and in the presence of palladium-charcoal as catalyst; b.p. 64–66° (4 mm.).

3-Fluoroacetanilide.[10] To the solution of 8.5 g. (0.75 mole) of 3-fluoroaniline in 50 ml. of benzene, a small excess of acetic anhydride was added. When the exothermic reaction had subsided, the mixture was kept at room temperature for 12 hr., and the volatile constituents were removed *in vacuo*. The residue crystallized spontaneously in form of colorless needles, m.p. 84°, yield, 11.5 g. (98%).

2,4-Dinitro-5-fluoroacetanilide. With stirring and cooling (ice-salt mixture), 11 g. (0.7 mole) of the foregoing substance was added in small quantities to a mixture of 30 g. of concd. nitric acid (d = 1.49) and 90 g. of concd. sulfuric acid. After 1 hr., the mixture was poured onto ice and the solid filtered, washed, and recrystallized from alcohol; m.p. 119°, yield, 7.2 g. (42%).

Anal. Calcd. for $C_8H_6FN_3O_5$: C, 39.5; H, 2.5; N, 17.3. Found: C, 39.4; H, 2.4; N, 17.4.

2,4-Dinitro-5-fluoroaniline. The mixture of 10 g. (0.05 mole) of the foregoing compound and 30 ml. of 50% sulfuric acid was refluxed for 2 hr. and poured onto ice. The solid product was filtered and recrystallized from alcohol; m.p. 186–187°; yield, 8 g. (96%).

Anal. Calcd. for $C_6H_4FN_3O_4$: N, 21.0; F, 9.5. Found: N, 21.0; F, 9.7.

Preparation of N-(2,4-dinitro-5-acetamidophenyl) glycine. To the solution of 0.17 g. (0.002 mole) of glycine and 0.5 g. of sodium bicarbonate in 10 ml. of water, there was added a solution of 1.2 g. (0.006 mole) of 2,4-dinitro-5-fluoroacetanilide in 50 ml. of alcohol. The mixture was stirred at room temperature for 2 hr., the alcohol removed *in vacuo* and water added. The excess of the reagent was then removed by filtration and the filtrate acidified with dilute hydrochloric acid. The yellow precipitate was recrystallized from alcohol; m.p. 243°; yield, 0.7 g. (87%). $\lambda_{max}^{C_2H_5OH}$ 334 mμ (4.32); 410 mμ (4.02).

Anal. Calcd. for $C_{10}H_{10}N_4O_7$: C, 40.3; H, 3.3; N, 18.71. Found: C, 40.7; H, 3.3; N, 18.2.

The analogous reactions with other amino acids are summarized in Table II.

*Preparation of N-(2,4-dinitro-5-aminophenyl)-*DL*-phenylalanine.* The mixture of 0.8 g. (0.05 mole) of DL-phenylalanine, 0.9 g. of sodium bicarbonate, 1.5 g. (0.14 mole) of 2,4-dinitro-5-fluoroaniline, and 30 ml. of alcohol was heated until a clear solution resulted. After 30 min. at room temperature, 20 ml. of water was added, and the filtered solution heated *in vacuo*, in order to remove the alcohol, and acidified with dilute hydrochloric acid; from methanol, m.p. 235°, yield, 1.6 g. (93%). $\lambda_{max}^{C_2H_5OH}$ 334 mμ (4.26); 410 (3.96).

Anal. Calcd. for $C_{15}H_{14}N_4O_6$: C, 52.0; H, 4.0; N, 16.2. Found: C, 52.2; H, 4.3; N, 16.1.

The analogous reactions with other amino acids are summarized in Table III; in these cases 50% alcohol was used as the reaction medium.

Diazotization and coupling with α-naphthol. To an ice-cold solution of 0.004 mole of the 2,4-dinitro-5-aminophenyl derivative in 5 ml. of 10% hydrochloric acid, 1.4 ml. of a 20% sodium nitrite solution was added with agitation, followed by 0.6 g. of α-naphthol, dissolved in 6 ml. of 10% sodium hydroxide solution.

Procedure for paper chromatography. The test solution was applied to the paper with a glass capillary until a round spot of about 1 cm. diameter formed. The spot was left to dry for a minute or two.

The filter paper used was Whatman's No. 1. The solvent was *n*-butyl alcohol, saturated with water. The developed chromatogram was sprayed successively with 10% hydrochloric acid, a 1% solution of sodium nitrite, and a solution of 1 g. of α-naphthol in 10 ml. of 10% sodium hydroxide. The chromatogram was then dried at 50–60°.

TEL-AVIV, ISRAEL

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Synthesis of Selectively Protected Homoserine and α,γ-Diaminobutyric Acid Derivatives[1]

T. SHERADSKY,[2] Y. KNOBLER, AND MAX FRANKEL

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The interaction between α-halogeno-γ-butyrolactone, *N*-acylated-α-amino-γ-butyrolactones, or α-benzamido-γ-halogenobutyric acid esters and between ammonia, benzylamine, and dibenzylamine was studied. α-Dibenzylamino-γ-butyrolactone was employed in the synthesis of a series of homoserine and α,γ-diaminobutyric acid derivatives, in which functional groups appeared selectivity masked or free for reaction.

