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139. Yuichi Kanaoka, Minoru Machida, Osamu Yonemitsu, and Yoshio Ban: Polyphosphate Esters as a Synthetic Agent. III.[*1] Amide and Peptide Syntheses.[*2,3]

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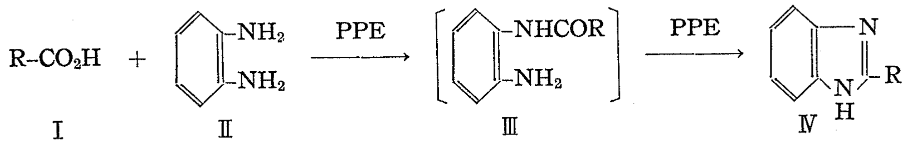
Phosphorus pentoxide in diethyl phosphite was used originally by Schramm and Wissmann for peptide synthesis[1] under the name of "polyphosphate esters." Erlanger and Kokowsky also employed the same mixture in a similar manner.[2] In the course of our study on polyphosphate esters (PPE), interest has been centered on the activation of carboxylic group in the presence of PPE for general synthetic purpose. The present paper describes amide synthesis from free carboxylic and primary amine, together with the reinvestigation of peptide synthesis, by means of PPE, which is prepared invariably by reaction of diethyl ether with phosphorus pentoxide in this case.

Our earlier work showed that carboxylic acid (I) reacts with *o*-phenylenediamine (II) by heating with PPE to yield 2-substituted benzimidazole (IV).[3] The initial phase of this synthesis may involve, as an intermediate step, the formation of amide (III) from I and II, which was, in fact, occasionally isolated from reaction mixture. This observation indicated that amide formation with PPE takes place under rather mild conditions. Erlanger also suggested that phosphorus pentoxide in diethyl phosphite may be useful for preparation of some amide-type compounds.[2]



I II III IV

Table I. Benzanilide[a)]

PPE (equiv.)[b)]	Et₃N (mole)	Yield (%)[c)] Room temp. (24 hr.)	Reflux (1 hr.)	(2 hr.)
1	0		42	
3	0	25	46	53
3	3		75	
6	0	36	48	50
10	0	34	46	50
15	0	36	40	31

a) Molar ratio of benzoic acid and aniline, 1:1.1; solvent, chloroform.
b) EtO_3P taken as one equivalent.
c) m.p. 158~160°.

[*1] Part II: Tetrahedron Letters, **1964**, 2419.

[*2] Presented at the Hokkaido Branch Meeting of the Pharmaceutical Society of Japan, June, 1964, Sapporo.

[*3] This paper constitutes Part I of the series, "Amino Acids and Peptides."

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1) G. Schramm, H. Wissmann: Chem. Ber., **91**, 1073 (1958).

2) B.F. Erlanger, N. Kokowsky: J. Org. Chem., **26**, 2534 (1961).

3) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, Y. Ban: This Bulletin, **12**, 773 (1964).

Experimental conditions for amide formation was now examined with benzanilide as an example, as shown in Table I. In the presence of PPE, as expected, benzanilide was formed from benzoic acid and aniline in moderate yields either at room temperature for 24 hours or at refluxing in chloroform solution for an hour. During the course of reaction water is produced and may rapidly react with PPE to hydrolyze its P-O-P linkage. Therefore, as an agent in condensation reaction, PPE will react rather on this stoichiometric basis than catalytic. Based on the results in Table I, six equivalents were taken as standard working amount of PPE in most of our experiments.

Amide formation by means of polyphosphoric acid (PPA) was examined earlier by Snyder.[4] In the presence of PPA, amines were generally incapable of forming amide with carboxylic acid. Only such a weak base as *p*-nitroaniline afforded corresponding amide with benzoic acid. This pronounced difference in behavior of PPA and PPE to amide formation reaction must be noted here. This difference may be rationalized by considering different proton content in both media. Since PPA is a mixture of polyphosphoric acid species,[5] a medium of PPA contains certain amount of acid proton in the form of various polyphosphoric acids. These protons may, as a Brønsted acid, readily trap amine nitrogens to diminish their nucleophilic reactivity thus resulting in failure of amide formation. Conversely, PPE contains at least theoretically no acid proton as would be expected from the process of preparation. Although any practical process dealing with commercial phosphorus pentoxide seems unable to be free from trace of water,[6] there is no doubt that proton content of PPE is far below that of PPA. This aprotic medium of PPE is evidently more favorable to amide formation than that of PPA.

