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Phosphorus in Organic Synthesis. IX.[1] On the Mechanism of Esterification of Malonic Acid Half Esters by Diphenyl Phosphorazidate[2]

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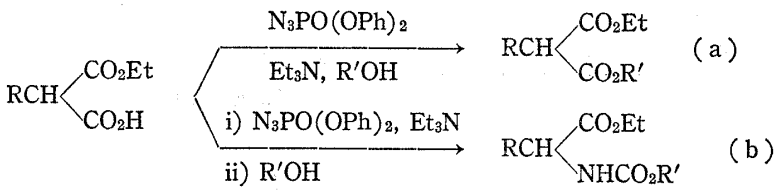
The mechanism of esterification of malonic acid half esters by diphenyl phosphorazidate (DPPA) was investigated by treatment of some possible intermediates, such as mixed carboxylic phosphoric anhydrides and carboxylic acid azides, under similar reaction conditions to esterification, which revealed these are really intermediates of the esterification. Ethyl hydrogen (3,4-methylenedioxybenzyl)methylmalonate (XI), which has no α-hydrogen to ester group, smoothly underwent the Curtius rearrangement instead of esterification under usual reaction conditions for the modified Curtius reaction by DPPA. This demonstrates that esterification takes place if substrates have an acidic hydrogen at the α-position to electron-withdrawing groups, allowing the formation of ketene intermediates. The overall mechanism is summarized in Chart 3.

In the preceding paper[1] we reported the reaction between malonic acid half esters and diphenyl phosphorazidate (DPPA) in the presence of triethylamine and alcohols. The reaction course depends on the reaction procedure as follows:



One-step procedure (a) gave mainly diesters whereas two-in-one-reaction procedure (b) afforded mainly the Curtius-type products. Cyanoacetic acid and malonmonoamide also underwent the esterification by the same one-step procedure. Since the ester formation reaction is rather abnormal in contrast with the results of the modified Curtius reaction by DPPA,[4] we investigated some mechanistic details.

As described in the preceding paper,[1] the participation of DPPA in the esterification is clear because cyanoacetic acid does not undergo the esterification with triethylamine but without DPPA in *tert*-butyl alcohol. Methyl hydrogen succinate and 3-cyanopropionic acid mainly underwent the Curtius reaction by DPPA to give methyl 3-(*tert*-butoxycarbonyl)-aminopropionate in 82% yield and *tert*-butyl N-(2-cyanoethyl)carbamate in 75% yield, respectively. Levulinic acid also afforded the Curtius-type products as described in our previous

$$XCH_2CH_2CO_2H \xrightarrow[Et_3N,\ t\text{-}BuOH]{N_3PO(OPh)_2} XCH_2CH_2NHCO_2t\text{-}Bu$$

$X = CO_2CH_3,\ CN,\ COCH_3$

1) Part VIII: K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 1398 (1974).
2) Presented in part at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 6, 1973.
3) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, **30**, 2151 (1974).

paper.[4] These results suggest us the ester formation reaction would be specific to some acetic acids containing electron-withdrawing functional groups at α-position.

As an initial product by the interaction between the carboxylic acid and DPPA in the presence of triethylamine will be a mixed carboxylic and phosphoric anhydride,[4] the possible intermediacy of the anhydride was investigated. The mixed anhydride (I) prepared from ethyl hydrogen benzylmalonate and diphenyl phosphorochloridate was refluxed in *tert*-butyl alcohol in the presence of either triethylamine or triethylammonium azide. The main product was ethyl *tert*-butyl benzylmalonate (II) in either case, proving that the mixed anhydride is an intermediate of esterification. It is rather surprising, however, that no urethane (III) formation was observed on a thin-layer chromatogram when triethylammonium azide was used.

