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The ring-opening addition reaction of phthaloylasparic anhydride (I) with *o*-phenylenediamine (II) in a solution is affected by the polarity of the solvent used. At the molar ratio of 1:1, I and II undergo a β -oriented ring-opening reaction in polar solvents, such as DMF, DMAC, and DMSO; while in weaker polar solvents, such as dioxane and tetrahydrofuran, α -orientation predominates. By heating in a solvent mixture of DMF and xylene, the ring-opening products undergo condensation, and are converted into two isomers. One is methanol soluble 3-phthalimido-3-(2)benzimidazolylpropanoic acid (V) resulting from the α -oriented ring-opening reaction, the other is the sparingly soluble (in DMF) 2-phthalimido-3-(2)benzimidazolylpropanoic acid (VI) resulting from the β -oriented ring-opening reaction. The soluble V can be precipitated as cotton-like crystals from methanol and chloroform. When treated with acetic anhydride, V and VI are converted to other isomers, namely 3-phthalimidobenzimidazopyrrolone (VII) and 2-phthalimidobenzimidazopyrrolone (VIII). The isomers were identified by spectral analysis.

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Introduction.

Polyimidazopyrrolone (1,2,3), a polymer of outstanding thermal stability, is formed by reaction of aromatic dianhydride with aromatic tetraamines. The mechanism of this reaction has been studied in detail by many authors (4,5,6). Previous reports showed that the reaction in polar solvents produced pyrrolone *via* the intermediate of imide-amine, but Young (5,6) suggested that pyrrolone is formed through imidazolecarboxylic acid rather than imide-amine according to a model reaction of phthalic anhydride and pyromellitic anhydride with *o*-phenylenediamine. Generally, an acid anhydride reacts with equimolar 2-arylenediamine in solution by a two-step mechanism. In the first step, acid anhydride undergoes ring-opening addition with one of the amino groups of *o*-arylenediamine to give amide-acid-amine. In the second step, the amide-acid-amine undergoes condensation by heating to give the heterocyclic compound (pyrrolone) through the formation of imide-amine or imidazolecarboxylic acid. In the case of asymmetrical acid anhydrides, the reaction would be more complicated and give more isomers by differently orientated ring-opening. The author had synthesized the polymer of benzimidazopiperidone (7), and illustrated the reaction orientation and ring-closure route in DMF with the aid of a model reaction of phthaloylglutamic anhydride with *o*-phenylenediamine. This article with the help of a model reaction of phthaloylasparic anhydride with *o*-phenylenediamine is concerned with the reaction route and the structures of its polymerization products using unsymmetric di-five-membered ring anhydride, *e.g.* *N,N'*-(pyromellitoyl)diasparic dianhydride (8), and aromatic tetraamine. Up to now, no reference concerning about the ring-opening reaction and the condensation products of phthaloylasparic anhydride with *o*-phenylenedi-

amine has been reported. We have utilized nmr spectra to identify the reaction products.

Results and Discussion.

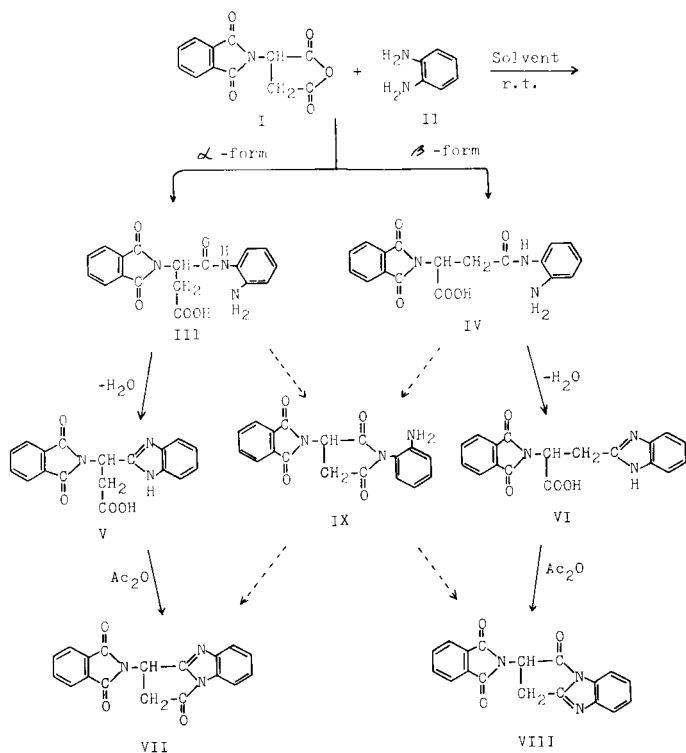
Synthesis.

