Stereospecific and Stereoselective Reactions. II.[1] Preparation of Esters of *N*-Phthaloyl-α-amino Acid from Esters of α-Hydroxy Acid

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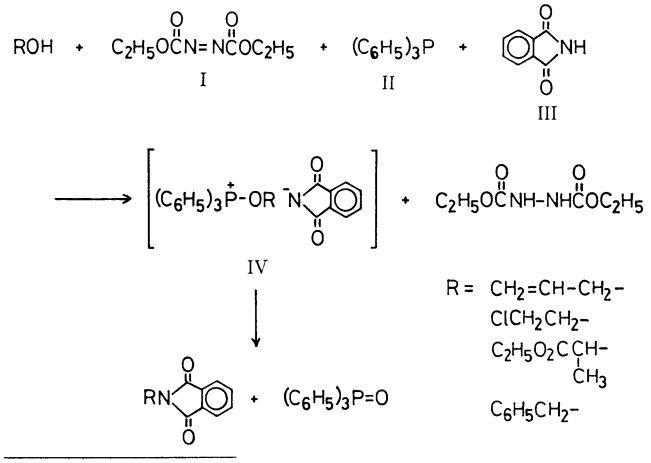
Functional selectivity and stereospecificity of the intermolecular dehydration between alcohols and phthalimide (III) by means of diethyl azodicarboxylate (I) and triphenylphosphine (II) was examined. The reaction of allyl alcohol, 2-chloroethanol or (±)-ethyl lactate with I, II, and III led to the formation of corresponding *N*-alkylphthalimide. The reaction was further applied to the synthesis of esters of *N*-phthaloyl-α-amino acid. (*S*)-(−)-ethyl 2-hydroxy-3-phenylpropionate was converted into (*R*)-(+)-*N*-phthaloylphenylalanine ethyl ester with high stereospecificity.

In previous reports, we described the efficient, stereospecific intermolecular dehydration between alcohols and acidic compounds with $pK_a<13$ by means of diethyl azodicarboxylate (I) and triphenylphosphine (II).[2] The present work was undertaken to examine functional selectivity of the reaction and stereospecific α-amino acid synthesis.

Functional Selectivity. Intermolecular dehydration by means of I and II proceeds under mild neutral conditions. Thus, when alcohols bearing another functional group such as halogen or double bond were used, the hydroxyl group would selectively undergo the reaction giving the corresponding condensation products which can be used in the subsequent displacement or addition reaction.

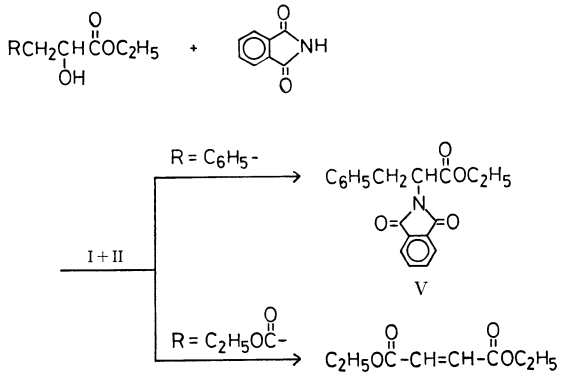
When allyl alcohol, 2-chloroethanol or (±)-ethyl lactate was allowed to react with I, II and phthalimide (III) at room temperature, *N*-allyl-, *N*-(2-chloroethyl)-phthalimide and (±)-*N*-phthaloylalanine ethyl ester was obtained in 73, 72, and 58% yield, respectively. No affection of functional groups other than the hydroxyl group was observed. It would be reasonable to assume the formation of an alkoxyphosphonium salt (IV) as an intermediate.

The reaction of benzyl alcohol with I and II resulted in the formation of diethyl *N*-benzylhydrazodicarboxylate and triphenylphosphine oxide in good yields.[3] Benzyl-oxygen bond in a benzyloxyphosphonium salt is readily cleaved by the attack of nucleophiles.[4] These facts led us to test the benzylation of III by the present method. When benzyl alcohol was treated with I, II, and III in a similar manner to that described above, *N*-benzylphthalimide was isolated in a 70% yield and no diethyl *N*-benzylhydrazodicarboxylate was obtained.



