[Chem. Pharm. Bull. 22(6)1398—1404(1974)]

UDC 547.461.3'262.04 : 547.467.3'558.04

Amino Acids and Peptides. XII.[1] Phosphorus in Organic Synthesis. VIII.[2] Reaction of Malonic Acid Half Esters with Diphenyl Phosphorazidate[3]

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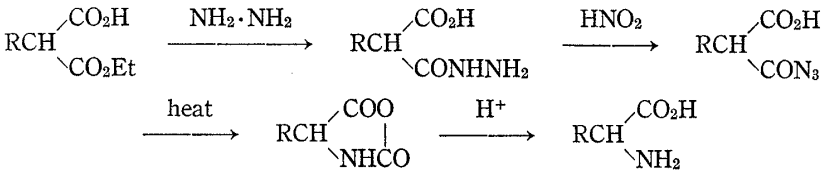
(Received January 11, 1974)

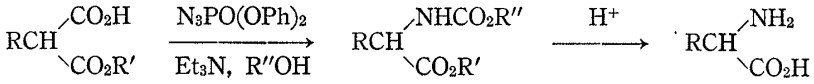
Application of the modified Curtius reaction by DPPA to some malonic acid half esters revealed that esterification occurred in a one-step process but the rearrangement reaction took place in a two-in-one-reaction procedure, the results of which are summarized in Tables I and II. The latter procedure may provide a new simple method for the synthesis of α-amino acids.

One method for the synthesis of α-amino acids is that malonic acid half esters are allowed to react with hydrazine to form hydrazide acids, which are degradated through azide acids to α-amino acids *via* the Curtius rearrangement[5]:



As the processes are rather lengthy and the overall yield is not good, the method is only historically important and of limited applicability.

In our preceding paper,[2] we described diphenyl phosphorazidate (DPPA) was a convenient reagent for a modified Curtius reaction. We thought that α-amino acids or their derivatives may be conveniently prepared by application of the DPPA method to malonic acid half esters, which is represented in broad outline as follows:



If this scheme could be achieved, the combination of the DPPA method and the classical Curtius method would allow us to obtain any isomer of optically active α-amino acids very freely: the optical resolution of racemic malonic acid half esters would give (*R*)- and (*S*)-isomers, both of which would undergo the Curtius rearrangement with retention of configuration[6] to furnish the same optically active α-amino acid by the proper use of the DPPA method and the classical one. For example, L-α-amino acid could be obtained from both (*R*)-isomer by the DPPA method and (*S*)-isomer by the classical one, shown in Chart 1.

1) Part XI: T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 859 (1974).
2) Part VII: K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, "in press."
3) Preliminary communication: S. Yamada, K. Ninomiya, and T. Shioiri, *Tetrahedron Letters*, **1973**, 2343. Presented in part at the Symposium on Organo-sulfur and -phosphorus Compounds, Kyoto, February 10, 1973, Abstracts, p. 79.
4) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
5) P.A.S. Smith, *Org. Reactions*, **3**, 337 (1946).
6) P.A.S. Smith, "Molecular Rearrangements," Vol. I, edited by P. de Mayo, Interscience, New York, 1963, p. 457; K.K. Lee, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2540 (1969).

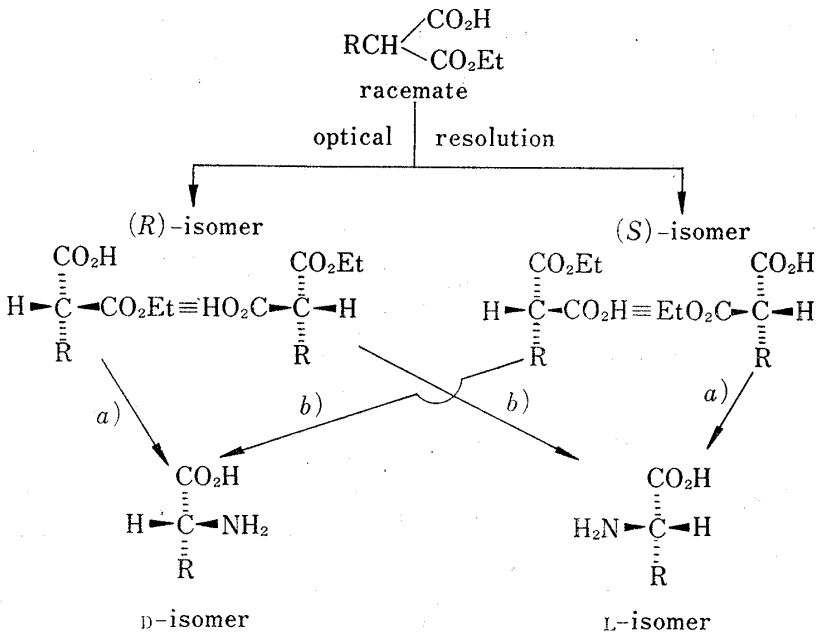


Chart 1

a) classical method *b*) DPPA method

Furthermore, the recent publication[7] of a simple, efficient synthesis of malonic acid half esters by α-carboxylation of carboxylic acid esters prompted us to realize the DPPA method.