The ring-opening reaction of phthalic anhydride with *o*-phenylenediamine gives only one amide-acid-amine product (5). But phthaloylasparic anhydride (I) reacted with *o*-phenylenediamine (II) to produce isomers of amide-acid-amine III and IV, as shown in Scheme 1, due to ring-openings of α -orientation and β -orientation, respectively. These two compounds, on heating, are liable to dehydrate to give imidazolecarboxylic acid V and VI, or imide-amine IX. These can be condensed to give imidazopyrrolone isomers of the α -form VII and the β -form VIII. Earlier reports (10) have shown that the orientation of ring-opening of phthaloylasparic anhydride with ammonia depends on the solvents used in the reaction. In aqueous alcohol, the reaction gave predominately the α -amide; in anhydrous ether, the β -amide predominated. This may be related to the specific character of the solvents used, *i.e.* α -orientation predominates in solvents of high dielectric constant and β -orientation in those of low dielectric constant. So far, no research concerning the reaction of phthaloylasparic anhydride with *o*-phenylenediamine has been reported. This article, hence, reports the reaction products of each step in the ring-opening reaction in many different solvents used in the process. The ir and nmr spectra were used to identify the structure of each product. Facilitating the following two properties, (1) III and IV, are air sensitive and thermally unstable, (2) V and VI, on the other hand, are more stable and have different solubilities in different solvents and are thus easy to obtain.

We studied the structures of V and VI to determine the

orientation of the ring-opening. The structures of the isomers were identified by determining the structures of the double condensation products VII and VIII. In a typical reaction, the ring opening was conducted in one of the solvents listed in Table 1, then, the solvent was removed, and the reaction residue was allowed to undergo ring-closure reaction under nitrogen with refluxing DMF-xylene

Scheme 1



(10:12 volume ratio) to give V and VI, that is the intramolecular condensation only to the first step. Compound VI was much less soluble and precipitated out during the reaction, and the precipitate was filtered after being reacted for three hours to give compound VI. The filtrate, with the solvent removed, was mixed with methanol, treated with activated carbon, concentrated, and mixed with chloroform and allowed to stand overnight, then compound V was obtained as cotton-like crystals. The results

Table 1

The Relationship of the Products V and VI of the Ring-opening Reaction of Phthaloylasparic Anhydride With *o*-Phenylenediamine in Solution in Different Solvents

Name	Solvents Dielectric constant	Products Yield (%)	
		VI	V
dioxane	2.9	10-23	40-65
THF	3.2	10-25	32-50
DMF	38	47-63	10-20
DMAC		50-55	10-20
DMSO	48	50-55	10-18

were taken by averaging data from many runs and summarized in Table 1. In solvents of low dielectric constant such as dioxane and tetrahydrofuran, V was obtained in higher yield. Whereas in solvents of high dielectric constant such as DMF, DMAC, and DMSO, VI predominated. From Scheme 1, V was the product from the ring-closure of α -oriented ring-opening reaction and VI was from β -oriented ring-opening, although compound IX was not isolated and identified. If it is supposed that the formation of IX from IV and III were in proportion to the formation of VI from IV and V from III, respectively, then the yields of V and VI should be equal or nearly so to the yields of III and IV. From Scheme 1, III and V were products from α -oriented ring-opening and IV and VI were from β -oriented ring-opening. Thus, the results are in contrast to those of phthaloylasparic anhydride and ammonia (10). It is suspected that the structure of *o*-phenylenediamine may have some effect on the reaction.