α-Hydroxy acids are easily dehydrated to afford the corresponding alkenes if carbon-carbon double bonds formed are particularly stabilized by conjugation with carbonyl and phenyl groups. In order to know limitations of the present procedure, the following reactions were attempted. (*S*)-(−)-Ethyl 2-hydroxy-3-phenylpropionate was allowed to react with equimolar amounts of I, II, and III, *N*-phthaloylphenylalanine ethyl ester (V) being isolated in a 46% yield. When the reaction was carried out by the use of 2 molar equivalents each of I and II, the yield of V increased to 66%. The reaction of methyl 2-hydroxy-2-methylpropionate, a tertiary alcohol, with I, II, and III gave only a 15% yield of methyl 2-phthalimido-2-methylpropionate. On the other hand, the reaction of diethyl malate with I, II, and III exclusively gave diethyl fumarate in a 59% yield. Diethyl fumarate was also obtained when the reaction was carried out in the absence of III.

The reaction can be explained by assuming the formation of an alkoxyphosphonium salt (VI). The



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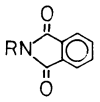
1) This work has been presented in part at the 26th Meeting of the Chemical Society of Japan, April 3, 1972. For paper I. see Ref. 2a.

2) a) O. Mitsunobu, M. Wada, and T. Sano, *J. Amer. Chem. Soc.*, **94**, 679 (1972); b) M. Wada and O. Mitsunobu, *Tetrahedron Lett.*, **1972**, 1279.

3) O. Mitsunobu, M. Yamada, and T. Mukaiyama, This Bulletin, **40**, 935 (1967).

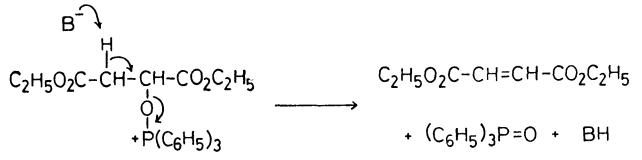
4) a) O. Mitsunobu, T. Obata, and T. Mukaiyama, *J. Org. Chem.*, **30**, 1071 (1965); b) T. Mukaiyama, O. Mitsunobu, and T. Obata, *ibid.*, **30**, 101 (1965).

TABLE 1. PREPARATION OF ESTERS OF *N*-PHTHALOYL-α-AMINO ACID

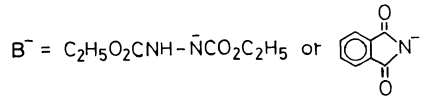
α-Hydroxy acid ROH R	*N*-Phthaloyl-α-amino acid  R	Yield, %
CH_3–CH–$CO_2C_2H_5$	CH_3–CH–$CO_2C_2H_5$	58
$C_6H_5CH_2$–CH–$CO_2C_2H_5$	$C_6H_5CH_2$–CH–$CO_2C_2H_5$	46 (66)[a]
$(CH_3)_2$C–CO_2CH_3	$(CH_3)_2$C–CO_2CH_3	15
$C_2H_5O_2C$–CH_2–CH–$CO_2C_2H_5$	$C_2H_5O_2C$–CH_2–CH–$CO_2C_2H_5$	0[b]

a) ( ): Two molar equivalents of I and II were used.
b) Diethyl fumarate was obtained in a 59% yield.

hydrogen atom at α'-carbon of the intermediate was abstracted by the anion of diethyl hydrazodicarboxylate giving diethyl fumarate, diethyl hydrazodicarboxylate and triphenylphosphine oxide. An alternative process in which active hydrogen atom at α'-carbon was abstracted by the anion of phthalimide is conceivable. Such a reaction has also been observed in the anhydrobond formation of uridine.[2b,5] Whether intermolecular dehydration takes place or intramolecular dehydration occurs would depend on relative acidities of active hydrogen of the alkoxyphosphonium salt, diethyl hydrazodicarboxylate and/or phthalimide.

