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The Preparation of 2-Alkoxy-1, 3, 2-oxazaphospholidines and Some Reactions

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The preparation of 2-alkoxy-1, 3, 2-oxazaphospholidines and some reactions will be described. 2-Alkoxy-1, 3, 2-oxazaphospholidines were prepared either from ethyl phosphorodichloridite and aminoethanols or, more conveniently, from tris[diethylamino]phosphite, aminoethanols and alcohols. 2-Alkoxy-1, 3, 2-oxazaphospholidines reacted easily with alcohols or *p*-toluenesulfonic acid monohydrate to give dialkyl aminoethyl phosphites or alkyl aminoethyl phosphite by the ring-opening at the P–N linkage of the phospholidines. It was oxidized by means of sulfur or nitrogen tetroxide to give 2-thione or 2-one in high yields. Further, it was found that it reacted with ethyl isocyanate to form 1 : 1 adducts. The structure of the adducts was confirmed, by a study of its chemical transformations, to be a seven-membered cyclic compound. It also reacted with carbon dioxide at about 120°C to yield the phosphorous-containing polyamide.

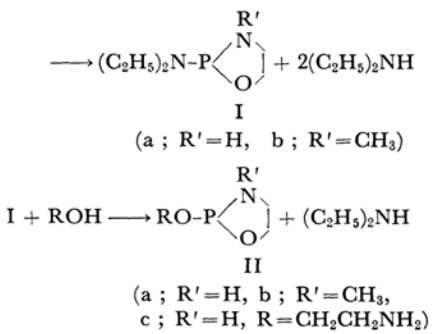
It has been reported in a previous paper[1] that 2, 3-diphenyl-1, 3, 2-oxazaphospholidine can be prepared by treating phenyl phosphinous dichloride with 2-phenylaminoethanol in the presence of two molecular equivalents of triethylamine.

It was also found by the present work that 2-alkoxy-3-methyl-1, 3, 2-oxazaphospholidine (IIb) can be prepared in a 69% yield from ethyl phosphorodichloridite and 2-methylaminoethanol. However, 2-alkoxy-1, 3, 2-oxazaphospholidine (IIa) could not be obtained by the use of 2-aminoethanol, which has a primary amino group, whereas 2-(2-aminoethyl)-1, 3, 2-oxazaphospholidine (IIc)[2] resulted in a 25% yield. It was further established that the phospholidines can be conveniently prepared from aminoethanols and tris[diethylamino]-phosphite. Various 2-alkoxy-1, 3, 2-oxazaphospholidines (II) were synthesized by the reaction

1) T. Mukaiyama and Y. Yokota, This Bulletin, **38**, 858 (1965).

2) R. Burgada, *Ann. Chim.*, **8**, 348 (1963).

of alcohols with 2-diethylamino-1, 3, 2-oxazaphospholidine (I), which had been prepared from tris-[diethylamino]phosphite and aminoethanols, as is shown in the following scheme. These results

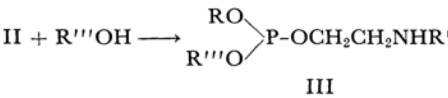


are summarized in Table I.

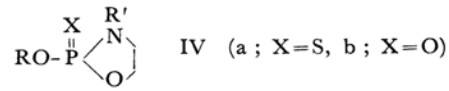
TABLE I. PREPARATION OF 2-ALKOXY-1, 3, 2-OXAZAPHOSPHOLIDINES

Alcohol	B. p. °C/mmHg	Yield %	Anal. N, % Calcd.	Found
C_2H_5OH	62—67/17	80	9.40	9.16
n-C_3H_7OH	83—85/20	79	8.59	8.70
i-C_3H_7OH	57—60/10	66	8.59	8.38
n-C_4H_9OH	98—100/21	77	7.91	8.16
t-C_4H_9OH	75—86/15	80	7.91	8.05
CH_2=$CHCH_2OH$	75—77/13	76	8.69	8.75
$CH_3NHCH_2CH_2OH$	105—107/0.14	80	15.73	15.91