First, ethyl hydrogen malonate was refluxed with an equimolecular mixture of DPPA and triethylamine in *tert*-butyl alcohol according to the general procedure of the modified Curtius reaction by DPPA.[2] Contrary to our expectation, however, the main product was not the Curtius-type product N-*tert*-butyloxycarbonylglycine ethyl ester, but the esterification product ethyl *tert*-butyl malonate. Only a trace of another Curtius-type product N-azidoformylglycine ethyl ester was detected by the infrared spectrum. When benzyl alcohol was used as an alcohol component, esterification mainly occurred again, and no or little rearranged product expected could be found.

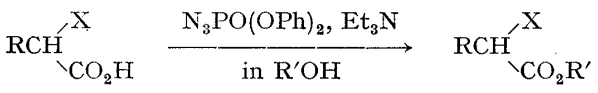
Generally, the ester formation reaction was found little in the modified Curtius reaction by DPPA.[2] A significant example of esterification was observed in the rearrangement of the ethyleneketal derivative of levulinic acid, but even in this case the yield of esterification was only 6% in contrast to 91% of the rearrangement yield.[2]

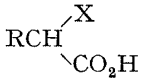
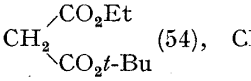
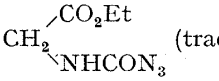
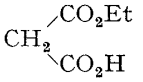
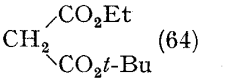
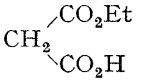
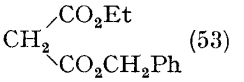
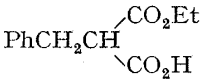
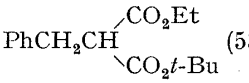
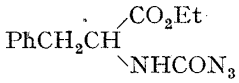
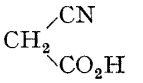
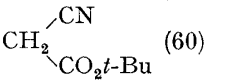
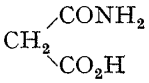
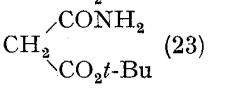
Ethyl hydrogen benzylmalonate, cyanoacetic acid, and malonmonoamide afforded mainly the corresponding *tert*-butyl esters under the same reaction conditions as above. Thus, the esterification by DPPA seems to be common to acetic acids containing electron-withdrawing groups at α-position. The result is summarized in Table I. These is no question about the participation of DPPA in the esterification because cyanoacetic acid was recovered unchanged when it was treated with triethylamine in *tert*-butyl alcohol but without DPPA.

In general, the modified Curtius procedure by DPPA is carried out in the presence of alcohols from the initial stage of the reaction. However, the formation of the isocyanate, an obvious intermediate of the Curtius reaction,[5] does not necessarily require alcohols. The urethane will be formed when the carboxylic acid azide produced by the reaction of carboxylic acid with DPPA are converted to the isocyanate by the thermal treatment, followed by the addition of alcohol.

7) S. Reiffers, H. Wynberg, and J. Strating, *Tetrahedron Letters*, **1971**, 3001.

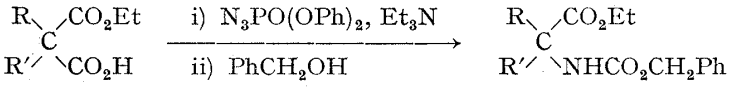
TABLE I

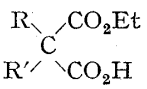
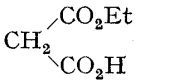
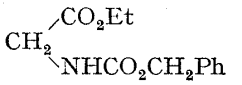
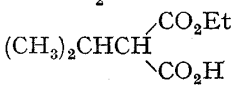
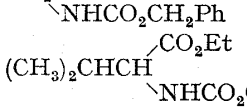
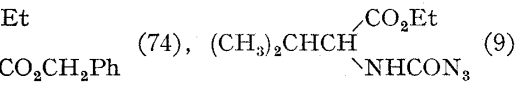
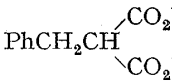
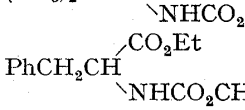
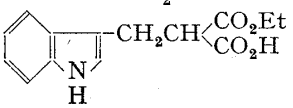
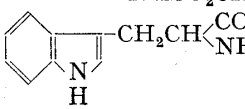
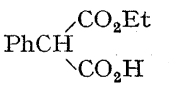
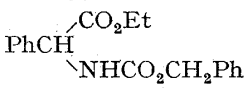
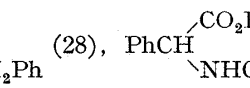
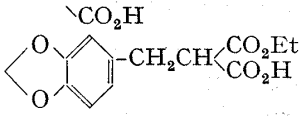
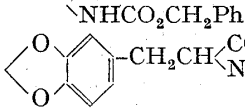
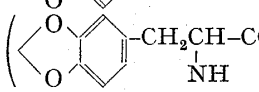
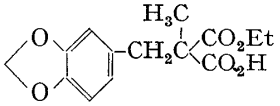
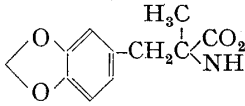