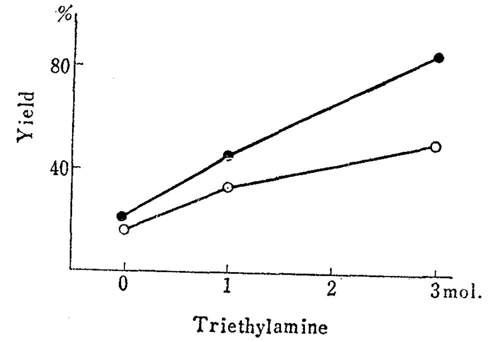

Fig. 1. Effect of added Base in Amide Synthesis

——○—— Phthaloylglycine benzylamide (V)
——●—— Phthaloyl-β-alanine benzylamide (VI)

Addition of triethylamine to a reaction mixture improved yield of benzanilide as shown in Table I. While condensation proceeds, content of acid proton of reaction mixture increases in consequence of water liberation, which will lead to more unfavorable medium for amine activation. In cases where strong base is present in a medium, it would interact with newly formed phosphoric protons to neutralization. The promoting influence of tertiary amine on the amide formation may be explained in terms of this buffering effect of an added base as a proton acceptor. This participation of tertiary amine was systematically observed in the preparation of benzylamide of N-phthaloylglycine (V) and N-phthaloyl-β-alanine (VI) as shown in the Fig. 1. Addition of three moles of triethylamine raised yields of amides up to 3~4 times.

A variety of amides and imides were synthesized by this procedure as summarized in Table II. Amides were synthesized from aliphatic and aromatic acids and amines. Equimolar amounts of carboxylic acid and primary amine were heated in chloroform or acetonitrile solution with PPE in the presence of three molar equivalents of triethylamine. Acetanilide was readily obtained. As an illustration of heterocyclic acid, nicotinic and 2-furoic acid gave corresponding anilide, VII and VIII, in good yields. Amide

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4) H.R. Snyder, C.J. Elston: J. Am. Chem. Soc., **76**, 3039 (1954).

5) F. Uhlig, H.R. Snyder: "Advances in Organic Chemistry," Vol. 1, p. 35 (1960), Interscience Publishers, N.Y.

6) W. Wieker, H.P. Walter, E. Thilo: Chem. Ber., **97**, 2385 (1964).

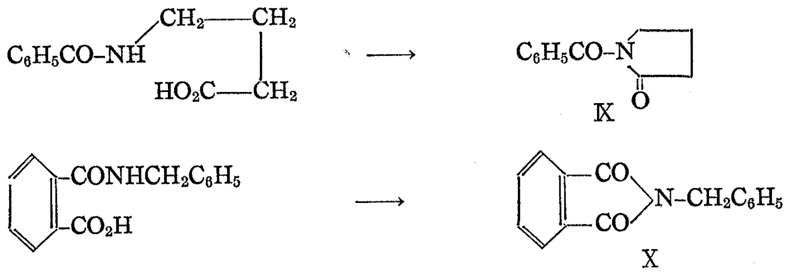
Table II. Amides and Imides

Product	PPE (equiv.)	Et_3N (mole)	Ref. time (hr.)	Solvent	Yield (%)
Acetanilide	15	3	24[a)]	$CHCl_3$	34
	10	3	1	〃	70
Nicotinanilide (VII)	6	3	1	CH_3CN	77
	10	3	1	$CHCl_3$	79
2-Furanilide (VIII)	6	3	1	CH_3CN	85
	10	3	1	$CHCl_3$	70
1-Benzoyl-2-pyrrolidinone (IX)	15	3	24[a)]	〃	30
	10	3	1	〃	57
N-Benzylphthalimide (X)	10	3	1	〃	48

a) at room temp.

synthesis by means of PPE thus provides a convenient preparative route from carboxylic acid to amide under mild conditions.

