglycerino-3-methyl-1,3,2-oxazaphospholidine.—A solution of 2-diethylamino-3-methyl-1,3,2-oxazaphospholidine (1.76 g, 0.01 mole) and 1,2-acetoneglycerine (1.32 g, 0.01 mole) in 15 ml of benzene was refluxed for 2 hr. After removal of benzene under reduced pressure, 1.75 g (74%) of 2-acetoneglycerino-3-methyl-1,3,2-oxazaphospholidine (bp 83–87° at 0.14 mm) was obtained by distillation.

Anal. Calcd for $C_9H_{18}NO_4P$: N, 5.96. Found: N, 6.15.

Oxidation of 2-Acetoneglycerino-3-methyl-1,3,2-oxazaphospholidine by Means of Nitrogen Tetroxide.—To a solution of 2-acetoneglycerino-3-methyl-1,3,2-oxazaphospholidine (2.35 g, 0.01 mole) in 15 ml of dichloromethane was added dropwise a solution of nitrogen tetroxide in dichloromethane at −78° until the color of solution turned blue. Removal of the solvent under reduced pressure gave 2.40 g (96%) of 2-acetoneglycerino-3-methyl-1,3,2-oxazaphospholidin-2-one which decomposed at about 180° under reduced pressure. The product showed one spot at R_f 0.77 in its paper chromatograph (n-PrOH:NH_4OH:H_2O = 6:3:1) and the infrared spectrum exhibited a new strong absorption band at 1250 cm^{-1} indicative of the P=O bond.

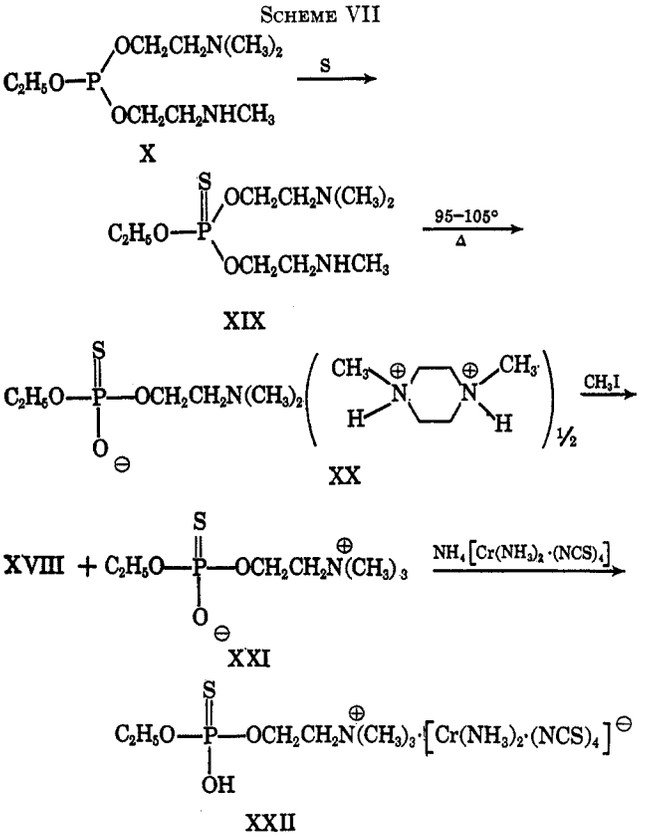
Anal. Calcd for $C_9H_{18}NO_5P$: N, 5.58. Found: N, 5.84.

Preparation of the *p*-Toluenesulfonium Salt of Acetoneglycerylphosphoryl-2-methylaminoethanol.—To a solution of 2-acetoneglycerino-3-methyl-1,3,2-oxazaphospholidin-2-one (2.51 g, 0.01 mole) in 20 ml of benzene was added *p*-toluenesulfonic acid monohydrate (1.90 g, 0.01 mole) in small portions with vigorous stirring at room temperature. After stirring for additional 2 hr, the reaction mixture was allowed to stand overnight at room temperature. Benzene was removed by decantation, and the oily substance was rinsed three times with benzene (10 ml) in order to remove by-product. The *p*-toluenesulfonium salt of acetoneglycerylphosphoryl 2-methylaminoethanol (4.0 g, 91%) was obtained. The product showed one spot at R_f 0.22 in its paper chromatograph and the infrared spectrum exhibited absorption bands at 1250 and 1050 cm^{-1} indicating the existence of the P=O and P—O—C bonds.