Intramolecular condensation of V and VI gave phthalimidobenzimidazopyrrolone VII and VIII, respectively. The reaction was conducted in acetic anhydride to give products of higher yields and purity. The formation of an inner salt between the carboxylic acid and the imidazole moiety made the fusion method impractical.

Of the isomers studied, VI and VIII have higher melting points and lower solubilities than those of V and VII as reported in the experimental section.

IR Spectra of Isomers.

The ir spectra of isomers 3- and 2-phthalimido-3-(2)benzimidazolypropanoic acid, V and VI, are shown in Figure 1. Both display absorption peaks at 1770, 1715,

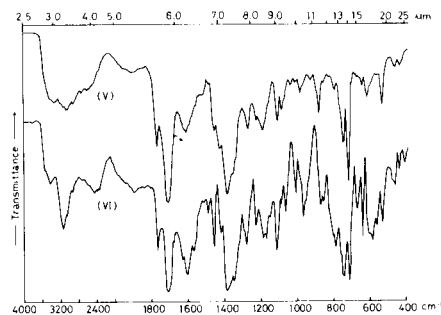


Fig. 1. Infrared spectra of the compounds V and VI in KBr

1390, 1110, and 720 cm^{-1} characteristic of the imide group and those at 1390, 1190, 985 (970) cm^{-1} characteristic of the benzimidazole group. They both show broad absorption bands from 1700 to 1500 cm^{-1} . In this region, V shows a weak absorption peak from 1600 to 1610 cm^{-1} and VI shows a strong peak at 1610 cm^{-1} . The occurrence of the broad absorption bands are due to the formation of the Zwitter ions. In addition, VI absorbs more intensely at 1485 and 1350 cm^{-1} than V. In the fingerprint region, VI

absorbs rather strongly at 1280, 1235, 1080, 1010, 965, 870, 790, 745, 665, 640, and 590 cm^{-1} , while V absorbs at 1270, 1220, 1090, 1030, 985, 880, 790, 740, 640, and 615 cm^{-1} , respectively.

The ir spectra of 3- and 2-phthalimidobenzimidazopyrrolone isomers, VII and VIII, as shown in Figure 2, differ markedly from those of 3- and 2-phthalimidobenzimidazolylpropanoic acid V and VI. Hence, the formation of pyrrolone ring can be proved easily by ir analysis. Compound VII displays intense absorption peaks at 1752, 1615, 1560, 1447, 1335, and 1155 cm^{-1} and VIII absorbs at 1758, 1615, 1567, 1447, 1335, and 1150 cm^{-1} . The ir spec-

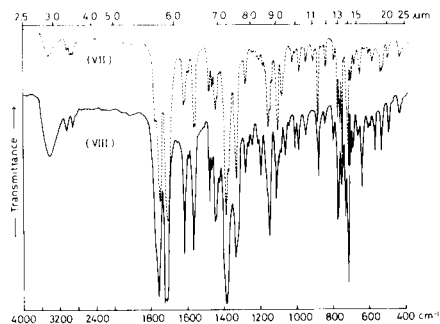


Fig 2 Infrared spectra of the compounds VII and VIII in KBr

tra of the above ring-closed isomers, VII and VIII, can not be clearly distinguished from each other. Fortunately the ratio of intensities of some adjacent absorption lines can be calculated and compared for identification. For example, the ratios of absorption intensity of VIII at 1770/1758 and 1615/1567 cm^{-1} are greater than those of VII at 1770/1752 and 1615/1657 cm^{-1} , and the ratios of absorption of four absorption peaks in 800 to 700 cm^{-1} are different with each other.

^1H NMR Spectra of Isomers.

^1H NMR Spectra of Isomeric Compounds V and VI.