Upon treatment with PPE in a similar way, 4-benzamidobutyric acid was cyclized to yield 1-benzoyl-2-pyrrolidinone (IX). N-Benzylphthalamic acid gave N-benzylphthalimide (X). These results show that PPE procedure is applicable also to imide cyclization.



IX

X

Many phosphorus compounds have been introduced as coupling agent in the field of peptide synthesis.[7~10)] These coupling methods by means of phosphorus derivatives, including various types of phosphate and phosphite, were referred to as mixed anhydride method with phosphoric and phosphorus acid,[8)] since reagent primarily forms mixed anhydride with carboxylic acid component. In the phosphite method, however, reagent reacts also with amine component to give a reactive intermediate, namely phosphorus amide or imide, among which phosphorazo compound is a typical example.[9)] Thus the nature of the intermediate depends upon the order of mixing the reactants.[11)] When phosphorus pentoxide in diethyl phosphite was used for coupling purpose, metaphosphate ester was assumed to be an actual reactive species by Schramm. Less racemization observed by them was ascribed to that the reaction might proceed by way of phosphorazo intermediate to obviate carboxylic group activation, which is generally assumed to be largely responsible for racemization during coupling process.[1)]

Table III gives the coupling experiments with N-phthaloylglycine and glycine ethyl ester hydrochloride (XI) to form N-(N-phthaloylglycyl)glycine ethyl ester (XII). Peptide

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7) J. P. Greenstein, M. Winitz: "Chemistry of the Amino Acids," p. 982, 988, 999, 1006 (1961), J. Wiley, N. Y.

8) N. F. Albertson: "Organic Reactions," Vol. 12, p. 156 (1962), J. Wiley, N. Y.

9) S. Goldschmidt, H. L. Krauss: "Newer Methods of Preparative Organic Chemistry," Vol. 2, p. 31 (1963), Academic Press, N. Y.

10) T. Wieland, H. Determann: Angew. Chem. Int. Ed., 2, 365 (1963).

11) G. W. Anderson, J. Blodinger, A. D. Welcher: J. Am. Chem. Soc., 74, 5309 (1952).

Table III. Phth·Gly·Gly·OEt (XII)

PPE (equiv.)	Et_3N (mole)	Ref. time (hr.)	Solvent	Yield (%)
3	1	1	$CHCl_3$	45
3	2	1	〃	46
3	3	1	〃	63
6	1	1	〃	64
6	2	1	〃	65
6	3	1	〃	67
15	3	3	〃	81
6	3	1	CH_3CN	75
15	1.5	1	〃	65
15	3	1	〃	77
6	3	1	THF	69
6	3	1	EtOAc	59
15	1.5	24[a]	CH_3CN	24
15	3	24[a]	〃	46

[a] at room temp.

Table IV. Peptide Derivatives[a]

Product	PPE (equiv.)	Et_3N (mole)	Ref. time (hr.)	Solvent	Yield (%)
Cbz·Gly·Gly·OEt (XVIII)	6	3	1	CH_3CN	71
Cbz-DL-Ala·Gly·OEt (XIX)	6	3	1	〃	77
Phth-β-Ala·Gly·OEt (XX)	6	3	1	〃	70
Bz-DL-Ala·Gly·OEt (XXI)	6	3	1	$CHCl_3$	47
	15	3	1	〃	55
Bz-DL-Phe·Gly·OEt (XXII)	15	3	3	〃	75
Phth·Gly·Gly·Gly·OEt (XXIII)	6	3	1	CH_3CN	61
Bz-DL-Leu·Gly·OEt[b]	6	3	1	〃	71
Cbz·Gly-DL-Phe·Gly·OEt[b]	15	1	1	$CHCl_3$	62

[a] The abbreviations are: Cbz: carbobenzoxy; Bz: benzoyl; Phth: phthaloyl; OEt: ethyl ester; Gly: glycine; Ala: alanine; Leu: leucine; Phe: phenylalanine.