Anal. Calcd for $C_{16}H_{28}NO_9P$: N, 3.18. Found: N, 3.47.

Reaction of 2-Allyloxy-3-methyl-1,3,2-oxazaphospholidine with Monobromocyanoacetamide and Ethanol.—To a solution of monobromocyanoacetamide (1.63 g, 0.01 mole) and ethanol (1.38 g, 0.03 mole) in 20 ml of tetrahydrofuran was added dropwise a solution of 2-allyloxy-3-methyl-1,3,2-oxazaphospholidine (1.61 g,

SCHEME VII



X

XIX

XX

XXI

XXII

0.01 mole) in 10 ml of THF with stirring at room temperature. After the reaction mixture was kept standing overnight at room temperature, it was dried under reduced pressure and the residue was treated with 10 ml of chloroform to precipitate cyanoacetamide. The filtration of the precipitate gave 0.53 g (64%) of crude cyanoacetamide. After the chloroform was removed from the filtrate, 1.05 g (64%) of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidin-2-one (bp 87–98° at 0.14 mm) was obtained by vacuum distillation.

Anal. Calcd for $C_5H_{12}NO_3P$: N, 8.48. Found: N, 8.52.

In a similar way, 2-*n*-propoxy-, 2-*n*-butoxy-, and 2-isopropoxy-3-methyl-1,3,2-oxazaphospholidin-2-ones were obtained. These results are summarized in Table I. Further, in the case of cyclohexyl alcohol, the expected oxazaphospholidin-2-one could not be obtained by vacuum distillation, although 0.52 g (63%) of cyanoacetamide was obtained.

Reaction of 2-Ethoxy-3-methyl-1,3,2-oxazaphospholidine with Choline Bromide.—A solution of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine (1.49 g, 0.01 mole) and choline bromide (1.84 g, 0.01 mole) in 20 ml of benzene was refluxed for about 10 hr. After cooling to room temperature, a crystalline substance was collected by filtration; 1.52 g (83%) of choline bromide was recovered; and, after the filtrate had been condensed to dryness, 1.05 g (71%) of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine was also recovered by distillation. In a similar manner, the reaction was examined by the use of choline chloride instead of choline bromide, but the expected product could not be obtained. Further, the reaction was examined in a solution of ether, tetrahydrofuran, or acetonitrile instead of benzene, but the expected substance could not be obtained and the starting material of choline halide was recovered.

Reaction of Ethyl 2-Methylaminoethyl-2-dimethylaminoethyl Phosphite with Phenyl Isocyanate and Sodium Ethoxide.[12]—To a solution of ethyl 2-methylaminoethyl-2-dimethylaminoethyl phosphite (2.38 g, 0.01 mole) in 20 ml of benzene was added a a solution of phenyl isocyanate (1.19 g, 0.01 mole) in 5 ml of benzene with stirring at room temperature. After it was stirred for an additional hour, sodium ethoxide, which had been prepared from 0.23 g of metallic sodium and ethanol, was added to the mixture and then refluxed for 2 hr more. After the mixture was allowed to stand overnight at room temperature, it was evaporated to dryness under reduced pressure, and the residue was treated with 15 ml of water. Crude needle-like crystals of N-methyl-N'-phenyl-2-imidazolidone (mp 104–105°) were collected by filtration. The yield of the imidazolidone was 0.88 g (50%). Recrystallization from ethyl acetate gave an analytical sample (mp 108–109°).

Anal. Calcd for $C_{10}H_{12}NO$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.18; H, 6.94; N, 15.99.

The filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in 20 ml of benzene. To the benzene solution was added sulfur (0.32 g, 0.01 mole) in small portions with stirring at room temperature and then it was refluxed for about 3 hr. After the solvent was removed under reduced pressure, 0.27 g (84%) of unreacted sulfur was recovered.

Preparation of Ethyl Bis(2-dimethylaminoethyl) Phosphate.—To a solution of sodium 2-dimethylaminoethanol in 50 ml of benzene, prepared from 2-dimethylaminoethanol (4.45 g, 0.05 mole) and metallic sodium (1.15 g), was added a solution of ethyl dichlorophosphate (4.08 g, 0.025 mole) in 10 ml of benzene with stirring at room temperature. After stirring for an additional hour, the reaction mixture was poured into 150 ml of ether with stirring. The precipitate of sodium chloride was filtered, and the filtrate was evaporated to dryness under reduced pressure. The vacuum distillation of the residue gave 3.57 g (75%) of bis(2-dimethylaminoethyl) phosphate (bp 103–106° at 0.06 mm).