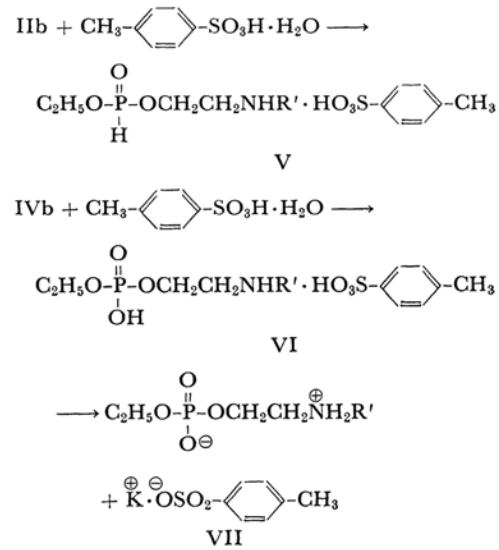
The phospholidines react with alcohols in refluxing benzene to give dialkyl 2-aminoethyl phosphites (III) in excellent yields by ring opening at the P–N linkage of the phospholidine. These results are summarized in Table II.



The phospholidines were oxidized easily by means of sulfur in benzene at room temperature or by means of nitrogen tetroxide in dichloromethane at −78°C, thus forming 2-alkoxy-1, 3, 2-oxazaphospholidine-2-thione (IVa) or 2-one (IVb) in 86% or 61% yields respectively.



When the phospholidines were treated with an equimolecular amount of p-toluenesulfonic acid monohydrate in benzene at room temperature, a ring-opening reaction took place exclusively at the P–N linkage of the phospholidine, giving the p-toluenesulfonium salt of ethyl 2-methylaminoethyl phosphite (V) in a quantitative yield. In a similar way, the p-toluenesulfonium salt of ethyl 2-methylaminoethyl phosphate (VI) was obtained in an excellent yield from IVb. It was then converted to the ethyl 2-methylaminoethyl phosphate (VII), which was identified as a barium salt, by treating it with barium hydroxide in an ethanol solution.



The phospholidines react with an equimolecular amount of ethyl isocyanate at about 110—120°C, resulting in the formation of 1 : 1 adducts (VIII).

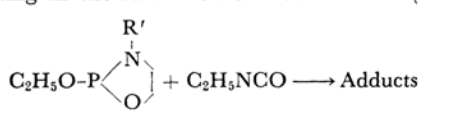
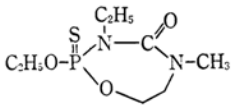


TABLE II. REACTION OF 2-ETHOXY-1, 3, 2-OXAZAPHOSPHOLIDINES WITH ALCOHOLS

R′	R‴OH	B. p. °C/mmHg	Yield %	Anal. N, % Calcd.	Found
CH_3	C_2H_5OH	50—51/1	67	7.18	7.25
CH_3	n-C_3H_7OH	52—53/1	68	6.70	6.76
CH_3	i-C_3H_7OH	79—83/7	73	6.70	6.74
CH_3	t-C_4H_9OH	44—47/6	46	6.28	6.29
CH_3	CH_2=$CHCH_2OH$	72—84/2	84	6.76	6.59
H	C_2H_5OH	50—52/2	56	7.73	7.76
H	n-C_3H_7OH	60—63/1	75	7.18	7.37
CH_3	$CH_3NHCH_2CH_2OH$	77—83/4	58	12.50	13.32

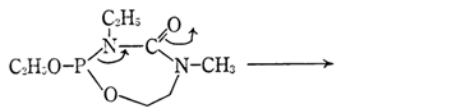
The structures of these adducts VIII were confirmed to be seven-membered cyclic ureid derivatives (XI) by the following spectral data and their chemical transformations. The infrared spectra of these adducts (VIII) showed an absorption at 1660 cm^{-1} due to the ureid carbonyl group. VIII was oxidized exothermally by means of sulfur in a benzene solution at room temperature to yield IX in a 89% yield. This was in turn hydrolyzed to the *p*-toluenesulfonium salt (X) by ring opening when treated with *p*-toluenesulfonic acid monohydrate in refluxing benzene.