	R'OH	Product (Yield, %)
	*t*-BuOH	 (54),  (trace)
	*t*-BuOH	 (64)
	$PhCH_2OH$	 (53)
	*t*-BuOH	 (53),  (trace)
	*t*-BuOH	 (60)
	*t*-BuOH	 (23)

Ph=phenyl

TABLE II



	Product (Yield, %)
	
	 (27)
	 (74),  (9)
	 (79)
	 (65)
	 (28),  (6), $PhCH_2CO_2Et$ (24)
	 (78)
	 C=O (5)
	 (80)

Ph=phenyl

Accordingly, ethyl hydrogen benzylmalonate was first refluxed with DPPA and triethylamine in benzene for 1 hr, and then, after addition of benzyl alcohol, the mixture was refluxed for 17 hr. The desired Curtius-type product N-benzyloxycarbonylphenylalanine ethyl ester was obtained in 79% yield. This change of the reaction course was really dramatic, which encouraged the hope that the two-in-one-reaction procedure could be applied to the synthesis of α-amino acid derivatives.

In fact, N-benzyloxycarbonyl α-amino acid ethyl esters were obtained in satisfactory yields from malonic acid half esters by the two-in-one-reaction procedure using benzyl alcohol. The result is summarized in Table II. It would be worth noting that N-benzyloxycarbonyl-3-(3,4-methylenedioxyphenyl)alanine ethyl ester and its 2-methylated analog could be prepared in satisfactory yields since they might be easily converted to medicinally important 3,4-dihydroxyphenylalanine (dopa) and α-methyl-3,4-dihydroxyphenylalanine (α-methyldopa), respectively. The total yield of the rearrangement of ethyl hydrogen phenylmalonate was rather unsatisfactory. This will be due to partial decarboxylation of ethyl hydrogen phenylmalonate in the presence of base,[8] affording ethyl phenylacetate.

The starting ethyl hydrogen alkylmalonates were prepared mainly by the alkylation of diethyl malonate followed by partial hydrolysis of the diesters. Ethyl hydrogen phenylmalonate was prepared by carboxylation of α-lithio-phenylacetate.[7] Lithiation of ethyl hydrogen (3,4-methylenedioxybenzyl)malonate with lithium diisopropylamide, followed by treatment with methyl iodide[9] afforded ethyl hydrogen (3,4-methylenedioxybenzyl)methylmalonate.

As N-benzyloxycarbonyl α-amino acid ethyl esters could be very easily converted to α-amino acids,[10] the method will constitute a new synthetic method for α-amino acids.[11] Mechanistic studies on what factors will decide the reaction course, either esterification or rearrangement, will be reported in the following paper.

Preparation of optically active α-amino acids according to the scheme in Chart 1 is now under way.

Experimental

Unless otherwise stated, melting points were measured on a hot stage apparatus and uncorrected; infrared (IR) spectra were measured either in nujol mulls (for crystals) or in liquid films (for oils); nuclear magnetic resonance (NMR) spectra (60 or 100 MHz) were measured in deuterochloroform, and chemical shifts (δ) are given in ppm relative to internal tetramethylsilane. Silica gel (Wakogel C-200) was used for column chromatography. The organic solutions were dried over sodium sulfate before vacuum evaporation.

Starting Materials

DPPA was prepared according to our previous report.[12] Cyanoacetic acid was of commercial origin. Ethyl hydrogen malonate,[13] ethyl hydrogen benzylmalonate,[14] ethyl hydrogen isopropylmalonate,[8] and malonmonoamide[15] were prepared according to the literatures.

Ethyl Hydrogen (3-Indolylmethyl)malonate——Prepared from the corresponding diethyl ester[16] according to the usual method,[13] mp 102—106°, IR 3375, 1740, 1715, 750 cm^{-1}.