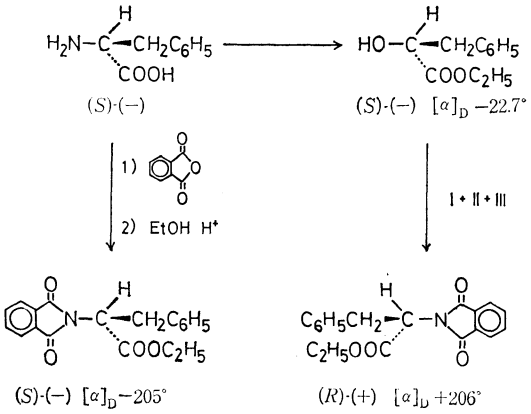


VI



Stereospecificity. Various esters of α-hydroxy acid were converted into the corresponding esters of *N*-phthaloyl-α-amino acid. The results are summarized in Table 1. For the preparation of α-amino acids, it is necessary to determine the steric course. In view of the results so far obtained,[2a,6] the present reaction can be expected to proceed with the inversion of configuration when displacement occurs at an asymmetric carbon.

N-Phthaloylphenylalanine ethyl ester (V) prepared by the reaction of (*S*)-(−)-ethyl 2-hydroxy-3-phenylpropionate with I, II, and III had $[\alpha]_D$ +206±4°. That V possesses *R*-configuration was established by comparison with the reference compound, (*S*)-(−)-*N*-phthaloylphenylalanine ethyl ester ($[\alpha]_D$ −205±1°), prepared from (*S*)-(−)-phenylalanine by stereochemically unambiguous sequences. This result indicates that the complete or almost complete inversion occurred in the intermolecular dehydration reaction.



Experimental

The IR spectra were measured on a Nippon Bunko IR-G spectrophotometer. The NMR spectra were obtained on a Hitachi Perkin-Elmer R-20 high resolution spectrometer at 60 MHz. The chemical shifts (δ) are expressed in ppm from internal tetramethylsilane. The optical rotation was measured with JASCO ORD/UV-5. Thin layer chromatography (tlc) was carried out on Wakogel B-5 or Merck PF_{254}.

N-Allyl- and N-(2-Chloroethyl)-phthalimide. A solution of I (174 mg, 1 mmol) in tetrahydrofuran (THF, 2 ml) was added dropwise to a solution of II (262 mg, 1 mmol), III (147 mg, 1 mmol) and either allyl alcohol (117 mg, 2 mmol) or 2-chloroethanol (161 mg, 2 mmol) in THF (3 ml) with stirring at room temperature. After the solution was kept standing overnight, it was applied to a silica gel plate which was then developed in benzene giving the desired products.

N-Allylphthalimide: 136 mg, 73%, mp 72—73 °C (from *n*-heptane). NMR (CCl_4); 4.2 (2H, $-CH_2-$), 5—6.2 (3H, $-CH=CH_2$), 7.7 (4H, aromatic H).

N-(2-Chloroethyl)phthalimide: 151 mg, 72%, mp 82—84 °C (from *n*-heptane containing a small amount of ether). NMR (CCl_4); 3.5—4.1 (4H, $-CH_2-CH_2-$), 7.75 (4H, aromatic H).

N-Phthaloylalanine Ethyl Ester. (±)-Ethyl lactate (118 mg, 1 mmol) was treated with I (147 mg, 1 mmol), II (262 mg, 1 mmol) and III (147 mg, 1 mmol) in THF (3 ml) in the same manner as above. After 3.5 hr, the solution was concentrated and applied to a silica gel plates, developed in chloroform giving *N*-phthaloylalanine ethyl ester; 144 mg, 58%, mp 60—61 °C (from petroleum ether). Found: C, 63.14; H, 5.30%. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30%.

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6) a) W. Gerrard and W. J. Green, *J. Chem. Soc.*, **1951**, 2550; b) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965); c) J. B. Lee and I. M. Dowie, *Tetrahedron*, **23**, 359 (1967); d) J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, **46**, 86 (1968); e) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970); f) O. Mitsunobu and M. Eguchi, This Bulletin, **44**, 3427 (1971). g)R Aneja, A. P. Davies, and J. A. Knaggs, *Chem. Comm.*, **1973**, 110.