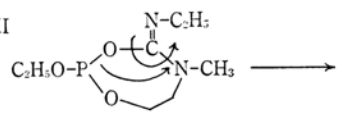
IX

X

When heated at about 180°C, the adducts decomposed to give ethyl isonitrile (XIII) and oxazaphospholidine-2-one (IVb) by way of an internal nucleophilic displacement, as is shown below.



XI



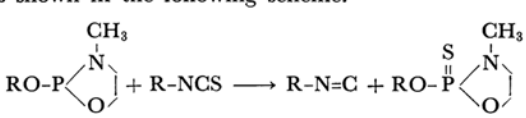
XII

IVb + $C_2H_5N{=}C$

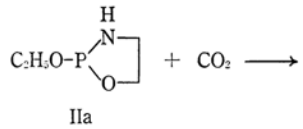
XIII

On the other hand, the reaction of phenyl isocyanate and the phospholidine at 110—120°C gave an undistillable oily substance, which decomposed to give a small amount of phenyl isonitrile and oxazaphospholidine-2-one (IVb) along with a glassy, hygroscopic resinous substance.

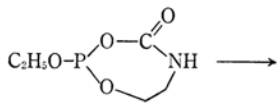
Similarly, isonitriles and oxazaphospholidine-2-thione were prepared when ethyl isothiocyanate or phenyl isothiocyanate was heated with II, as is shown in the following scheme.



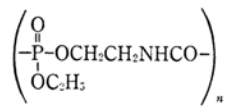
2-Ethoxy-1, 3, 2-oxazaphospholidine (IIa) absorbed carbon dioxide at 0°C, giving a viscous oily adduct (XIV) with infrared absorptions at 1650 and 1565 cm^{-1} due to the amide carbonyl group. When XIV was heated under reduced pressure, 35% of the IIa was recovered, whereas when it was heated at 110—120°C in a sealed tube or under a carbon dioxide atmosphere, a glassy, hygroscopic polymer (XV), m. p. 186—188°C, was produced.



IIa



XIV



XV

Experimental

All melting points and boiling points are uncorrected.

Solvents and Reagents.—The solvents and alcohols were dried and purified by ordinary procedures.

The Preparation of 2-Alkoxy-3-methyl-1, 3, 2-oxazaphospholidine (IIb).—A mixture of 2-methylaminoethanol (3.75 g., 0.05 mol.) and triethylamine (15.45 g., 0.125 mol.) was added, drop by drop, into a solution of ethyl dichloro phosphite (7.35 g., 0.05 mol.) in 100 ml. of ether at 0°C with stirring. After the solution had been stirred for 2 hr. at room temperature, the precipitate of triethylammonium hydrochloride was filtered and washed twice with ether (10 ml.). After the ether had been removed under reduced pressure, 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (IIb) (b. p. 62—67°C/17 mmHg, 3.1 g., 69%) was obtained.

Found : N, 9.16. Calcd. for $C_5H_{12}O_2NP$: N, 9.40%.

The Reaction of Ethyl Dichloro Phosphite with 2-Aminoethanol. — A mixture of 2-aminoethanol (3.05 g., 0.05 mol.) and triethylamine (10.1 g., 0.10 mol.) was added, drop by drop, into a solution of ethyl dichloro phosphite (7.35 g., 0.05 mol.) in 70 ml. of ether at 0°C with stirring. After the mixture had been stirred for 2 hr. at room temperature, the precipitate of triethylammonium hydrochloride was removed from the reaction mixture. The removal of the solvent from the filtrate under reduced pressure gave an oily product which crystallized after it had been allowed to stand overnight. The needle crystalline of 2-(2-aminoethyl)-1, 3, 2-oxazaphospholidine (IIc) (m. p. 106—120°C, 3.7 g., 25%) was collected. Recrystallization from benzene gave an analytical sample (m. p. 116°C).

Found : N, 9.45. Calcd. for $C_4H_{11}O_2N_2P$: N, 9.33%.

