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Polyphosphate Ester as a Synthetic Agent. XI.[1] Synthesis of 2-(1′-Aminoalkyl)benzimidazoles from N-Benzoylamino Acids[2,3]

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The most familiar preparative route to 2-substituted benzimidazoles lies in the action of a carboxylic acid derivative on *o*-phenylenediamine **1**.[5] Ladenburg early noted that thermal dehydration of monoacyl *o*-phenylenediamine derivatives formed corresponding benzimidazoles.[6] The important improvement of the reaction was "Phillips method", in which **1** and a carboxylic acid were heated in 4N hydrochloric acid.[5] Recently polyphosphate ester (PPE) was shown to be a very good agent for this type of condensation.[7] Thus various 2-substituted benzimidazoles were prepared from **1** and carboxylic acids by means of PPE under mild conditions.[7]

Crawford and Edward examined the condensation of Bz–Gly, Bz–Ala, and Bz–Phe with **1** by fusion reaction.[8] Although 2-benzamidoalkylbenzimidazoles were obtained in moderate yields, rather drastic treatment was required. Cescon and Day reported the reaction of amino

Table I. 2-(1′-Benzamidoalkyl)benzimidazoles **3**

Substrate	Compd. No.	R	Yield[a] (%)	Appearance[b] mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Bz.Gly	**3a**	H	66	grains 226—228[c]							
Bz.DL-Ala	**3b**	Me	49	powder[d] 253—255[e]							
Bz.L-Phe	**3c**	$PhCH_2$	47	powder[d] 236—237[f]							
Bz.L-Val	**3d**	Me_2CH	25	powder[d] 213 (decomp.)	$C_{18}H_{19}ON_3$	73.69	6.53	14.33	73.88	6.67	14.49
Bz.L-Leu	**3e**	Me_2CHCH_2	20	powder[d] 256 (decomp.)	$C_{19}H_{21}ON_3$	74.24	6.89	13.67	74.45	6.85	13.61
Bz.L-Ile	**3f**	MeEtCH	17	powder[d] 287 (decomp.)	$C_{19}H_{21}ON_3$	74.24	6.89	13.67	74.40	6.91	13.53

a) Yield is of pure product. *b*) Colorless; recrys. solvt. is EtOH unless otherwise stated.
c) lit[8]., mp 228° *d*) Recrys.solvt., EtOAc *e*) lit[8]., mp 254° *f*) lit[8]., mp 237°

1) Part X: Y. Kanaoka, K. Miyashita and O. Yonemitsu, *Tetrahedron*, **25**, 2757 (1969).
2) The paper forms also Part VI of "Amino Acid and Peptides". For Part V see: O. Yonemitsu, T. Hamada and Y. Kanaoka, *Tetrahedron Letters*, **1969**, 1819.
3) Abbreviations used: Ala, alanine; Gly, glycine; Ile, isoleucine; Leu, leucine; Phe, phenylalanine; Val, valine; Bz, benzoyl.
4) Location: *Kita-12, Nishi-6, Sapporo.*
5) S. Shipper and A.R. Day, "Heterocyclic Compounds," Vol. 5, ed. R.C. Elderfield, John Wiley and Sons, Inc., New York, 1957, p. 274.
6) A. Ladenburg, *Ber.*, **8**, 677 (1875); *ibid.*, **11**, 826 (1878).
7) Y. Kanaoka, O. Yonemitsu, K. Tanizawa and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **12**, 773 (1964); *a*) For a review see: Y. Kanaoka, *Kagaku*, **24**, 234 (1969).
8) R. Crawford and J.T. Edward, *J. Chem. Soc.*, **1956**, 673.

acids and **1** under Phillips' conditions, in which greatly extended refluxing period (30—100 hr) was necessary.[9]