Ethyl Hydrogen Phenylmalonate——Prepared from ethyl phenylacetate in the same way as in the preparation of methyl hydrogen phenylmalonate,[7] 67% yield, mp 78.5—80° (recrystallized from a mixture of benzene and *n*-hexane, Lit.[8] mp 76—77°). IR 1740, 1720, 1660, 730, 700 cm^{-1}. NMR 1.23 (3H, t, $J=7$ Hz, CH_3), 4.19 (2H, q, $J=7$ Hz, CH_2), 4.58 (1H, s, CH), 7.34 (5H, m, C_6H_5), 9.84 (1H, s, CO_2H).

8) E.J. Corey, *J. Am. Chem. Soc.*, **74**, 5896 (1952).
9) *cf.* P.L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); *idem*, *Org. Syn.* **50**, 58 (1970).
10) E. Schröder and K. Lübke, "The Peptides," Vol. I, Academic Press, NewYork and London, 1965.
11) *cf.* S. Yamada, T. Oguri, and T. Shioiri, *J.C.S. Chem. Comm.*, **1972**, 623.
12) T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 849 (1974).
13) R.E. Strube, *Org. Syn.*, Coll. Vol. **4**, 417.
14) *cf.* Reference 5), P.A.S. Smith, *Org. Reactions*, **3**, 384 (1946).
15) G.H. Jeffery and A.I. Vogel, *J. Chem. Soc.*, **1934**, 1101.
16) H.R. Snyder, C.W. Smith, and J.M. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944); see also T.A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).

Diethyl (3,4-Methylenedioxybenzyl)malonate——To a stirred suspension of sodium hydride (obtained from 5.28 g of a 50% oil dispersion by washing with dry pentane) in dry tetrahydrofuran (250 ml) was added diethyl malonate (17.6 g) under nitrogen, followed by the addition of 3,4-methylenedioxybenzyl chloride (17.85 g).[17] The mixture was refluxed for 17 hr, poured into dil. hydrochloric acid, and extracted with benzene. The benzene extracts were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Drying followed by evaporation gave an oily residue, which was distilled at 187—191° (3 mmHg) to give a colorless oil (13 g, 40%); IR 1755, 1735, 1503, 1495, 855, 805 cm^{-1}. NMR 1.18 (6H, t, $J=7$ Hz, $2\times CH_3$), 3.04 (2H, d, $J=7$ Hz, $C\underline{H}_2CH$), 3.51 (1H, t, $J=7$ Hz, $C\underline{H}CH_2$), 4.09 (4H, q, $J=7$ Hz, $2\times C\underline{H}_2CH_3$), 5.78 (2H, s, $-OCH_2O-$), 6.58 (3H, s, aromatic protons).

Ethyl Hydrogen (3,4-Methylenedioxybenzyl)malonate——Partial hydrolysis of the above diester was carried out according to the usual method[13] to give colorless needles (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 49—50.5°. IR 1755, 1715, 1495, 815 cm^{-1}. NMR 1.19 (3H, t, $J=7$ Hz, CH_3), 3.09 (2H, d, $J=7$ Hz, $C\underline{H}_2CH$), 3.59 (1H, t, $J=7$ Hz, CH), 4.12 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.81 (2H, s, $-OCH_2-O-$), 6.62 (3H, s, aromatic protons), 10.42 (1H, s, CO_2H). *Anal.* Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.15; H, 5.24.

Ethyl Hydrogen (3,4-Methylenedioxybenzyl)methylmalonate——To a stirred solution of diisopropylamine (3.79 g) in dry tetrahydrofuran (30 ml) was added *n*-hexane solution of 1.48N *n*-butyllithium (25.4 ml) at −50—−70° under nitrogen. Ethyl hydrogen (3,4-methylenedioxybenzyl)malonate (4.5 g) in dry tetrahydrofuran (25 ml) was added to the mixture at −70°, followed by the addition of methyl iodide (3.12 g) in dry tetrahydrofuran (10 ml) at −60°. The reaction mixture was gradually warmed up to room temperature, and poured onto ice-water. The aqueous layer separated was washed with diethyl ether, acidified with 1N hydrochloric acid to pH 2, salted out, and extracted with diethyl ether. Drying followed by evaporation gave a brown oil, which was crystallized from a mixture of methylene chloride and *n*-hexane to give colorless prisms (3.74 g, 79%), mp 83—86°. IR 1760, 1715, 1497, 815 cm^{-1}. NMR 1.28 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2$), 1.40 (3H, s, CH_3C), 3.17 (2H, s, CH_2–C), 4.19 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.88 (2H, s, $-OCH_2O-$), 6.58 (3H, s, aromatic protons), 10.80 (1H, s, CO_2H). *Anal.* Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.79; H, 5.74.