Anal. Calcd for $C_{10}H_{25}N_2O_4P$: N, 10.45. Found: N, 10.35.

Preparation of the Tetramethylpiperazinium Salt of Ethyl 2-Dimethylaminoethylphosphoric Acid.—Ethyl bis(2-dimethylaminoethyl) phosphate (2.68 g, 0.01 mole) was heated at 110–120° for 3 hr in a sealed tube. After cooling to room temperature, a white hygroscopic, prism crystalline was obtained. Recrystallization from acetone–methanol gave 2.05 g (76%) of tetramethylpiperazinium salt of ethyl 2-dimethylaminoethylphosphoric acid (mp 192–193°).

Anal. Calcd for $C_{10}H_{25}N_2O_4P$: C, 44.78; H, 9.33; N, 10.45. Found: C, 43.27; H, 9.38; N, 10.28.

Reaction of the Tetramethylpiperazinium Salt of Ethyl 2-Dimethylaminoethylphosphoric Acid with Methyl Iodide.—To a solution of the tetramethylpiperazinium salt of ethyl 2-dimethylaminoethylphosphoric acid (1.34 g) in 20 ml of ethanol was added excess methyl iodide (5 g), drop by drop, with stirring at room temperature. After the reaction mixture was allowed to stand overnight at room temperature, the tetramethylpiperazinium diiodide (0.95 g, 48%) was collected by filtration. Recrystallization from ethanol–water gave an analytical sample (mp >250°).

Anal. Calcd for $C_8H_{20}I_2N_2$: C, 24.12; H, 5.00; N, 7.04. Found: 24.14; H, 5.06; N, 7.09.

The filtrate was poured into a freshly prepared solution of ammonium reineckate (3.0 g) in 150 ml of ethanol with stirring at room temperature. After the mixture allowed to stand overnight at room temperature, it was filtered. The precipitate was washed thoroughly with ethanol and water, and then dried *in vacuo* over phosphorus pentoxide to a constant weight. The dry reineckate was powdered and dissolved in acetone–water and filtered. The solution was poured into ethanol. The precipitate was filtered and dried *in vacuo* over phosphorus pentoxide to a constant weight (mp 175–178°). The yield of the Reinecke salt of ethylphosphorylcholine was 2.65 g (50%).

Anal. Calcd for $C_{11}H_{25}CrN_7O_4PS_4$: C, 24.91; H, 4.72; N, 18.49. Found: C, 25.39; H, 5.36; N, 18.39.

Preparation of Ethyl Bis(2-dimethylaminoethyl) Phosphite.—To a solution of ethyl phosphorodichloridite (14.7 g, 0.1 mole) in 800 ml of ether was added a mixture of 2-dimethylaminoethanol (17.8 g, 0.2 mole) and triethylamine (25 g) with stirring at 0°. After the mixture was allowed to stand overnight at room temperature, the precipitate of triethylammonium hydrochloride was filtered. After the solvent was removed under reduced pressure, 16.6 g (66%) of ethyl bis(2-dimethylaminoethyl) phosphite (bp 90–119° at 4 mm) was obtained by vacuum distillation.

Anal. Calcd for $C_{10}H_{25}N_2O_3P$: N, 11.11. Found: N, 10.92.

In a similar way, 8.4 g (60%) of *n*-butyl bis(2-dimethylaminoethyl) phosphite (bp 99–109° at 0.5 mm) was obtained by the reaction of *n*-butyl phosphorodichloridite (7.95 g, 0.05 mole) with 2-dimethylaminoethanol (8.9 g, 0.1 mole) and triethylamine (15 g).

Anal. Calcd for $C_{12}H_{29}N_2O_3P$: N, 10.00. Found: N, 9.87.

Preparation of Ethyl Bis(diethylaminoethyl) Phosphite.—A solution of ethyl bis(diethylamino) phosphite (2.20 g, 0.01 mole) and 2-diethylaminoethanol (2.34 g, 0.01 mole) in 20 ml of benzene was refluxed for about 2 hr. After removal of solvent under reduced pressure, the vacuum distillation of the residual oil gave 1.88 g (59%) of ethyl bis(2-diethylaminoethyl) phosphite (bp 108–113° at 2 mm).