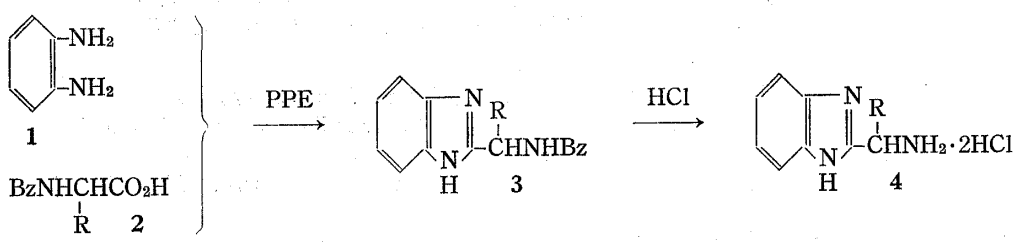
In connection with our studies on peptide chemistry[2] including C-terminal modification, the reaction of N–Bz-amino acids with **1** in the presence of PPE was now examined. In view of that the benzimidazole ring has often been encountered in biologically active agents,[10] these products seemed also of some pharmacological interest.

Table II. 2-(1′-Aminoalkyl)benzimidazole Dihydrochlorides **4**

Compd. No.	R	Time of hydrol. (hr)	Yield[a] (%)	Appearance	mp(°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4a	H	1.5	67	fine[b] needles	261—264[d] (decomp.)							
4b	Me	1.5	74	fine[b] needles	112—113 (decomp.)	$C_9H_{11}N_3 \cdot 2HCl$	46.25	5.60	17.95	46.28	5.83	18.27
4c	$PhCH_2$	7	71	fine[b] needles	162—166	$C_{15}H_{15}N_3 \cdot 2HCl$	58.07	5.52	13.54	57.97	5.49	13.51
4d	Me_2CH	5	88	powder[c]	184—192[e]	$C_{11}H_{15}N_3 \cdot 2HCl$	50.39	6.54	16.65	50.42	6.54	16.65
	picrate				232 (decomp.)	$C_{23}H_{21}O_{14}N_9$	42.48	3.24	19.49	42.83	3.73	19.42
4e	Me_2CHCH_2	5	87	powder[c]	184—193[e]	$C_{12}H_{17}N_3 \cdot 2HCl$	52.14	6.94	15.22	52.32	6.77	15.22
	picrate				220 (decomp.)	$C_{24}H_{23}O_{14}N_9$	43.69	3.47	19.02	43.71	3.64	19.21
4f	MeEtCH	5	69	powder[c]	235—242[e]	$C_{12}H_{17}N_3 \cdot 2HCl$	52.14	6.64	15.22	52.41	7.61	15.51
	picrate				216 (decomp.)	$C_{24}H_{23}O_{14}N_9$	43.69	3.47	19.02	43.46	3.73	18.99

a) Yield is of pure product. *b*) recrys. solvt., EtOH–AcOEt
c) recrys. solvt., EtOH–ether *d*) lit[9]., mp 267° *e*) broad mp with sintering

Simple N–Bz-amino acids **2** carrying no functional group in the residue were heated with **1** in the presence of PPE at 100° for 10 min. Corresponding 2-substituted benzimidazoles **3** were readily obtained although yields were rather moderate or low. The data of synthesis and properties of **3** are listed in Table I. Optically active amino acids gave inactive products due to racemization in the course of the reaction. From amino acids with functional groups, the formation of benzimidazoles was negligible presumably due to side reactions involving the functional groups present. Subsequent hydrolysis of **3** with 6N hydrochloric acid smoothly yielded 2-(1′-aminoalkyl)benzimidazole dihydrochlorides **4**. Table II contains the data con-



9) L.A. Cescon and A.R. Day, *J. Org. Chem.*, **27**, 581 (1962).
10) A. Burger, "Medicinal Chemistry", 2nd ed., Interscience Pub., Inc., New York, 1960, p. 262; D.G.O. Sullivan and P.W. Sadler, *Nature*, **192**, 341 (1961); K. Otaki, J. Inoue, Z. Yamazaki, M. Itaya, Y. Takai, M. Yasue and D. Mizuno, *Yakugaku Zasshi*, **85**, 926 (1965); H.D. Cossey, J. Judd and F.F. Stephens, *J. Chem. Soc.*, **1965**, 954; A.F. Casy and J. Wright, *ibid.*, **1966**, 1511.