Ester Formation Reaction

Ethyl *tert*-Butyl Malonate——(i) A mixture of ethyl hydrogen malonate (1.32 g), DPPA (2.75 g), and triethylamine (1.05 g) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 23 hr. Evaporated residue of the reaction mixture was dissolved in ethyl acetate, and the solution was successively washed with 5% aqueous citric acid, water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. Drying and evaporation gave an oily residue, which was purified by silica gel column chromatography with a mixture of benzene, chloroform, and ethyl acetate (20: 4: 3), followed by distillation at 60—61° (1.5 mmHg) (Lit.[13] 107—109° (24 mmHg)) to give ethyl *tert*-butyl malonate (1.02 g, 54%) as a colorless oil. IR 1760—1735 cm^{-1}. NMR 1.17 (3H, t, $J=7$ Hz, CH_3), 1.45 (9H, s, *tert*-butyl), 3.13 (2H, s, $COCH_2CO$), 4.14 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$).

The IR spectrum of the distillation residue showed azide, ester, and amide absorptions, which exhibits the presence of N-azidoformylglycine ethyl ester.

(ii) A mixture of ethyl hydrogen malonate (2.6 g), DPPA (5.5 g), and triethylamine (2.2 g) in *tert*-butyl alcohol (60 ml) was stirred at 50° for 24 hr, and refluxed for 4 hr. Work-up as in (i) gave an oily neutral fraction, which was distilled at 95—100° (7 mmHg) to give ethyl *tert*-butyl malonate (2.4 g, 64%).

Benzyl Ethyl Malonate——A mixture of ethyl hydrogen malonate (2.6 g), DPPA (5.5 g), and triethylamine (2.2 g) in benzene (60 ml) was stirred at room temperature for 10 min. After the addition of benzyl alcohol (2.3 g), the mixture was refluxed for 20 hr, and worked up as in the case of ethyl *tert*-butyl malonate. Distillation of the crude product at 140—144° (5 mmHg) (Lit.[18] 145° (5 mmHg)) afforded benzyl ethyl malonate (2.33 g, 53%) as a colorless oil. IR 1740 cm^{-1}. NMR 1.18 (3H, t, $J=7$ Hz, CH_3), 3.16 (2H, s, $COCH_2CO$), 4.08 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.07 (2H, s, $C\underline{H}_2C_6H_5$), 7.24 (5H, s, C_6H_5).

Ethyl *tert*-Butyl Benzylmalonate——A stirred mixture of ethyl hydrogen benzylmalonate (1.11 g), DPPA (1.38 g), and triethylamine (0.55 g) in *tert*-butyl alcohol (30 ml) was refluxed for 5.5 hr, and worked up as in the case of ethyl *tert*-butyl malonate to give a reddish-brown oil, which was purified by column chromatography with a mixture of *n*-hexane, chloroform, and ethyl acetate (100: 20: 7) to furnish ethyl *tert*-butyl benzylmalonate (0.74 g, 53%) as a colorless oil, bp 108—110° (0.5 mmHg). IR 1740 cm^{-1}. NMR 1.20 (3H, t, $J=7$ Hz, CH_3), 1.40 (9H, s, *tert*-butyl), 3.16 (2H, d, $J=7.5$ Hz, $C\underline{H}_2CH$), 3.56 (1H, t, $J=7.5$ Hz, CH), 4.14 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 7.22 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.10; H, 8.06.

Further elution of the column afforded a yellow oil (0.1 g) whose IR and NMR spectra showed the presence of N-azidoformylphenylalanine ethyl ester together with some unknown materials.

17) S. Yamada, T. Fujii, and T. Shioiri, *Chem. Pharm. Bull.* (Tokyo), **10**, 680 (1962).
18) Beilstein's "Handbuch der Organischen Chemie," 6, E II, 418.

***tert*-Butyl Cyanoacetate**——A stirred mixture of cyanoacetic acid (0.85 g), DPPA (2.80 g), and triethylamine (1.06 g) in *tert*-butyl alcohol (30 ml) was refluxed for 5 hr, and worked up as in the case of ethyl *tert*-butyl malonate. The crude brown oil was distilled at 93° (13 mmHg) (Lit.[19] 107—108° (23 mmHg)) to give *tert*-butyl cyanoacetate (0.84 g, 60%) as a colorless oil. IR 2230, 1740 cm^{-1}. NMR 1.48 (9H, s, *tert*-butyl), 3.40 (2H, s, CH_2).

When the reaction was carried out exactly the same as above without DPPA, cyanoacetic was recovered in 65% yield but no esterified product could be found.

***α-tert*-Butyloxycarbonylacetamide**——A stirred mixture of malonmonoamide (0.52 g), DPPA (1.45 g), and triethylamine (0.56 g) in *tert*-butyl alcohol (30 ml) was refluxed for 17 hr, and worked up as in the case of ethyl *tert*-butyl malonate. The crude solid from the neutral fraction was recrystallized from a mixture of *n*-hexane and diethyl ether to give *α-tert*-butyloxycarbonylacetamide (0.18 g, 23%) as colorless crystals, mp 86—88°. IR 3430, 3210, 1730, 1660 cm^{-1}. NMR 1.46 (9H, s, *tert*-butyl), 3.18 (2H, s, CH_2), 6.2 (2H, broad s, NH_2). *Anal.* Calcd. for $C_7H_{13}O_3N$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.91; H, 8.19; N, 8.64.