To investigate whether the carboxylic acid azide, an intermediate of the Curtius reaction[4,5] is an intermediate of the esterification, ethyl 2-azidoformylacetate (IV) was refluxed in *tert*-butyl alcohol without any base to give the Curtius-type product N-*tert*-butoxycarbonylglycine ethyl ester (V), but no esterified product could be found. This result is in accord with that of the Curtius rearrangement of α-cyanocarboxylic acid azides[5] (VI) giving the corresponding urethanes (VII) under similar reaction conditions. However, when ethyl 3-(2-azidoformyl)-phenylpropionate (VIII) was refluxed in *tert*-butyl alcohol in the presence of triethylamine,

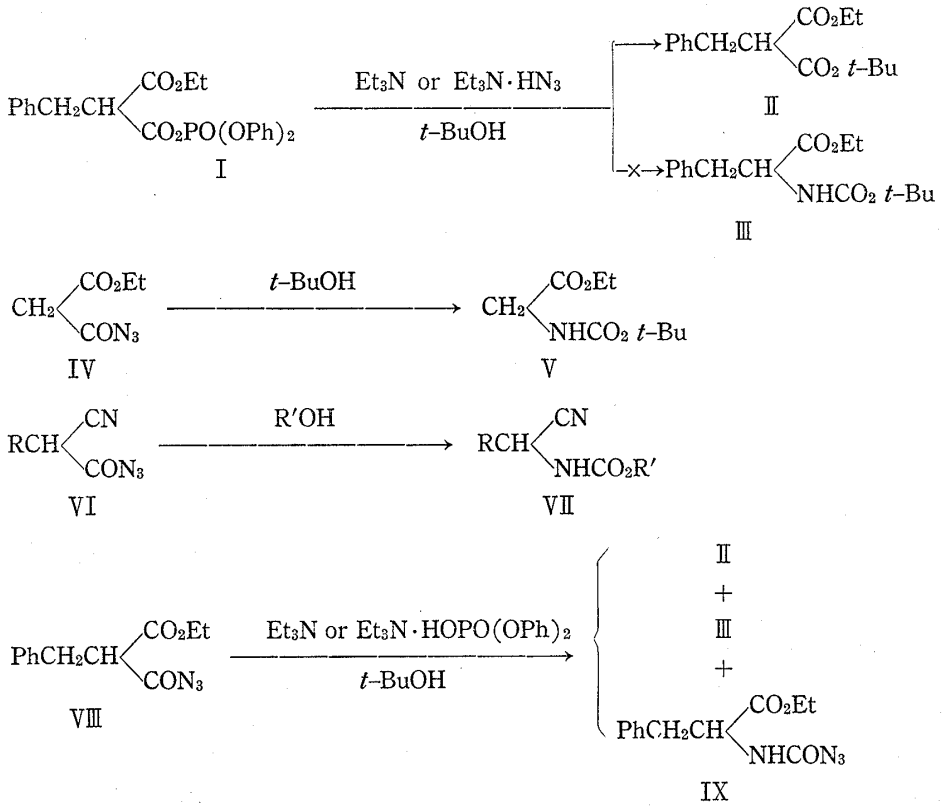


Chart 1

esterification mainly occurred and the ethyl *tert*-butyl ester (II) was obtained in 57% yield together with the rearranged products (III) and (IX) in 9% yield. Since triethylamine would form the salt with diphenyl hydrogen phosphate when the carboxylic acid azide was generated in the modified Curtius procedure by DPPA, refluxing the ester azide (VIII) in *tert*-butyl alcohol was carried out in the presence of both triethylamine and diphenyl hydrogen phosphate. Again the *tert*-butyl ester (II) was obtained in 48% yield, accompanying a mixture of the *tert*-butyl urethane (III) and the carbamoyl azide (IX) in 19% yield. These results

5) P.A.S. Smith, *Org. Reactions*, **III**, 337, (1946).

suggest that the carboxylic acid azide will also be an intermediate of the esterification as well as the Curtius rearrangement, especially in the presence of base. The direct conversion of the carboxylic acid azide to the ester, however, is doubtful since the former might be esterified only when treated with methanol.[5] Furthermore, all the substrates of the esterification reactions have an acidic hydrogen at the α-position to ester, nitrile or amide group,[1] allowing the formation of a ketene intermediate[6] (X) which will be formed from the carboxylic acid azide as well as the mixed carboxylic phosphoric anhydride and will give the diester by the addition of *tert*-butyl alcohol. If this is true, the α,α-disubstituted malonic acid half esters having no α-hydrogen would not undergo the esterification under usual reaction conditions for the modified Curtius reaction.