[b] Starting material was L-isomer.

synthesis was then carried out following the general procedure determined from the above model reaction as summarized in Table IV. Di- and tripeptide esters were obtained by coupling glycine ethyl ester hydrochloride with N-protected amino acids and N-protected dipeptides, respectively. In accord with the results in analogous phosphorus pentoxide method,[1,2] the use of PPE appeared convenient for the synthesis of simple peptide derivatives. However, in the case of optically active component, fully racemized product was isolated. In order to confirm the aspect of racemization, Anderson's[12] and Young's[13] tests were applied to this procedure. Both of N-[N-(N-benzyloxycarbonylglycyl)phenylalanyl]glycine ethyl ester and N-(N-benzoylleucyl)glycine ethyl ester thus obtained were racemic, no optically active product being detected. Neither the use of glycine ethyl ester in place of the hydrochloride and triethylamine[14] or adaptation of "amide procedure"[11] in experimental conditions changed the recemization extent. Thus, application of PPE for peptide synthesis is of only seriously limited value.

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12) G. W. Anderson, F. M. Callahan: J. Am. Chem. Soc., **80**, 2902 (1958).
13) M. W. Williams, G. T. Young: J. Chem. Soc., **1963**, 881.
14) *Idem*: *Ibid.*, **1964**, 3701.

Probably this results may be due to following reasons: First, PPE and the substance formed by reacting phosphorus pentoxide and diethyl phosphite are not exactly the same. Secondly, PPE, as a strong condensing agent, would cause rapid intermediate formation of oxazolone from acylamino acid or peptide, which, as generally assumed, would readily lead to racemization. Consequently, PPE would react not only with amine component but also with acid component[15] or both of them.

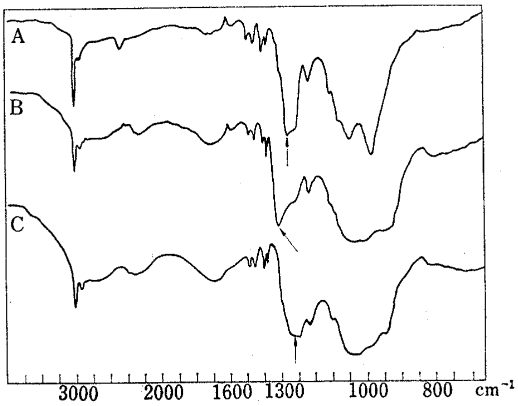
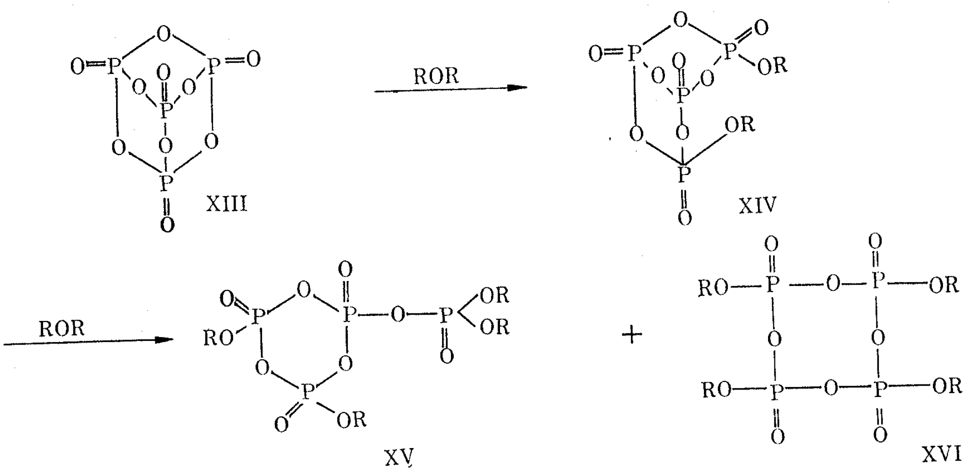


Fig. 2. Infrared Spectra of Polyphosphate Esters and Related Substances

A: Phosphorus pentoxide in diethyl phosphite ($CHCl_3$)
B: PPE in $CHCl_3$
C: PPE after treatment with trace of water ($CHCl_3$)