A Modified Curtius Reaction By DPPA (Two-in-one-reaction Procedure)

N-Benzyloxycarbonylglycine Ethyl Ester——A mixture of ethyl hydrogen malonate (1.32 g), DPPA (3.38 g), and triethylamine (1.05 g) in xylene (30 ml) was stirred at 60° for 1 hr, at 130° for 1 hr, and then refluxed for 15 min. Benzyl alcohol (1.3 g) was added to the mixture, which was refluxed for 5 hr and evaporated. The residue was dissolved in ethyl acetate, and the solution was successively washed with 5%) hydrochloric acid, water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. Drying and evaporation afforded the crude products, which were purified by column chromatography with a mixture of *n*-hexane and ethyl acetate (10: 1) to give N-benzyloxycarbonylglycine ethyl ester (0.61 g, 27%) as a colorless oil, bp 135° (0.2 mmHg) (Lit.[20] 147—151° (0.5—1 mmHg)). IR 3320, 1740, 1720, 1520 cm^{-1}. NMR 1.17 (3H, t, J=7 Hz, CH_3), 3.75 (2H, d, J=6 Hz, CH_2N), 4.06 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.98 (2H, s, $C\underline{H}_2C_6H_5$), 5.84 (1H, s, NH), 7.20 (5H, s, C_6H_5).

N-Benzyloxycarbonylvaline Ethyl Ester——A stirred mixture of ethyl hydrogen isopropylmalonate (1.74 g), DPPA (3.03 g), and triethylamine (1.08 g) was refluxed in benzene (30 ml) for 1 hr. After the addition of benzyl alcohol (1.2 g), the mixture was refluxed for 3.5 hr. Work-up as in the case of N-benzyloxycarbonyl glycine ethyl ester gave an oily product, which was fractionated by column chromatography with a mixture of *n*-hexane and ethyl acetate (20: 1). The first fraction to be eluted was N-azidoformylvaline ethyl ester (0.19 g, 9%) as a colorless oil. IR 3300, 2200, 1745, 1710, 1540 cm^{-1}. NMR 0.94 (6H, t, J=6.5 Hz, $(C\underline{H}_3)_2CH$), 1.29 (3H, t, J=7 Hz, CH_3), 2.19 (1H, m, $C\underline{H}(CH_3)_2$), 4.21 (2H, q, J=7 Hz, CH_2), 4.40 (1H, t, J=5 Hz, CHN), 6.01 (1H, d, J=8 Hz, NH).

The second fraction to be eluted was N-benzyloxycarbonylvaline ethyl ester (2.04 g, 74%) as colorless crystals (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 32—33° (Lit.[21] 32—33°). IR 3370, 1740, 1720, 1535, 750, 700 cm^{-1}. NMR 0.92 (6H, t, J=6.5 Hz, $(C\underline{H}_3)_2CH$), 1.22 (3H, t, J=7 Hz, CH_3), 2.13 (1H, m, $C\underline{H}(CH_3)_2$), 4.14 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.28 (1H, t, J=7 Hz, CHN), 5.08 (2H, s, $C\underline{H}_2C_6H_5$), 5.55 (1H, d, J=8 Hz, NH), 7.28 (5H, s, C_6H_5).

N-Benzyloxycarbonylphenylalanine Ethyl Ester——A mixture of ethyl hydrogen benzylmalonate (2.22 g), DPPA (2.88 g), and triethylamine (1.08 g) in benzene (30 ml) was refluxed with stirring for 1 hr. Benzyl alcohol (1.2 g) was added to the mixture, which was refluxed for 17 hr. Work-up as usual gave the crude product, which was recrystallized from a mixture of diethyl ether, petroleum ether, and benzene to give N-benzyloxycarbonylphenylalanine ethyl ester (2.01 g) as colorless crystals, mp 81.5—82.5°. IR 3270, 1740, 1675, 1515 cm^{-1}. NMR 1.16 (3H, t, J=7 Hz, CH_3), 3.06 (2H, *d*, J=7 Hz, $C\underline{H}_2CH$), 4.10 (2H, q, J= 7 Hz, $C\underline{H}_2CH_3$), 4.60 (1H, q, J=7 Hz, CHN), 5.06 (2H, s, $CO_2C\underline{H}_2C_6H_5$), 5.40 (1H, d, J=8 Hz, NH), 7.22 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.46; N, 4.28. Found: C, 70.19; H, 6.60; N, 4.25.