The ^1H nmr spectra of V and VI are shown in Figure 3 and 4. The signals were labelled a, b, c, d, and e. The chemical shift, splitting patterns, and coupling constants were tabulated in Table 2. The four protons (H_e) in

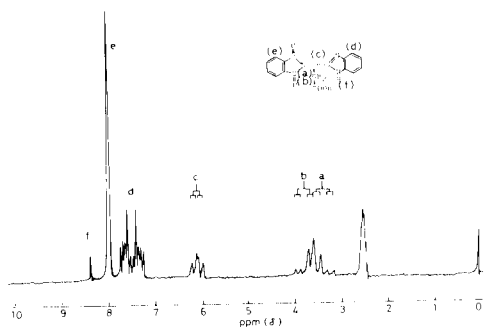


Fig 3 60MHz ^1H -NMR spectrum of compound V in DMSO-d_6 (TMS as internal standard)

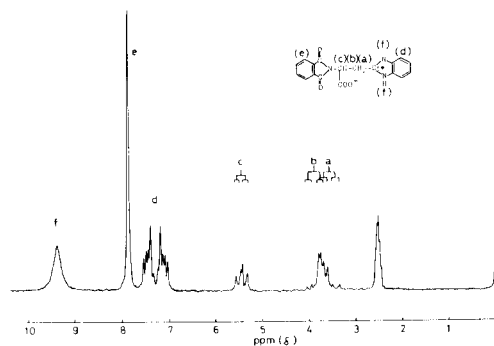


Fig 4 60MHz ^1H -NMR spectrum of compound VI in DMSO-d_6 (TMS as internal standard)

Table 2

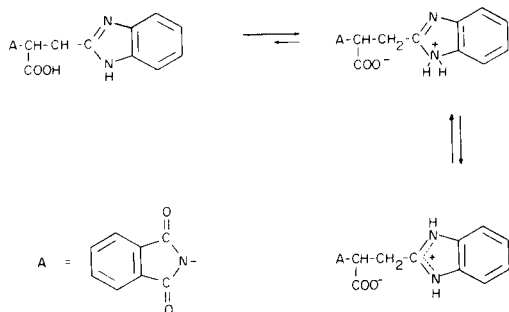
^1H NMR Spectral Data of Compounds V and VI

Compound	H	Chemical Shift (ppm)	Spectral Data	
			Splitting	Coupling Constant J (Hz)
V	a	3.40	d-d	$J_{ab} = 17$
	b	3.80	d-d	$J_{bc} = 6$
	c	6.10	d-d	$J_{ca} = 9$
	d	7.45	m	
	e	7.95	s	
	f	8.33	s	
VI	a	3.58	d-d	$J_{ab} = 16$
	b	3.90	d-d	$J_{bc} = 6$
	c	5.48	d-d	$J_{ca} = 9$
	d	7.33	m	
	e	7.90	s	
	f	9.5 (9.5 ~ 4.0)	s (broad)	

phthaloyl group gave a sharp singlet at 7.95 ppm for V and at 7.90 ppm for VI. The four protons (H_d) of benzene ring in the benzimidazole moiety showed multiplet signals centered at 7.45 ppm for V and at 7.33 ppm for VI. These signals were not useful for structure identification. However, the other protons absorption from 3.4 to 6.1 ppm can be utilized for this purpose. The two methylene protons (H_a and H_b) were not equivalent and appeared at 3.40 and 3.80 ppm for V and at 3.58 and 3.90 ppm for VI. The signals of methylene protons appear in lower field in VI than in V, indicated that the adjacent group possesses stronger electron-withdrawing effect. In previous article (7), it was reported the chemical shift of γ -methylene protons of γ -(2)benzimidazolylphthaloylglutamic acid appear in lower field than phthaloylglutamic acid. To verify this, 2-methylbenzimidazole was prepared to compare the chemical shift of the methyl proton with acetic acid. In DMSO-d_6 , the former appeared at 2.5 ppm whereas the latter at 1.95 ppm. This result showed that the benzimidazole moiety has a greater -I effect than the carboxylic group. The methine proton (H_c) appeared as a double-doublet for both V and VI due to coupling with the adjacent methylene protons. The chemical shifts centered at

6.10 ppm for V and at 5.48 ppm for VI. Obviously the former tends to shift to lower field than the latter, and, thus, the adjacent group to the former must have stronger electron-withdrawing ability. Since the benzimidazole moiety exerts a greater -I effect than the carboxylic group (7), the structure for V and VI were thus proved to be 3-phthalimido-3(2)-benzimidazolylpropanoic acid and 2-phthalimido-3(2)-benzimidazolylpropanoic acid, respectively.