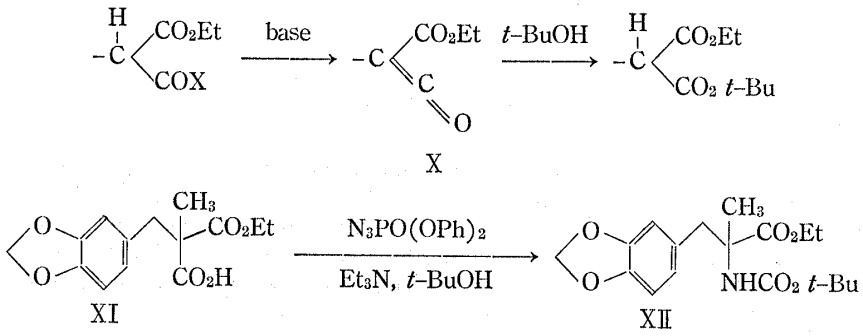


Chart 2

Indeed, when ethyl hydrogen (3,4-methylenedioxybenzyl)methylmalonate (XI) was refluxed in *tert*-butyl alcohol with an equimolecular mixture of DPPA and triethylamine, the Curtius rearrangement smoothly proceeded to give the *tert*-butyl urethane (XII) in 72% yield. None of the esterified product could be obtained.