Further crop (0.58 g) of the N-benzyloxycarbonyl derivative was obtained from the mother liquor of the recrystallization by column chromatography with a mixture of *n*-hexane and ethyl acetate (2: 3); total yield was 2.59 g (79%).

N-Benzyloxycarbonyltryptophan Ethyl Ester——A mixture of ethyl hydrogen (3-indolylmethyl) malonate (0.35 g), DPPA (0.39 g), and triethylamine (0.22 g) in benzene (20 ml) was refluxed with stirring for 45 min. Benzyl alcohol (0.16 g) was added to the mixture, which was refluxed for 12 hr. Work-up as usual followed by column chromatography with a mixture of *n*-hexane and diethyl ether (1: 1) afforded N-benzyloxycarbonyltryptophan ethyl ester (0.32 g, 65%) as colorless crystals (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 91—92.5° IR 3350, 1740, 1710, 1535 cm^{-1} NMR 1.15 (3H, t, J=7 Hz, CH_3), 3.26 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 4.08 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.68 (1H, m, CH), 5.07 (2H, s, $C\underline{H}_2C_6H_5$), 5.36 (1H, d, J=7.5 Hz, NH), 6.88—7.55 (5H, m, indole aromatic protons), 7.29 (5H, s, C_6H_5), 8.25 (1H, s, indole NH). *Anal.* Calcd. for $C_{21}H_{22}O_4N_2$: C, 68.83; H, 6.05; N, 7.65. Found: C, 68.86; H, 5.98; N, 7.80.

19) B. Abramovitch and C.R. Hauser, *J. Am. Chem. Soc.*, **64**, 2274 (1942).
20) A.E. Barkdole and W.F. Ross, *J. Am. Chem. Soc.*, **66**, 951 (1944).
21) S.W. Fox and H. Wax, *J. Am. Chem. Soc.*, **73**, 2936 (1951).

N-Benzyloxycarbonyl-α-phenylglycine Ethyl Ester——A stirred mixture of ethyl hydrogen phenylmalonate (1.04 g), DPPA (1.45 g), and triethylamine (0.55 g) in benzene (30 ml) was refluxed for 1 hr 20 min. Benzyl alcohol (0.65 g) was added to the mixture, which was refluxed overnight. The mixture was worked up as usual, followed by column chromatography with a mixture of *n*-hexane and ethyl acetate (10: 1). The first fraction to be eluted was benzyl azide (0.03 g, 6%) as a colorless oil. IR 2120, 745, 700 cm^{-1}. NMR 4.22 (2H, s, CH_2), 7.24 (5H, s, C_6H_5), identical with an authentic specimen prepared by the action of sodium azide with benzyl chloride in ethyl alcohol.[22]

The second fraction to be eluted was ethyl phenylacetate (0.20 g, 24%) as a colorless oil, identical with an authentic specimen of commercial origin.

The third fraction was N-azidoformyl-α-phenylglycine ethyl ester (0.07 g, 6%) as colorless crystals (recrystallized from a mixture of benzene and *n*-hexane), mp 102.5—104°. IR 3300, 2160, 1740, 1680, 1530, 750, 700 cm^{-1}. NMR 1.22 (3H, t, $J=7$ Hz, CH_3), 4.20 (2H, m, CH_2), 5.38 (1H, d, $J=7$ Hz, CH), 6.20 (1H, s, NH), 7.35 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{11}H_{12}O_3N_4$: C, 53.22; H, 4.87; N, 22.57. Found: C, 53.19; H, 4.95; N, 22.33.

The fourth fraction was N-benzyloxycarbonyl-α-phenylglycine ethyl ester (0.44 g, 28%) as colorless crystals (recrystallized from a mixture of diethyl ether and petroleum ether), mp 62.5—63.5°. IR 3320, 1740, 1690, 1520, 760, 730, 700 cm^{-1}. NMR 1.18 (3H, t, $J=7$ Hz, CH_3), 4.17 (2H, m, $C\underline{H}_2CH_3$), 5.08 (2H, s, $C\underline{H}_2C_6H_5$), 5.33 (1H, d, $J=7$ Hz, CH), 5.84 (1H, s, NH), 7.32 (10H, s, $2\times C_6H_5$). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.89; H, 6.05; N, 4.41.