Infrared spectra of PPE and a solution of phosphorus pentoxide in diethyl phosphite are given in Fig. 2. The spectrum of PPE is in good conformity with those of "Trimetaphosphat" or "Äthylmetaphosphat"[16] and "metaphosphate esters",[17] while the spectrum of phosphorus pentoxide in diethyl phosphite is somewhat different from that of PPE in support of the above postulate. It should be noted that the strong band of PPE near 1330 cm^{-1}, which was assigned for cyclic phosphate esters,[16,17] shifted to about 1260 cm^{-1} in the latter as shown by arrows in Fig. 2. When PPE was treated with trace of water, this band disappeared and new broad bands appeared between 1200~1260 cm^{-1} [17] (Fig. 2. C).

In regard to its high reactivity, mainly related to phosphorylation problem, the structure of PPE or metaphosphate recently received much attention.[3] Based on the titration study and other results, Schramm concluded that PPE or so-called "Langheld-Ester," prepared by reaction of phosphorus pentoxide with diethyl ether, is a mixture of approximately four parts of isometaphosphate ester (XV) and one part of tetrametaphosphate ester (XVI),[17] a conclusion close to that drawn by Thilo earlier.[18] This mixture was expected to form when two P-O-P linkages within the tetrahedral P_4O_{10} molecule (XIII) are split by etherolysis as shown in the accompanying equation. In their recent



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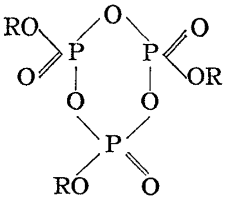
[15] Y. Kanaoka, K. Tanizawa: unpublished results.
[16] F. Cramer, H. Hettler: Chem. Ber., **91**, 1181 (1958).
[17] W. Pollmann, G. Schramm: Biochim. Biophys. Acta., **80**, 1 (1964).
[18] R. Rätz, E. Thilo: Ann., **572**, 173 (1951).

report,[6] Thilo, *et al.* reinvestigated the problem and revealed several points overlooked before. It was pointed out that Langheld-Ester, prepared even from phosphorus pentoxide purified by sublimation, contains invariably at least 0.8 free OH per four P atoms and this water content of metaphosphate may play a significant role. From this together with the paperchromatographic study, it was concluded by them that Langheld-Ester does not consist, or at least not only, of the quoted tetramers, but a mixture of various esters. They also showed that even "authentic" sample prepared from well-defined inorganic salt such as silver trimetaphosphate is not of simple structure as Cramer assumed when he proposed trimetaphosphate structure (XVII) for PPE.[3,16]

At present, we are not perfectly certain as to which of tetramers,[17,18] trimer,[16,19] monomer,[20] or others represents an appropriate structure of PPE.[*5] Most reasonable and safe interpretation may be, at least in principle, that PPE is a mixture of condensed phosphate esters which are in equilibrium presumably under structural reorganization.[6,21] Thus PPE may be tentatively represented as $(C_2H_5O_3P)_n$ or ethyl metaphosphate. In our works, $C_2H_5O_3P$ is taken simply in convenience as a unit or one equivalent of PPE. Although there have remained detailed structural problems unsolved, it seems still possible and significant to formulate and establish the utility of PPE as a synthetic tool on the well reproducible basis.[22]


XVII

Experimental[*6]

Preparation of Polyphosphate Esters (PPE)——PPE was prepared by the procedure essentially similar to Schramm's description.[17,23] Phosphorus pentoxide (225 g.) was added to a solution of dry $CHCl_3$ (225 ml.) and abs. ether (450 ml.), and the mixture was refluxed in a water-bath (65~70°) for 30~40 hr. $CHCl_3$ was, after usual purification, shaken with phosphorus pentoxide and filtered through glass wool then used immediately. After heating, the mixture was filtered using a glass-filter from some amount of undissolved material, and evaporated *in vacuo* below 65~70°. The residue is a viscous, slightly brown syrup (ca. 200 g.) and can be used as a synthetic agent without further purification.