The vaccum distillation of the filtrate gave an unidentified oil (b. p. 80—86°C/0.05 mmHg, 0.82 g.).

The Preparation of 2-Diethylamino-3-methyl-1, 3, 2-oxazaphospholidine (Ib).—A solution of tris[diethylamino]phosphite (4.94 g., 0.02 mol.) and 2-methylaminoethanol (1.50 g., 0.02 mol.) in 30 ml. of benzene was refluxed for 3 hr. After the benzene and diethylamine had been removed under reduced pressure, 2-diethylamino-3-methyl-1, 3, 2-oxazaphospholidine (b. p. 88—90°C/3 mmHg, 2.1 g., 60%) was obtained by vacuum distillation.

Found: N, 15.91. Calcd. for $C_7H_{17}ON_2P$: N, 15.91%.

The Preparation of 2-Diethylamino-1, 3, 2-oxazaphospholidine (Ia).—By a procedure analogous to that mentioned above, 2-diethylamino-1, 3, 2-oxazaphospholidine (b. p. 91—97°C/5 mmHg, 1.52 g., 47%) was obtained from the reaction of tris[diethylamino]-phosphite (4.94 g., 0.02 mol.) and 2-aminoethanol (1.42 g., 0.02 mol.). A small amount of the needle crystalline of 2-(2-aminoethyl)-1, 3, 2-oxazaphospholidine was also obtained as a by-product.

Found: N, 17.29. Calcd. for $C_6H_{15}ON_2P$: N, 16.95%.

The Preparation of 2-Alkoxy-1, 3, 2-oxazaphospholidines.—A solution of 2-diethylamino-2-methyl-1, 3, 2-oxazaphospholidine (1.76 g., 0.01 mol.) and ethanol (0.46 g., 0.01 mol.) in 20 ml. of benzene was refluxed for 2 hr. After the benzene and diethylamine had been removed under reduced pressure, 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (b. p. 62—67°C/17 mmHg, 1.19 g., 80%) was obtained by vacuum distillation.

In a similar fashion, the reaction of various alcohols and 2-diethylamino-1, 3, 2-oxazaphospholidine gave the corresponding 2-alkoxy-1, 3, 2-oxazaphospholidines. The results are summarized in Table I.

The Reaction of 2-Ethoxy-1, 3, 2-oxazaphospholidine with Alcohols.— A solution of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) and ethanol (0.46 g., 0.01 mol.) in 15 ml. of benzene was refluxed for 2 hr. After the solvent had been removed under reduced pressure, 2-methylaminoethyl diethyl phosphite (b. p. 49—51°C/1 mmHg, 1.3 g., 67%) was obtained by vacuum distillation.

In a similar fashion, the reaction of various alcohols and 2-ethoxy-1, 3, 2-oxazaphospholidines gave the corresponding dialkyl 2-aminoethyl phosphites, as is shown in Table II.

The Oxidation of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine by Means of Sulfur.—Into a solution of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) in 20 ml. of benzene was added sulfur in small portions with stirring at room temperature. After the stirring had been continued for an additional hour, the unreacted sulfur was removed by filtration. Benzene was removed from the filtrate under reduced pressure and the residue was distilled in a vaccum, giving 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-thione (b. p. 76—78°C/0.12 mmHg, 1.56 g., 86%).

Found: N, 7.53. Calcd. for $C_5H_{12}O_2SNP$: N, 7.73%.

The Oxidation of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine by Means of Nitrogen Tetroxide.—Into a solution of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) in 15 ml. of dichloromethane there was added, drop by drop, a solution of nitrogen tetroxide in dichloromethane at −78°C with stirring; this was continued until the solution turned blue. After the solvent had been removed under reduced pressure, 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-one (b. p. 90—91°C/0.2 mmHg, 1.0 g., 61%) was obtained.

Found: N, 8.52. Calcd. for $C_5H_{12}O_3NP$: N, 8.48%.