N-Benzyloxycarbonyl-3-(3,4-methylenedioxyphenyl)alanine Ethyl Ester——A mixture of ethyl hydrogen (3,4-methylenedioxybenzyl)malonate (2.64 g), DPPA (2.9 g), and triethylamine (1.7 g) in benzene (40 ml) was stirred at reflux for 50 min. Benzyl alcohol (1.5 g) was added to the mixture, which was refluxed for 17 hr. Work-up as usual followed by column chromatography with a mixture of *n*-hexane and diethyl ether (2: 1) afforded a colorless oil, from which benzyl alcohol was removed by high vacuum evaporation. Recrystallization of the residue from a mixture of chloroform and *n*-hexane gave N-benzyloxycarbonyl-3-(3,4-methylenedioxyphenyl)alanine ethyl ester (2.90 g, 78%) as colorless needles, mp 49—50°. IR 3320, 1735, 1700, 1540, 1500, 1490, 800, 735, 695 cm^{-1}. NMR 1.16 (3H, t, $J=7$ Hz, CH_3), 2.92 (2H, d, $J=6$ Hz, $C\underline{H}_2CH$), 4.06 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.46 (1H, m, CH), 4.98 (2H, s, $C\underline{H}_2C_6H_5$), 5.44 (1H, d, $J=8.5$ Hz, NH), 5.76 (2H, s, $-OCH_2O-$), 6.5 (3H, m, aromatic protons of methylenedioxyphenyl), 7.17 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{20}H_{21}O_6N$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.34; H, 5.64; N, 4.08.

Further elution of the column furnished the corresponding urea derivative (0.23 g, 5%) as colorless solid, mp 103—113°. IR 3300, 1735, 1648, 1498, 855, 792. NMR 1.21 (6H, t, $J=7$ Hz, $2\times CH_3$), 3.08 (4H, d, $J=7$ Hz, $2\times C\underline{H}_2$–CH), 4.09 (4H, q, $J=7$ Hz, $2\times C\underline{H}_2CH_3$), 4.68 (2H, q, $J=7$ Hz, $2\times$CH), 5.8 (2H, s, $2\times$NH), 5.82 (4H, s, $2\times -OCH_2O-$), 6.52 (6H, m, aromatic protons).

N-Benzyloxycarbonyl-2-methyl-3-(3,4-methylenedioxyphenyl)alanine Ethyl Ester——A mixture of ethyl hydrogen (3,4-methylenedioxybenzyl)methylmalonate (1.40 g), DPPA (1.45 g), and triethylamine (0.55 g) in benzene (30 ml) was stirred at reflux for 45 min. Benzyl alcohol (0.65 g) was added to the mixture, which was refluxed for 45 hr and worked up as usual. The crude product was purified by column chromatography with a mixture of *n*-hexane and diethyl ether (5: 1) to give N-benzyloxycarbonyl-2-methyl-3-(3,4-methylenedioxyphenyl)alanine ethyl ester (1.54 g, 80%) as a colorless viscous oil. IR 3400, 1740, 1725, 1520, 1500, 1490, 800, 770, 730, 685 cm^{-1}. NMR 1.23 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2$), 1.58 (3H, s, CH_3–C), 3.15 (2H, AB q, $J=14$ Hz, CH_2–C), 4.14 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.04 (2H, s, $C\underline{H}_2C_6H_5$), 5.42 (1H, s, NH), 5.80 (2H, s, $-OCH_2O-$), 6.42 (3H, m, aromatic protons of methylenedioxyphenyl), 7.24 (5H, s, C_6H_5).

The structure of the product was further confirmed by its conversion to the crystalline phenylurea derivative as follows: the product (0.58 g) in ethyl alcohol (20 ml) was hydrogenated over 5% Pd-C (0.05 g) at room temperature by bubbling hydrogen for 3 hr. 5% Pd-C (0.05 g) was further added to the mixture, and bubbling hydrogen was continued for 3 hr. The catalyst was filtered, and the filtrate was evaporated to give an oily residue, to which benzene (2×30 ml) was added and the mixture was evaporated. The residue was dissolved in benzene (5 ml), followed by the addition of phenylisocyanate (0.15 g). The mixture was refluxed for 2 hr, and then cooled to give N-(N-phenylcarbamoyl)-2-methyl-3-(3,4-methylenedioxyphenyl)-alanine ethyl ester (0.325 g) as a crystalline precipitate, which was recrystallized from a mixture of methylene chloride and benzene to give colorless crystals, mp 177.5—179°. IR 3400, 3340, 1740, 1725, 1525, 1500, 1490, 770, 730, 688 cm^{-1}. NMR 1.25 (3H, t, $J=7$ Hz, $C\underline{H}_3CH_2$), 1.58 (3H, s, CH_3–C), 3.23 (2H, AB q, $J=14$ Hz, CH_2–C), 4.10 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.71 (1H, s, NH–C), 5.77 (2H, s, $-OCH_2O-$), 6.51 (3H, m, aromatic protons of methylenedioxyphenyl), 6.99 (1H, s, $N\underline{H}C_6H_5$), 7.14 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{20}H_{22}O_5N_2$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.99; H, 5.99; N, 7.59.

Acknowledgement We wish to express our appreciation of partial support of our program by a Grant-in-Aid from the Ministry of Education.

22) T. Curtius and G. Ehrhart, *Ber.*, **55**, 1559 (1922).