General Procedure in Amide and Peptide Syntheses——Amino component (4 mmol.) and carboxylic acid component (4 mmol.) were dissolved or suspended in $CHCl_3$ or CH_3CN (twofold volume of weight of PPE). To this mixture triethylamine (12 mmol.) and PPE (6 equivalents or as specified in Tables or Figure) were added and refluxed on a steam-bath for 1 hr. Solvent was removed *in vacuo*, cracked ice and water were added to the residue and the whole was made alkaline by adding excess of powdered $NaHCO_3$ then stirred for 1 hr. to effect complete decomposition of the reagent. The mixture was extracted with EtOAc or $CHCl_3$ and the extract was washed with water, 10% HCl, water and dried (Na_2SO_4). Removal of solvent *in vacuo* left a solid mass, which was recrystallized to give amide or peptide derivative. In the case of peptide synthesis, the effective amount of triethylamine was mostly 2 molar equiv. since amino acid ester hydrochloride was usually used which consumes one equiv. of the amine by neutralization. In the case of amide synthesis, aq. NaOH was used in place of $NaHCO_3$.

N-Benzyl-2-phthalimidoacetamide (V)——N-Phthaloylglycine[24] and benzylamine were reacted as in the general procedure with or without triethylamine as specified in Fig. 1. V, colorless needles from EtOH, m.p. 214~216° (lit.,[25] m.p. 216~218°). IR cm^{-1} (Nujol): 1660 (amide I).

[*5] Note Added in Proof: A new study on the structure of PPE has been published by G. Burkhardt, M.P. Klein, M. Calvin (J. Am. Chem. Soc., **87**, 591 (1965)). The presence of tetrapolyphosphate ester, a linear tetramer, was proposed as one of components of PPE together with XIV, XV, and XVI based on NMR data.

[*6] Melting points are uncorrected.

19) T.M. Jacob, H.G. Khorana: J. Am. Chem. Soc., **86**, 1630 (1964).
20) Lord Todd: Pro. Chem. Soc., **1962**, 199.
21) E. Schwarzmann, J.R. Van Wazer: J. Am. Chem. Soc., **83**, 365 (1961).
22) Y. Kanaoka, *et al.*: to be published, and Part I and II of this series.
23) G. Schramm, H. Grotsch, W. Pollmann: Angew. Chem. Int. Ed., **1**, 1 (1962).
24) F.E. King, J.W. Clark-Lewis, R. Wade, W.A. Swindin: J. Chem. Soc., **1957**, 875.
25) J.C. Sheehan, V.S. Frank: J. Am. Chem. Soc., **72**, 1312 (1950).

N-Benzyl-3-phthalimidopropionamide (VI)——N-Phthaloyl-β-alanine[26] and benzylamine were reacted as above. Ⅵ, colorless fine needles from EtOH, m.p. 200~201°. IR cm^{-1}(Nujol) : 1635 (amide I). *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$(Ⅵ) : C, 70.11; H, 5.23; N, 9.09. Found : C, 70.17; H, 5.21; N, 9.21.

Nicotinanilide (VII)——Colorless prisms from benzene-petr. ether, m.p. 130~131° (lit.,[27] m.p. 124~126° (crude)). IR cm^{-1}(Nujol) : 1650 (amide I).

2-Furanilide (VIII)——Colorless fine needles from benzene, m.p. 121~123° (lit.,[28] m.p. 123.5°). IR cm^{-1}(Nujol) : 1655 (amide I).

1-Benzoyl-2-pyrrolidinone (IX)——4-Benzamidobutyric acid was prepared from 4-aminobutyric acid. Recrystallization from water then from benzene gave colorless needles of m.p. 86~88° (lit.,[29] m.p. 88~89°). This compound was treated with triethylamine (12 mmol.) and PPE (4.5 g.) as in the general procedure to give Ⅸ as colorless fine needles from water, m.p. 89~90° (lit.,[30] m.p. 91~92°). IR cm^{-1}(Nujol): 1750, 1670 (imide C=O).