The Reaction of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine with *p*-Toluenesulfonic Acid Monohydrate.—A solution of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) and *p*-toluenesulfonic acid monohydrate (1.90 g., 0.01 mol.) in 15 ml. of benzene was refluxed for an hour. A transparent viscous oil separated from the reaction mixture. After the mixture had been kept standing overnight at room temperature, the benzene was removed by decantation. The oil was then rinsed three times with benzene (10 ml.) in order to remove the by-products; this gave the *p*-toluenesulfonium salt of ethyl 2-methylamino phosphite (3.30 g., 97%).

Found: N, 4.37. Calcd. for $C_{12}H_{22}O_6NP$: N, 4.31%.

The Reaction of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-one with *p*-Toluenesulfonic Acid Monohydrate.—Into a solution of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-one (6.60 g., 0.04 mol.) in 50 ml. of benzene was added *p*-toluenesulfonic acid monohydrate (7.60 g., 0.04 mol.) in small portions with stirring at room temperature. After stirring had been continued for an additional 2 hr., the reaction mixture was kept standing overnight at room temperature. A transparent viscous oil thereupon separated from the reaction mixture. The benzene was removed by decantation and the oil was rinsed three times with benzene (10 ml.), thus giving *p*-toluenesulfonium salt of ethyl 2-methylaminoethyl phosphate (14.0 g., 98%).

Into a solution of the salt in 50 ml. of ethanol, a solution of potassium hydroxide (2.24 g., 0.04 mol.) in 50 ml. of ethanol was added, drop by drop, with stirring. A white precipitate, the potassium salt of *p*-toluenesulfonic acid (8.40 g., 74%), was then collected by filtration. To the filtrate there was added an aqueous solution of barium hydroxide; this gave a white precipitate of the barium salt of ethyl 2-methylaminoethyl phosphate (9.2 g., 52%).

Found: C, 22.33; H, 5.59; N, 4.73. Calcd. for $C_{10}H_{30}O_{10}N_2P_2Ba$: C, 22.07; H, 5.61; N, 5.21%.

The Reaction of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine with Ethyl Isocyanate.—A mixture of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) and ethyl isocyanate (0.71 g., 0.01 mol.) was heated at 110—120°C for 4 hr. in a sealed tube. The reaction mixture was then distilled under reduced pressure, thus obtaining a 1 : 1 adduct (b. p. 80—83°C/0.11 mmHg, 1.57 g., 68%). Its infrared spectrum showed absorptions at 1700 and 1660 cm^{-1}.

Found: N, 12.69. Calcd. for $C_8H_{17}O_3N_2P$: N, 12.71%.

The Oxidation of the Adduct by Means of Sulfur.—Into a solution of the adduct (2.20 g.) in 20 ml. of benzene was added sulfur in small portions with stirring at room temperature. After it had been stirred for additional 30 min., the reaction mixture was kept standing overnight. After the solvent had been removed under reduced pressure, IX (b. p. 111—126°C/

0.09 mmHg, 2.24 g., 89%) was obtained by vacuum distillation.

Found: N, 11.40. Calcd. for $C_8H_{17}O_2SN_2P$: N, 11.11%.

The Hydrolysis of IX by Means of *p*-Toluenesulfonic Acid Monohydrate.—Into a solution of IX (1.09 g.) in 10 ml. of benzene was added *p*-toluenesulfonic acid monohydrate (0.95 g.) with stirring at room temperature. The reaction soon started, with a liberation of heat. After stirring had been continued for 30 min., the reaction mixture was further refluxed for 2 hr., whereupon a transparent viscous oil was separated from the reaction mixture. After the solvent had been removed by decantation, the oil was rinsed twice with benzene (10 ml.). The *p*-toluenesulfonium salt of the thiophosphate X (2.04 g., 100%) was obtained.

Found: N, 6.89. Calcd. for $C_{15}H_{27}O_7N_2SP$: N, 6.83%.

The Thermal Decomposition of the Adduct.—The adduct (2.20 g.) was heated at 180°C for 2 hr. under nitrogen. The vacuum distillation of the adduct gave 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-one (b. p. 85—93°C/0.2 mmHg, 0.2 g.) and ethyl isonitrile (about 0.5 g.) which was trapped in dry-ice acetone bath, a resinous solid remained in a Claisen flask.