The chemical shift for NH proton (H_f) in imidazole moiety were quite different. In V, it appeared at 8.33 ppm, and did not shift with the water content in the solvent. Integration showed a one-proton signal. In VI, however it appeared in 9.5-8.3 ppm region, and the higher the water content was in the solvent or the longer the sample was stored, the higher the chemical shift is. It could shift to as far as 4 ppm and could overlap with the signals from water molecule eventually. It gave a two proton integration after calibration with the water content in the solvent. It might be that the strong acidic carboxylic acid proton tends to be draped to the imidazole ring and VI appeared as an intramolecular salt as below.



^1H NMR Spectra of Isomeric Compounds VII and VIII.

The ^1H nmr spectra of VII and VIII were shown in Figures 5 and 6. The chemical shifts, splitting patterns, and coupling constants were tabulated in Table 4. The

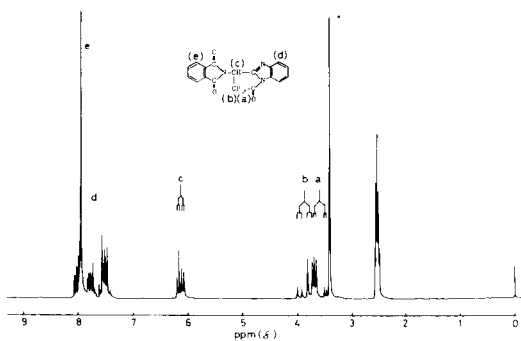


Fig. 5 100MHz ^1H -NMR spectrum of compound VII in $\text{DMSO}-d_6$ (TMS as internal standard).

average chemical shifts of the two methylene protons on the imidazopyrrolone ring of compound VII and VIII were

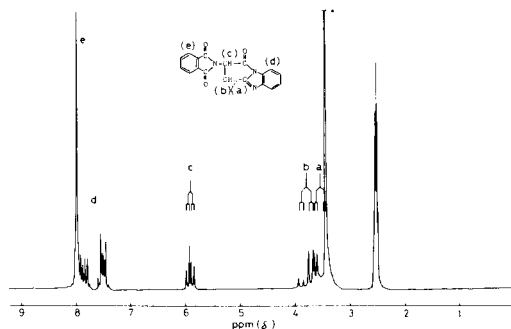


Fig. 6 100MHz ^1H -NMR spectrum of compound VIII in $\text{DMSO}-d_6$ (TMS as internal standard).

Table 3

^1H NMR Spectral Data of Compounds VII and VIII

Compound	H	Chemical Shift (ppm)	Spectral Data	
			Splitting	Coupling Constant J (Hz)
VII	a	3.40	d-d	$J_{ab} = 18.56$
	b	3.82	d-d	$J_{bc} = 8.30$
	c	6.089	d-d	$J_{ca} = 4.15$
	d	7.89	m	
	e	7.89	s	
VIII	a	3.44	d-d	$J_{ab} = 18.06$
	b	3.77	d-d	$J_{bc} = 8.54$
	c	5.871	d-d	$J_{ca} = 4.37$
	d	7.61	m	
	e	7.93	s	

quite close (3.61 ppm for the former, 3.605 ppm for the latter), but the chemical shift difference between the H_a and H_b were larger in the case of VII (0.42 ppm) than that in VIII (0.33 ppm). In both compounds, the H_a and H_b were a double-doublet (d-d) split into 8 peaks. The difference in chemical shifts of the methine protons among compound VII and VIII was 0.21 ppm (6.089 ppm for VII, 5.871 ppm for VIII). They both showed d-d splitting to be a quartet but their coupling constants were different, namely, $J_{ca} = 4.15$ cps, $J_{cb} = 8.30$ cps for VII, and $J_{ca} = 4.37$ cps, $J_{cb} = 8.54$ cps for VIII. Compared with the compounds before ring-closures, V and VI, the H_c shift did not change in VII but moved to lower field to as much as 0.39 ppm in VIII. This can be explained by the stronger electron-withdrawing of carboimidazole group than carboxylic group. Besides, the nmr spectra of the protons on the two end-benzene-rings of the isomers were not identical. The benzo proton on pyrrolone of VII has broader splitting region than that of VIII (7.35-8.1 ppm for the former, 7.35-7.9 ppm for the latter).