cerned. As an example of a peptide substrate, Bz–Gly–Gly was similarly condensed with **1** to form 2-hippuramidomethylbenzimidazole **5** in 19% yield. In support of the structure, paper chromatography of the hydrolysate of **5** gave only two spots of Gly and **4a**.

Studies of other applications of this procedure to peptide chemistry as well as pharmacological evaluation of the products are now in progress.

Experimental[11]

Synthesis of 2-(1′-Benzamidoalkyl)benzimidazoles 3; General Procedure (*cf.* Table I)——A mixture of **1** (8 mmoles) and PPE[12] (5 parts in wt.) was heated at 100° (bath-temp.) under mechanical stirring. After **1** went into a solution, **2** (5 mmoles) was added and heating continued for 10 min under stirring. The mixture was cooled to room temp., water (*ca.* 50 ml) was added to decompose PPE. Excess of powdered $NaHCO_3$ was added and the precipitated product was collected and recrystallized.

Synthesis of 2-(1′-Aminoalkyl)benzimidazole Dihydrochlorides 4 by the Hydrolysis of 3; General Procedure (*cf.* Table II)——Compound **3** (1 part) was suspended in 6N HCl (20 parts in wt.) and the whole was refluxed for 1.5—7 hr. After cooling, benzoic acid which separated was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was kept in a vacuum desiccator over KOH for 24 hr and recrystallized to give **4**.

Ultraviolet Spectra of 3 and 4——UV $\lambda_{max}^{ethanol}$ mμ (log ε): **3a**, 275(3.94), 281.5(3.94); **3b**, 275(3.93), 282 (3.92); **3c**, 275(4.11), 282(4.15); **3d**, 275(3.99), 281.5(4.03); **3e**, 275(4.01), 281.5(4.03); **3f**, 275(4.02), 281.5(4.06). UV $\lambda_{max}^{H_2O}$ mμ (log ε): **4a**, 275(4.09), 281(4.05); **4b**, 275(4.10), 281(4.08); **4c**, 275(4.13), 282(4.11); **4d**, 274(3.86), 281(3.85); **4e**, 274(3.85), 281(3.82); **4f**, 274 (3.84), 281(3.82).

Chromatography of 4——a) Paper chromatography (PC) was performed on Toyo Roshi No. 51 paper by the ascending method (solvent system; butanol saturated with 2% HCl) and benzimidazoles were located by spraying ninhydrin solution followed by heating. *Rf* values: **4a**, 0.09 (golden yellow); **4b**, 0.23 (golden yellow); **4c**, 0.87 (yellowish brown); **4d**, 0.77 (brown); **4e**, 0.81 (brown); **4f**, 0.80 (brown).

b) Thin-layer chromatography (TLC) was performed on a silica (Merck) plate with the same solvent and detecting systems as above to identify **4d—f**, which showed close *Rf* values in PC but gave better separation in TLC. An example of *Rf*: **4d**, 0.52; **4e**, 0.58.

2-Hippuramidomethylbenzimidazole 5——Recrystallized from aq. EtOH to form colorless needles of mp 186° (lit.,[8] mp 186°); 19%. IR ν_{max}^{Nujol} cm^{-1}: 1673 (CO, peptide); 1640 (CO, Bz). UV $\lambda_{max}^{ethanol}$ mμ (log ε): 275 (3.98), 281.5 (3.99). When hydrolyzed with 6N HCl, a sample of **5** yielded Gly and **4a** as shown by PC.

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11) All melting points are uncorrected.

12) Y. Kanaoka, M. Machida, O. Yonemitsu and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **13**, 1065 (1965).