The Reaction of 2-Ethoxy-1, 3, 2-oxazaphospholidine with Ethyl Isocyanate.—A solution of 2-ethoxy-1, 3, 2-oxazaphospholidine (1.35 g., 0.01 mol.) and ethyl isocyanate (0.71 g., 0.01 mol.) in 15 ml. of benzene was refluxed for 2 hr. After the benzene had been removed under reduced pressure, an adduct (b. p. 107—110°C/0.15 mmHg, 1.32 g., 64%) was obtained by vacuum distillation. Its infrared spectrum showed absorptions at 1700 and 1650 cm^{-1}.

Found: N, 13.51. Calcd. for $C_7H_{15}O_3N_2P$: N, 13.59%.

The Reaction of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine with Phenyl Isocyanate.—A mixture of 2-ethoxy-3-methyl-1, 3, 2-oxzaphospholidine (1.49 g., 0.01 mol.) and phenyl isocyanate (1.19 g., 0.01 mol.) was heated at 110—120°C for 4 hr. in a sealed tube. The fractional distillation of the mixture gave phenyl isonitrile (0.3 g.) and 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-one (0.2 g.), along with a large amount of a transparent, hygroscopic resinous solid.

The Reaction of 2-Ethoxy-3-methyl-1, 3, 2-oxazaphospholidine with Phenyl Isothiocyanate and Ethyl Isothiocyanate.—A mixture of 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) and phenyl isothiocyanate (1.35 g., 0.01 mol.) was heated at 110—120°C for 4 hr. in a sealed tube. The fractional distillation of the mixture gave phenyl isonitrile (b. p. 65—72°C/28 mmHg, 0.45 g., 45%) and 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-thione (b. p. 77—78°C/0.16 mmHg, 1.12 g., 62%). Similarly, the reaction of ethyl isothiocyanate (0.87 g., 0.01 mol.) and 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine (1.49 g., 0.01 mol.) gave ethyl isonitrile and 2-ethoxy-3-methyl-1, 3, 2-oxazaphospholidine-2-thione (1.40 g., 77%).

The Reaction of 2-Ethoxy-1, 3, 2-oxazaphospholidine with Carbon Dioxide.—A) 2-Ethoxy-1, 3, 2-oxazaphospholidine (2.31 g., 0.018 mol.) absorbed 0.24 g. of carbon dioxide under atmospheric pressure at 0°C, giving a transparent viscous oil. Its infrared spectrum showed absorptions at 1650 and 1565 cm^{-1}. The fractional distillation of the oily adduct recovered 2-ethoxy-1, 3, 2-oxazaphospholidine (0.8 g., 35%). A white glassy hygroscopic solid was obtained when the oily adduct was heated at 110—120°C for 6 hr. in a sealed tube. The resultant polymer was crushed, refluxed in 15 ml. of benzene, and collected (m. p. 186—188°C, 1.15 g.). Its infrared spectrum showed absorptions at 1650 and 1560 (CONH), 1220 (P=O), 1050 (POC) cm^{-1}. It did not dissolve in water, dichloromethane, benzene, acetonitrile or *o*-dichlorobenzene.

From the benzene extract, 0.9 g. of 2-ethoxy-1, 3, 2-oxazaphospholidine (b. p. 75—83°C/21 mmHg) was recovered.

B) 2-Ethoxy-1, 3, 2-oxazaphospholidine (3.0 g.) was heated at 110—120°C for 3 hr. under a carbon dioxide atmosphere of 55 kg./cm^2 in an autoclave. After the mixture had been kept standing overnight, a white glassy, hygroscopic solid was obtained. The polymer was crushed, refluxed in 20 ml. of benzene, and collected by filtration (m. p. 179—183°C, 3.7 g.). Its infrared spectrum showed absorptions at 1650 and 1540 (CONH), 1220 (P=O), and 1050 (POC) cm^{-1}.

The authors wish to express their hearty thanks to Dr. Oyo Mitsunobu for his helpful suggestion and Miss Keiko Nakamura for her microanalyses.