Anal. Calcd for $C_{15}H_{33}N_2O_3P$: N, 8.75. Found: N, 8.84.

Preparation of Ethyl Bis(2-monomethylaminoethyl) Phosphite.—After a solution of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine (1.49 g, 0.01 mole) and 2-methylaminoethanol (0.75 g, 0.01 mole) in 15 ml of benzene was refluxed for 2 hr, the solvent was removed under reduced pressure. The vacuum distillation of the residue gave 1.29 g (58%) of ethyl bis(2-monomethylaminoethyl) phosphite (bp 77–83° at 4 mm).

Anal. Calcd for $C_8H_{21}N_2O_3P$: N, 12.50. Found: N, 13.31.

Preparation of Alkylthiophosphorylcholines from Alkyl Bis(2-aminoethyl) Phosphites.—To a solution of ethyl bis(2-dimethylaminoethyl) phosphite (2.52 g, 0.01 mole) in 20 ml of benzene was added sulfur (0.32 g, 0.01 g-atom) in small portions with stirring at room temperature. After the mixture was allowed to stand overnight at room temperature, the solvent was removed under reduced pressure to give transparent, viscous oily substance. The product was heated at 130–150° for about 3 hr *in vacuo* and then dissolved into 20 ml of ethanol. To the solution was added dropwise methyl iodide (5 g) with stirring. After the mixture was allowed to stand overnight at room temperature, it was filtered to give 1.15 g (53%) of crude tetramethylpiperazinium diiodide. The filtrate was poured into a freshly prepared solution of ammonium reineckate (3.5 g) in 350 ml of ethanol with stirring. After the reaction mixture was allowed to stand overnight at room temperature, it was filtered. The precipitate was washed thoroughly with ethanol and water and dried *in vacuo* over phosphorus pentoxide to a constant weight. Reprecipitation from acetone and ethanol gave 2.9 g (52%) of pure Reinecke salt of ethylthiophosphorylcholine (mp 182–183°).

(12) O. Mitsunobu, T. Ohashi, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, in press.

Anal. Calcd for $C_{11}H_{25}CrN_7O_3S_5$: C, 24.18; H, 4.58; N, 17.95. Found: C, 25.08; H, 5.15; N, 18.19.

In a similar way, ethyl bis(2-diethylaminoethyl), ethyl bis(2-dimethylaminoethyl), and *n*-butyl bis(2-dimethylaminoethyl) phosphites were converted to the corresponding thiophosphoryl-2-aminoethanols. These results are summarized in Table II.

Preparation of Ethyl 2-Monomethylaminoethyl-2-dimethylaminoethyl Phosphite.—After a solution of 2-ethoxy-3-methyl-1,3,2-oxazaphospholidine (5.96 g, 0.04 mole) and 2-dimethylaminoethanol (3.00 g, 0.04 mole) in 50 ml of benzene was refluxed for 2 hr, the solvent was removed under reduced pressure. The vacuum distillation of the residue gave 6.7 g (70%) of ethyl 2-monomethylaminoethyl-2-dimethylaminoethyl phosphite (bp 70–89° at 1 mm).

Anal. Calcd for $C_9H_{23}N_2O_2P$: N, 11.76. Found: N, 11.61.

Preparation of Ethylthiophosphorylcholine from 2-Monomethylaminoethyl-2-dimethylaminoethyl Phosphite.—To a solution of ethyl 2-monomethylaminoethyl-2-dimethylaminoethyl phosphite (2.38 g, 0.01 mole) in 20 ml of benzene was added sulfur (0.32 g, 0.01 g-atom) in small portions with stirring at room temperature. After the mixture was allowed to stand overnight at room temperature, the solvent was removed under reduced pressure. The obtained viscous oily substance was heated at 95–105° for about 3 hr to give transparent resinous solid. The solid was dissolved in 20 ml of ethanol, and then 5 g of methyl iodide was added to the solution with stirring at room temperature. The precipitate of tetramethylpiperazinium diiodide (1.41 g, 57%) was collected by filtration. The filtrate was poured into a freshly prepared solution of ammonium reineckate (3.5 g) in 150 ml of ethanol with stirring. After the mixture was allowed to stand overnight at room temperature, it was filtered with suction. The precipitate was washed throughly with ethanol and water and then dried *in vacuo* over phosphorus pentoxide to a constant weight. Reprecipitation from acetone and ethanol gave 3.0 g (52%) of pure Reinecke salt of ethylthiophosphorylcholine (mp 182–184°), which was identified with an authentic sample.