EXPERIMENTAL

Reagents.

All starting materials were obtained from commercial sources (DL-

Asparic Acid-Sigma Grade, Phthalic Anhydride-Wako Pure, *o*-Phenylenediamine-Tokyo Kasei EP Grade). Solvents were used as received from suppliers.

Synthesis.

3-Phthalimido-3(2)benzimidazolylpropionic Acid (V).

To a solution of 1.08 g (0.01 mole) of *o*-phenylenediamine in 30 ml of dioxane was added, in portions, 2.45 g (0.01 mole) of *N*-phthaloylasparic anhydride (9) under a nitrogen atmosphere. The mixture was stirred for 40 minutes at room temperature and then the solvent was removed under reduced pressure. The solid residue was dissolved in 12 ml of DMF and 15 ml of xylene and the mixture was heated with reflux for 3 hours under a nitrogen atmosphere. It was cooled and the solid filtered to obtain compound VI. The filtrate was concentrated and the residue was dissolved in 50 ml methanol, treated with activated carbon and filtered. The methanol filtrate was concentrated to 8 ml and diluted with 50 ml of chloroform and stored in refrigerator overnight. The cotton-like precipitate was collected, washed with chloroform, and dried to give 1.57 g of V, yield 47%, mp 168°.

Anal. Calcd. for $C_{18}H_{13}N_3O_4$ (335.1): C, 64.47; H, 3.88; N, 12.53. Found: C, 64.44; H, 3.90; N, 12.19.

2-Phthalimido-3(2)benzimidazolylpropanoic Acid (VI).

o-Phenylenediamine (1.08 g, 0.10 mole) was dissolved in 20 ml of DMF, and 2.45 g (0.01 mole) of *N*-phthaloylasparic anhydride (9) was added portionwise under a nitrogen atmosphere and it was stirred at room temperature for about 1 hour, then 25 ml of xylene was added. The mixture was allowed to stir and reflux. In 0.5-1 hour, a white solid precipitated out. The refluxing was continued for 2 additional hours. It was cooled and the solid which formed was filtered, (If the filtrate was concentrated, the methanol-insoluble part is also compound VI and the soluble part contains compound V.), washed with methanol and dried to give 2.01 g of white solid compound VI, yield 60%, mp 267°.

Anal. Calcd. for $C_{18}H_{13}N_3O_4$ (335.1): C, 64.47; H, 3.88; N, 12.53. Found: C, 64.30; H, 3.89; N, 12.56.

3-Phthalimidobenzimidazopyrrolone (VII).

A solution of 0.5 g of 3-phthalimido-3(2)benzimidazolylpropanoic acid (V) in 5 ml of acetic anhydride was heated at 100° for 20 minutes. After the removal of excess anhydride, the residue was poured into 50 ml of distilled water. The solid which was formed was collected to give 4.16 g of compound VII, yield 88%, mp 224-226°. It was recrystallized from methanol to give needle-like crystals, mp 226°.

Anal. Calcd. for $C_{18}H_{11}N_3O_3$ (317.1): C, 68.14; H, 3.47; N, 13.25. Found: C, 68.27; H, 3.58; N, 13.26.

2-Phthalimidobenzimidazopyrrolone (VIII).

In a 25 ml flask, 0.5 g of 2-phthalimido-3(2)benzimidazolylpropanoic acid (VI) was added to 8 ml of acetic anhydride and heated until all the solid dissolved (about 135°). It was cooled and allowed to stand overnight. The solid formed was filtered, washed with methanol and water and dried to obtain 4.01 g of solid (compound VIII), yield 85%, mp 240-241°. The filtrate was poured into distilled water and was filtered 2 hours later to give 0.053 g of solid. This made the total yield 98%. The solid formed was recrystallized with dioxane to obtain white powder with mp 243°.

Anal. Calcd. for $C_{18}H_{11}N_3O_3$ (317.1): C, 68.14; H, 3.47; N, 13.25. Found: C, 68.50; H, 3.60; N, 13.25.

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