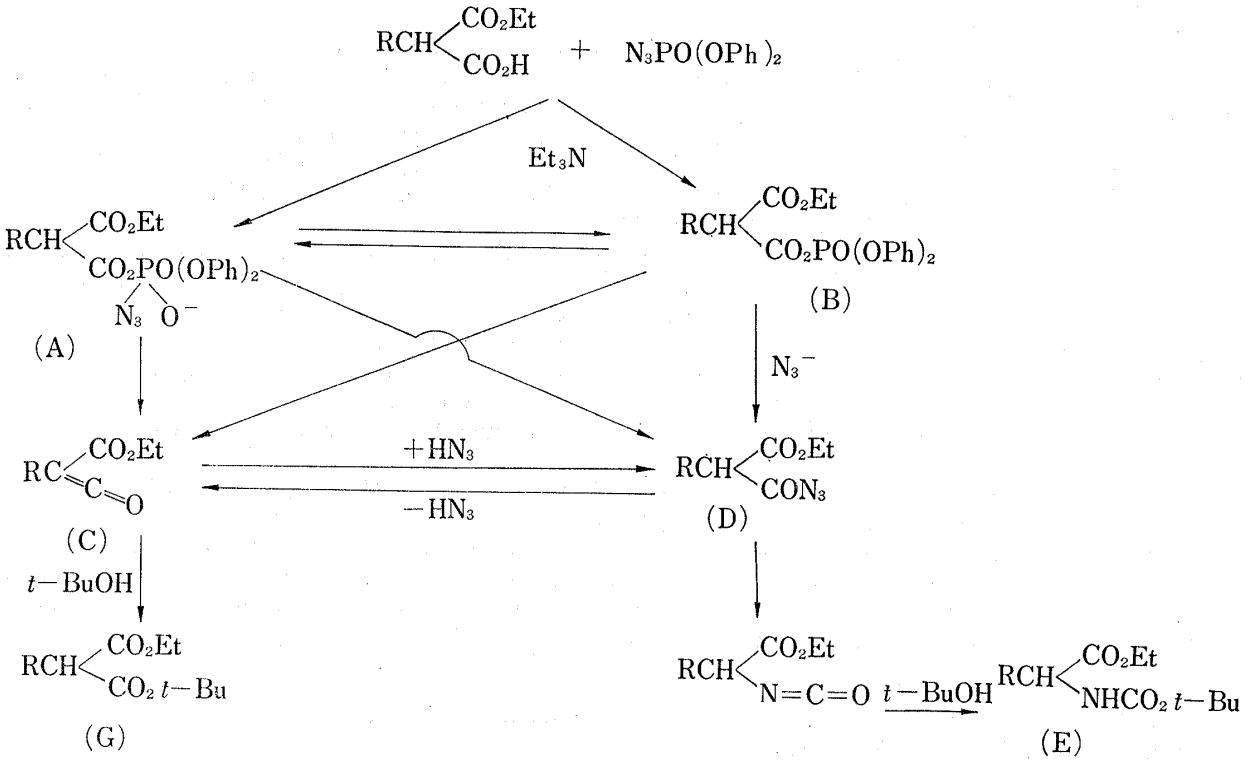


Chart 3

6) *cf.* M.S. Newman and E.A. Zuech, *J. Org. Chem.*, 27, 1436 (1962).

In consequence, the mechanism summarized in Chart 3 will warrant the consideration. The interaction of the malonic acid half ester with DPPA in the presence of triethylamine will give mixed anhydrides (A) and (B) which will coexist at equilibrium. These mixed anhydrides will afford the ketene intermediate (C) as well as the carboxylic acid azide (D). The latter (D) might undergo the rearrangement to furnish the Curtius-type product (E) *via* the isocyanate (F), but the α-hydrogen of (D) will be much more easily eliminated under weakly basic conditions to give the ketene (C). Addition of *tert*-butyl alcohol to the ketene (C) will finally give the diester (G). In the initial stage of the two-in-one-reaction procedure where alcohols are not present,[1] the ketene (C), even if formed, can not give the diester (G) but the acid azide (D), affording the isocyanate (F) by an irreversible process. The addition of alcohols to the isocyanate (F) completes the reaction sequence to furnish the Curtius-type product (E).

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. DPPA was prepared according to our previous report.[7]

Methyl 3-(*tert*-Butoxycarbonyl)aminopropionate——A stirred mixture of methyl hydrogen succinate[8] (1.32 g), DPPA (2.9 g), and triethylamine (1.1 g) in *tert*-butyl alcohol (30 ml) was refluxed for 20 hr. Evaporated residue of the reaction mixture was dissolved in benzene, 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 fractionated by silica gel column chromatography with a mixture of *n*-hexane, benzene, and diethyl ether (4: 2: 1) to give methyl 3-(N-*tert*-butoxycarbonyl)aminopropionate (1.67 g, 82%) as a colorless oil, bp 84—85° (0.4 mmHg); IR 3270, 1740, 1710, 1520 cm^{-1}; NMR 1.39 (9H, s, *tert*-butyl), 2.50 (2H, t, J=6 Hz, CH_2CO), 3.32 (2H, q, J=6 Hz, CH_2N), 3.62 (3H, s, CO_2CH_3), 5.50 (1H, s, NH). *Anal.* Calcd. for $C_9H_{17}O_4N$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.26; H, 8.61; N, 6.68.

***tert*-Butyl N-(2-Cyanoethyl)carbamate**——A mixture of 3-cyanopropionic acid[9] (0.20 g), DPPA (0.61 g), and triethylamine (0.23 g) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 20 hr, and worked up as above. Column chromatography of the crude product with a mixture of *n*-hexane and diethyl ether (2: 1) gave *tert*-butyl N-(2-cyanoethyl)carbamate (0.26 g, 75%) as colorless crystals (recrystallized from a mixture of diethyl ether and petroleum ether), mp 44—45°; IR 3340, 2240, 1690, 1530 cm^{-1}; NMR 1.41 (9H, s, *tert*-butyl), 2.55 (2H, t, J=6 Hz, CH_2CN), 3.30 (2H, q, J=6 Hz, CH_2N), 5.49 (1H, s, NH). *Anal.* Calcd. for $C_8H_{14}O_2N_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.27; H, 8.47; N, 16.51.

Ethyl *tert*-Butyl Benzylmalonate (II)——A mixture of a mixed anhydride (I) of ethyl hydrogen benzylmalonate with diphenyl hydrogen phosphate (2.27 g) (prepared from ethyl hydrogen benzylmalonate[1] and diphenyl phosphorochloridate in the presence of triethylamine[7,10]) and triethylamine (0.52 g) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 20 hr, and worked up as above. The crude product was purified by column chromatography with a mixture of *n*-hexane and diethyl ether (10: 1) to give ethyl *tert*-butyl benzylmalonate (II) (0.90 g, 65%) as a colorless oil, identical with an authentic specimen.[1]

The similar result was obtained when triethylammonium azide[11] was used in place of triethylamine in the above reaction.