N-Benzylphthalimide (X)——N-Benzylphthalamic acid[31] was cyclized as above to give Ⅹ as colorless needles of m.p. 113~115° from EtOH, which was shown to be identical with the authentic specimen by direct comparison.[32]

N-(N-Phthaloylglycyl)glycine Ethyl Ester (XII)——N-Phthaloylglycine[24] was coupled with glycine ethyl ester hydrochloride (Ⅺ)[33] as in the general procedure. Instead of extraction, precipitate was collected by suction, washed with water, 10% HCl and water, dried and recrystallized from EtOH to give colorless needles of m.p. 192~194° (lit.,[34] m.p. 191~193°). IR cm^{-1}(Nujol) : 1660 (amide I). The ester (Ⅻ) was hydrolyzed by refluxing in aq. acetone containing 4*N* HCl for 1 hr. to give N-(N-phthaloylglycyl)-glycine as colorless needles of m.p. 227~229° from EtOH in 84% yield (lit.,[24] m.p. 231~232°).

N-(N-Benzyloxycarbonylglycyl) glycine Ethyl Ester (XVIII)——N-Benzyloxycarbonylglycine[35] was coupled with Ⅺ following the general procedure to give colorless prisms from EtOH, m.p. 78~80° (lit.,[1] m.p. 81°). For further confirmation of the structure, the ester was hydrolyzed by standing in MeOH solution containing *N* NaOH at room temp. for 1 hr. N-(N-Benzyloxycarbonylglycyl)glycine was obtained as colorless fine needles from EtOAc, m.p. 177~178° (lit.,[1] m.p. 178°).

N-(N-Benzyloxycarbonyl-DL-alanyl)glycine Ethyl Ester (XIX)——N-Benzyloxycarbonyl-DL-alanine[36] was coupled with Ⅺ as in the general procedure to give colorless needles from benzene, m.p. 81~82° (lit.,[1] m.p. 85°). IR cm^{-1}(Nujol) : 1670 (amide I). The ester was hydrolyzed as in the case of ⅩⅧ to yield N-(N-benzyloxycarbonyl-DL-alanyl)glycine as colorless blades from water, m. p. 132~133° (lit.,[37] m.p. 130~131°).

N-(N-Phthaloyl-β-alanyl)glycine Ethyl Ester (XX)——N-Phthaloyl-β-alanine[27] was coupled with Ⅺ as in the case of Ⅻ. Recrystallization from EtOH gave colorless fibers of m.p. 157~158°. The low melting point in the lit.[38] (m.p. 136~141°) may be ascribed to possible impurity in view of its broad range. IR cm^{-1}(Nujol) : 1648 (amide I). *Anal.* Calcd. for $C_{15}H_{16}O_5N_2$(XX) : C, 59.20; H, 5.30; N, 9.21. Found : C, 59.08; H, 5.23; N, 8.90.

N-(N-Benzoyl-DL-alanyl)glycine Ethyl Ester (XXI)——N-Benzoyl-DL-alanine[39] was coupled with Ⅺ as above. Recrystallization from benzene gave colorless plates of m.p. 106~108°. IR cm^{-1}(Nujol) : 1680, 1640 (amide I). *Anal.* Calcd. for $C_{14}H_{18}O_4N_2$(XXI) : C, 60.42; H, 6.52; N, 10.07. Found : C, 60.39; H, 6.44; N, 9.73.

N-(N-Benzoyl-DL-phenylalanyl)glycine Ethyl Ester (XXII)——N-Benzoyl-DL-phenylalanine[40] was coupled with Ⅺ as in the general procedure to give colorless fine needles from EtOH, m.p. 158~160° (lit.,[41] m.p. 162°). IR cm^{-1}(Nujol) : 1650, 1635 (amide I). IR of the ester was identical with that of the sample prepared from N-benzoyl-DL-phenylalanine and Ⅺ by the conventional coupling using DCC.