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Reactions of Phosphorus Compounds. IX. Synthesis of a Series of 2H-1-benzopyrans and Determination of the Mechanism of Reaction

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A series of 2-alkyl and 2,2-dialkyl-2H-1-benzopyrans have been synthesized from substituted allyltriphenylphosphonium halides and sodium salicylaldehyde. The mechanism for this reaction has been shown to be one of initial attack on the aldehyde function to form the *cis* and *trans* Wittig products, followed by closure of the *cis* adduct to the 2H-1-benzopyran system.

Continuing our interest in the reactions of phosphonium salts, it has been shown[1] that sodium salicylaldehyde (I) will react with substituted allyltriphenylphosphonium salts to give a series of 2H-1-benzopyrans.

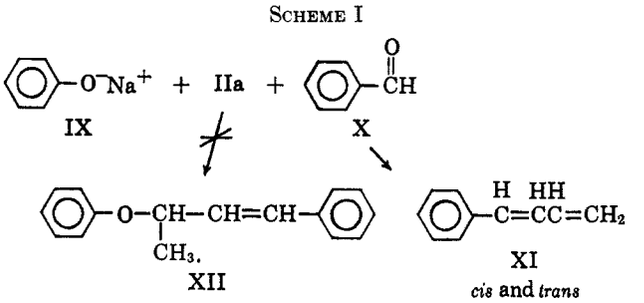
Allyltriphenylphosphonium bromide (IIa) will react with I in dimethylformamide (DMF) to give 2-methyl-2H-1-benzopyran (IIIa) in up to 34% yield.

The previously reported[2] preparation of 2H-1-benzopyran from vinyltriphenylphosphonium bromide and I led to the initial assumption that the present reaction is the result of a base-catalyzed isomerization[3] of the allyl salt, IIa, to the corresponding propenyltriphenylphosphonium bromide (VIII) followed by ring closure as described in our earlier paper.[2] Keough and Grayson[3] have shown, however, that the characteristic phosphonioethylation reactions of vinylphosphonium salts do not occur with the propenyl salt, VIII.

We have also shown[1] that the reaction of sodium phenoxide (IX) and salt, IIa, in the presence of benzaldehyde (X) gives only the two geometric isomers of phenylbutadiene (XI). None of the phenoxy adduct (XII), which would be expected if the reaction were the result of an initial isomerization of IIa to VIII followed by a Michael-type addition of phenoxide and then a Wittig reaction with benzaldehyde, was observed. (See Scheme I.)

Further work has shown that the mechanism for the formation of the substituted 2H-1-benzopyrans consists of an initial Wittig reaction with the aldehyde function of I, followed by addition to the butadiene system.

SCHEME I



If the salt, IIa, is allowed to react with I in DMF at 0°, two products are formed. These products cannot be isolated owing to polymerization and ring closure, but, when the mixture of the two is hydrogenated, 2-*n*-butylphenol (VIa) is isolated as the only product. This shows that the two intermediates must have been *cis*- and *trans*-O-(1,3-butadienyl)phenol (IVa and Va).

When the allyl salt, IIa, is allowed to react in refluxing ethanol with I, followed by neutralization of the reaction mixture with gaseous HBr, 1-vinyl-2-(O-hydroxyphenol)vinyltriphenylphosphonium bromide (XII) can be isolated.

One may postulate the formation of XIII as shown in Scheme II.

When the allyl salt, IIa, is allowed to react with I in $DOCH_3$, the product obtained is the 2-deuteriomethyl-3-deuterio-2H-1-benzopyran (XIV) (9% yield). This shows that there is indeed a base-catalyzed equilibrium in the salt giving XV before Wittig reaction (Scheme III).

(1) E. E. Schweizer and C. J. Berninger, *Chem. Comm.* (London), 92 (1965).
(2) E. E. Schweizer, *J. Am. Chem. Soc.*, **86**, 2744 (1964).
(3) P. T. Keough and M. Grayson, *J. Org. Chem.*, **29**, 631 (1964).