NMR (CCl_4); 1.25 and 4.2 (3H and 2H, CH_3–CH_2–O–), 1.7 (3H, >CH–C$\underline{H}_3$), 4.85 (1H, >C$\underline{H}$–CH_3), 7.75 (4H, aromatic H). IR (KBr) cm^{-1}; 1780, 1720 (C=O).

N-Benzylphthalimide and Methyl 2-Phthalimido-2-methylpropionate. In the same manner as above, *N*-benzylphthalimide was isolated in a 75% yield by preparative tlc (benzene). When the reaction was carried out in an ice bath, the yield of *N*-benzylphthalimide decreased to 70%; NMR (CCl_4): 4.75 (2H, $-CH_2-$), 7—8 (9H, aromatic H). IR (KBr) cm^{-1}: 1770, 1720 (C=O).

Similarly, methyl 2-hydroxy-2-methylpropionate was converted into methyl 2-phthalimido-2-methylpropionate in a 15% yield. NMR (CCl_4): 1.8 (6H, $(CH_3)_2C<$), 3.7 (3H, CH_3O-), 7.74 (4H, aromatic H). IR (liquid film) cm^{-1}: 1770, 1730 (C=O).

Reaction of Diethyl Malate with I and II in the Presence or Absence of III. Diethyl malate (190 mg, 1 mmol) was allowed to react with equimolar amounts of I, II, and III in THF (4 ml) at room temperature for 3 hr. The reaction mixture was separated by preparative tlc (chloroform) giving diethyl fumarate; 105 mg, 59%. NMR: 1.30 and 4.18 (6H and 4H, CH_3–CH_2–O–), 6.75 (2H, $^{H}>C=C<_{H}$). IR (liquid film) cm^{-1}: 1715 (C=O), 1640 (>C=C<). When the reaction was carried out in the absence of III, diethyl fumarate was afforded in a 51% yield.

(R)-(+)-N-Phthaloylphenylalanine Ethyl Ester. (*S*)-(−)-Ethyl 2-hydroxy-3-phenylpropionate[7] (194 mg, 1 mmol, $[\alpha]_D$ −22.7° (*c* 4.52 in benzene); lit,[7a] $[\alpha]_D^{24}$ −22.6° (*c* 4.33 in benzene)) was allowed to react with equimolar amounts of I, II, and III at room temperature for 3 hr. The reaction mixture was separated by preparative tlc (benzene) giving (*R*)-(+)-*N*-phthaloylphenylalanine ethyl ester; 148 mg, 46%, mp 65—66 °C. NMR (CCl_4): 1.2 and 4.2 (3H and 2H, CH_3–CH_2–O–), 3.5 (2H, $C_6H_5C\underline{H}_2$–), 5.05 (1H, >C–H), 7.1 and 7.6 (5H and 4H, aromatic H). IR cm^{-1}: 1780, 1720 (C=O). $[\alpha]_D$ +210.6° (*c* 0.470 in benzene) and +201.5° (*c* 0.428 in benzene). Average $[\alpha]_D$ +206±4°.

(S)-(−)-N-Phthaloylphenylalanine Ethyl Ester. Dry hydrogen chloride was passed through a solution of (*S*)-(−)-phthaloylphenylalanine[8] (2.95 g, 10 mmol) in ethanol (9.20 g) for 1 hr and the solution was refluxed for 1 hr. After removal of the solvent, the residue was applied to a silica gel plate which was developed in benzene. The crude (*S*)-(−)-*N*-phthaloylphenylalanine ethyl ester (1.31 g) thus obtained was again purified by tlc, mp 56—57 °C. This product was further recrystallized from petroleum ether; $[\alpha]_D$ −206.2° (*c* 0.456 in benzene) and −204.1° (*c* 0.446 in benzene). Average $[\alpha]_D$ −205±1°.

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