Ethyl 2-Azidoformylacetate (IV)——To sodium azide (2.6 g) in water (4 ml) was added with ice-cooling and stirring ethyl 2-chloroformylacetate[12] (4.0 g) in acetone (8 ml). The mixture was stirred at room temperature for 1 hr. After the addition of water (3 ml), the mixture was further stirred at room temperature for 1 hr. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were successively washed with saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. Drying followed by evaporation at room temperature af-

7) T. Shioiri and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 849 (1974).
8) J. Cason, *Org. Syntheses*, Coll. Vol. **3**, 169.
9) D.J.G. Ives and K. Sames, *J. Chem. Soc.*, **1943**, 513.
10) *cf.* F. Cramer and M. Winter, *Chem. Ber.*, **94**, 989 (1961).
11) C.S. Cleaver and C.G. Krespan, *J. Am. Chem. Soc.*, **87**, 3716 (1965).
12) D.S. Breslow, E. Baumgarten, and C.R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

forded ethyl 2-azidoformylacetate (IV) (2.95 g, 71%) as a slightly yellow oil, IR 2210, 2100, 1745, 1720 cm^{-1}, which was directly used for the next reaction without further purification.

This oil crystallized upon standing at room temperature for several days. The structure of the crystals was proved to be N,N'-diethoxycarbonylmethylurea (see the next reaction).

N-*tert*-Butoxycarbonylglycine Ethyl Ester (V)——Ethyl 2-azidoformylacetate (IV) (1.57 g) was refluxed in *tert*-butyl alcohol for 20 hr. Evaporation followed by tritulation of the residue with *n*-hexane containing a small amount of ethyl acetate afforded N,N'-diethoxycarbonylmethylurea (0.05 g, 2%) as colorless needles (recrystallized from ethyl acetate), mp 149—151°; IR 3320, 1750, 1630—1570 (broad) cm^{-1}. *Anal.* Calcd. for $C_9H_{16}O_5N_2$: C, 46.54; H, 6.94; N, 12.06. Found: C, 46.49; H, 6.89; N, 12.00.

The mother liquor was evaporated to give the residue, which was purified by column chromatography with a mixture of *n*-hexane and ethyl acetate (10: 1) to give N-*tert*-butoxycarbonylglycine ethyl ester (V) (1.22 g, 60%) as a colorless oil, bp 83° (0.34 mmHg) (lit.[13] 93—97° (0.65—0.7 mmHg)); IR 3330, 1750, 1715, 1520 cm^{-1}; NMR 1.27 (3H, t, J=7 Hz, CH_3), 1.44 (9H, s, *tert*-butyl), 3.85 (2H, d, J=6 Hz, CH_2N), 4.18 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.34 (1H, s, NH).

Ethyl 3-(2-Azidoformyl)phenylpropionate (VIII)——To thionyl chloride (7 ml) was added ethyl hydrogen benzylmalonate[1] (6.72 g) in methylene chloride (4 ml). The mixture was stirred at 50—75° for 2.5 hr. Evaporation followed by distillation at 150° (3 mmHg) gave ethyl 3-(2-chloroformyl)phenylpropionate (4.24 g, 59%) as a colorless oil; IR 1795, 1745, 740, 695. This ester chloride was treated with sodium azide as in the case of IV to give VIII as a colorless oil (3.6 g), IR 2140, 1750, 1723, 745, 695 cm^{-1}. This was used directly for the next step.

Reactions of Ethyl 3-(2-Azidoformyl)phenylpropionate (VIII) in *tert*-Butyl Alcohol——(i) With Triethylamine: A mixture of VIII (2.5 g) and triethylamine (1.02 g) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 22 hr, and worked up as in the case of methyl 3-(*tert*-butoxycarbonyl)aminopropionate to give the crude products, which were fractionated by column chromatography with a mixture of *n*-hexane and diethyl ether (10: 1).