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[38] C.L. Stevens : U.S. Pat., 2,820,781 (1958); C.A., **52**, 10181 d (1958).
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[40] ref. 7), p. 1271.
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N-[N-(N-Phthaloylglycyl)glycyl]glycine Ethyl Ester (XXIII)——N-(N-Phthaloylglycyl)glycine, prepared from Ⅻ by hydrolysis, was coupled with Ⅺ as above to give colorless fine feathers from EtOH, m.p. 228\~230° (lit.,[24] m.p. 229\~230°; lit.,[38] m.p. 226\~227°). IR cm^{-1} (Nujol): 1655 (sh.), 1645 (amide I). IR of this ester was identical with that of the sample prepared from N-(N-phthaloylglycyl)glycine and Ⅺ by the coupling using DCC. For further confirmation of the structure, this ester was hydrolyzed by treating with warm MeOH containing *N* NaOH for 1.5 hr. N-[N-(N-Phthaloylglycyl)glycyl]glycine was obtained as colorless fine needles from EtOH, m.p. 229\~231° (lit.,[42] m.p. 234\~235°; lit.,[43] m.p. 238° (decomp.)).

Racemization Studies——a) Young's test: To a solution of N-benzoyl-L-leucine ($[\alpha]_D^{21}$ −6.1 (c=9.5, 0.5*M* KOH); 5 mmol.) and freshly distilled glycine ethyl ester (5 mmol.) in CH_3CN, a solution of PPE (3.3 g., 6 equiv.) in CH_3CN was added. Total amount of CH_3CN was 6.6 ml. After refluxing for 1 hr., the solvent was removed *in vacuo*, and to the residue ice and water were added followed by $NaHCO_3$ powder and the whole was stirred for 1 hr. to effect decomposition of the reagent. The mixture was extracted with EtOAc, the extract was washed with water, 10% HCl, water, satd. $NaHCO_3$, water and dried (Na_2SO_4). Removal of the solvent *in vacuo* left a solid residue; $[\alpha]_D^{27}$ 0° (c=10, EtOH). Recrystallization from EtOAc gave 66% of racemic N-(N-benzoylleucyl)glycine ethyl ester, m.p. 143\~145° (lit.,[13] m.p. 146°) as colorless needles. IR cm^{-1} (Nujol): 1660, 1635 (amide I). For further confirmation of the structure, this ester was saponified by treating with *N* NaOH in aq. dioxane (3:1) at room temp. for 1 hr. to give N-(N-benzoyl-DL-leucyl)glycine in 91% yield as colorless fine needles from water, m.p. 161\~162° (lit.,[13] m.p. 165°). In a similar manner, the racemate was obtained in 71% yield using Ⅺ and triethylamine.

b) Anderson's test: N-(N-Benzyloxycarbonylglycyl)-L-phenylalanine[12] ($[\alpha]_D^{21}$ +36.6 (c=5, EtOH)) and freshly distilled glycine ethyl ester were coupled in the presence of PPE as above. The crude product showed no optical activity. Recrystallization from EtOH gave 59% of racemic N-[N-(N-benzyloxycarbonylglycyl)phenylalanyl]glycine ethyl ester as colorless fine needles of m.p. 128\~130° (lit.,[12] m.p. 132\~133°), which was shown to be identical with the sample prepared according to Erlanger[2] by mixed melting point and IR comparison.

Infrared Spectra of Polyphosphate Esters (PPE) and Related Substances (Fig. 2)——a) A mixture of phosphorus pentoxide (140 mg.) and diethyl phosphite (0.7 ml.) was warmed in a water-bath to effect complete solution (ca. 30 min.). This solution was diluted with $CHCl_3$ to 4% for IR measurement. b) PPE in $CHCl_3$ solution (3%). c) To a solution of PPE (0.5 g.) in $CHCl_3$ (2 ml.) a drop of water was added and stood for 5 days. The solution was treated with Na_2SO_4, filtered, and diluted with $CHCl_3$ to 3% for IR measurement. IR spectra were determined using Koken DS-301 spectrophotometer with NaCl optics. Cell thickness: 0.1 mm.

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Summary

PPE (polyphosphate esters) was shown to be a good agent for amide synthesis from a variety of carboxylic acids and primary amines. It also effected imide cyclization. Though in the presence of PPE peptide derivatives were obtained by coupling amino acids or peptides, full racemization took place. The structure of PPE was discussed with brief review of literatures.

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