The first fraction to be eluted was the ethyl *tert*-butyl ester (II) (1.59 g, 57%). The second fraction to be eluted was N-*tert*-butoxycarbonylphenylalanine ethyl ester (III) (0.035 g, 1%) as colorless crystals (recrystallized from a mixture of diethyl ether and *n*-hexane), mp 82—83° (lit.[14] 79.5°); IR 3360, 1745, 1715, 1513, 745, 695 cm^{-1}; NMR 1.21 (3H, t, J=7 Hz, CH_3), 1.40 (9H, s, *tert*-butyl), 3.07 (2H, d, J=7 Hz, $C\underline{H}_2CH$), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.54 (1H, m, CH), 4.98 (1H, s, NH), 7.20 (5H, m, C_6H_5).

The third fraction to be eluted was N-azidoformylphenylalanine ethyl ester (IX) (0.215 g, 8%) as a colorless oil which was solidified on standing; IR 3300, 2120, 1745, 1710, 1525 cm^{-1}; NMR 1.2 (3H, t, J=7 Hz, CH_3), 3.05 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.7 (1H, m, CH), 6 (1H, m, NH), 7.15 (5H, s, C_6H_5).

(ii) With Triethylamine and Diphenyl Hydrogen Phosphate: A mixture of (VIII) (0.96 g), triethylamine (0.40 g), and diphenyl hydrogen phosphate (0.97 g) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 20 hr. Work-up as in (i) afforded the ethyl *tert*-butyl ester (II) (0.515 g, 48%) and a mixture (0.22 g) of the urethane (III, 4% yield) and the carbamoyl azide (IX, 15% yield), the respective yields of which were calculated from its NMR spectrum.

N-*tert*-Butoxycarbonyl-2-methyl-3-(3,4-methylenedioxyphenyl)alanine Ethyl Ester (XII)——A mixture of ethyl hydrogen (3,4-methylenedioxybenzyl)methyl malonate[1] (XI) (0.765 g), DPPA (0.77 g), and triethylamine (0.31 g) in *tert*-butyl alcohol (30 ml) was stirred at reflux for 48 hr, and worked up as in the case of methyl 3-(*tert*-butoxycarbonyl)aminopropionate. Purification of the crude product was carried out by column chromatography with a mixture of *n*-hexane and diethyl ether (8: 1) to give XII (0.69 g, 72%) as a colorless viscous oil; IR 3430, 1740, 1725, 1530, 1510, 1500, 810, 780 cm^{-1}; NMR 1.27 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$), 1.45 (9H, s, *tert*-butyl), 1.52 (3H, s, CH_3–C), 3.19 (2H, AB q, J=14 Hz, CH_2–C), 4.14 (2H, q, J= 7 Hz, $C\underline{H}_2CH_3$), 5.20 (1H, s, NH), 5.83 (2H, s, $-OCH_2O-$), 6.52 (3H, m, aromatic protons).

The structure of the product was further confirmed by its conversion to the crystalline phenylurea derivative as follows: the product (263 mg) was treated with 20% ethanolic hydrogen chloride (20 ml) at room temperature for 50 min. The mixture was evaporated to an oily residue, which was dissolved in benzene, followed by the addition of triethylamine (80 mg). Triethylamine hydrochloride precipitated was filtered, and to the filtrate was added phenylisocyanate (72 mg). The mixture was heated at 70° for 1 hr, and then cooled to give N-(N-phenylcarbamoyl)-2-methyl-3-(3,4-methylenedioxyphenyl)alanine ethyl ester (160 mg) as a crystalline precipitate, which was recrystallized from a mixture of methylene chloride and benzene to give colorless crystals, mp 177.5—180° (lit.[1] 177.5—179°) identified with a sample obtained in the preceding paper.[1]

13) D.S. Tarbell and M.A. Insalaco, *Proc. Natl. Acad. Sci. U.S.*, **57**, 233 (1967).
14) W.J. Bailey and J.R. Griffith, *Am. Chem. Soc., Div. Polymer Chem.*, Preprints **5**, 266 (1964).