The occurrence in nature of homoserine[3] and of α,γ-diaminobutyric acid[4] lends interest to the synthesis of these compounds and of such of their derivatives in which protection as well as activation of the functional groups is selectively provided for.

In this work, α-dibenzylamino-γ-butyrolactone, an intermediate in homoserine synthesis, was used as a fundamental substance for conversion to linear, lactonic, and lactamic homoserine and α,γ-diaminobutyric acid derivatives, with the three functional groups, in part or *in toto* selectively protected. The derivatives prepared in this manner are arrived at directly, obviating the preparation of the acids themselves.

The reaction between α-bromo-γ-butyrolactone[5] and dibenzylamine yielded α-dibenzylamino-γ-

(1) Presented in part before the XXVIth Scientific Meeting of the Israel Chemical Society, Jerusalem, April 1960, *cf.* M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Res. Counc. Israel*, **9A**, 56 (1960).

(2) Part of a Ph.D. Thesis to be submitted to the Hebrew University.

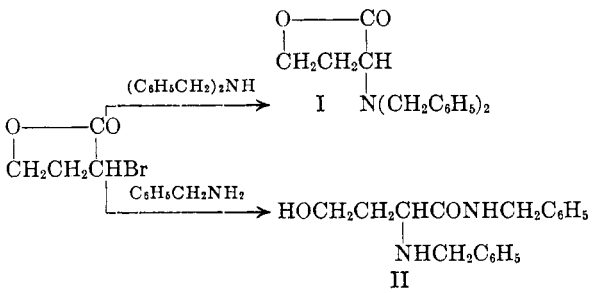
(3) A. I. Virtanen and J. K. Miettinen, *Biochim. et Biophys. Acta*, **12**, 181 (1953); A. I. Virtanen, *Acta Chem. Scan.*, **11**, 747 (1957).

(4) J. R. Catch, T. S. G. Jones, and S. Wilkinson, *Ann. N. Y. Acad. Sci.*, **51**, 917 (1949); W. Hausmann and L. C. Craig, *J. Am. Chem. Soc.*, **76**, 4892 (1954).

(5) J. E. Livak, E. C. Britton, J. C. Vander Weele, and M. F. Murray, *J. Am. Chem. Soc.*, **67**, 2218 (1945).

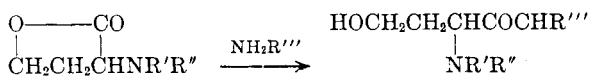
butyrolactone (I) in exclusive α-amination, without opening the lactone ring by γ-amination or by amide formation, even with excess of dibenzylamine.

The failure of dibenzylamine to open the lactone ring, as well as the increased ring stability caused by the α-introduction of the dibenzylamino group, should be attributed to steric hindrance. This becomes apparent on comparing the parallel reactions of α-bromo-γ-butyrolactone, of *N*-acylated-α-amino-γ-butyrolactone, or of α-dibenzylamino-γ-butyrolactone with ammonia, with benzylamine or with dibenzylamine.



α-Bromo-γ-butyrolactone reacts with aqueous ammonia to give α-amino-γ-hydroxybutyramide,[6] and with benzylamine to give α-benzylamino-γ-hydroxy-*N*-benzylbutyramide (II), while, as mentioned above, with dibenzylamine only replacement of the halogen by the dibenzylamino group takes place, leaving the lactone ring unaffected.

Among *N*-substituted α-amino-γ-butyrolactones, α-benzamido-γ-butyrolactone[6] (Ia) or α-carbobenzoxyamino-γ-butyrolactone[6] (Ib) reacted with ammonia or with benzylamine to give the corresponding γ-hydroxyamides (III,IV,V,VI), but no reaction occurred with dibenzylamine.



I. R′ = R″ = $CH_2C_6H_5$
Ia. R′ = H, R″ = COC_6H_5
Ib. R′ = H, R″ = $OCOCH_2C_6H_5$
III. R′ = R‴ = H, R″ = COC_6H_5
IV. R′ = H, R″ = COC_6H_5, R‴ = $CH_2C_6H_5$
V. R′ = R‴ = H, R″ = $OCOCH_2C_6H_5$
VI. R′ = H, R″ = $OCOCH_2C_6H_5$, R‴ = $CH_2C_6H_5$
VII. R′ = R″ = R‴ = $CH_2C_6H_5$

α-Phthalimido-γ-butyrolactone,[7] as well, was found unaffected by dibenzylamine. Its reaction with ammonia or benzylamine could not be compared with that of the other *N*-acylated lactones, because of partial removal of the phthalyl group.

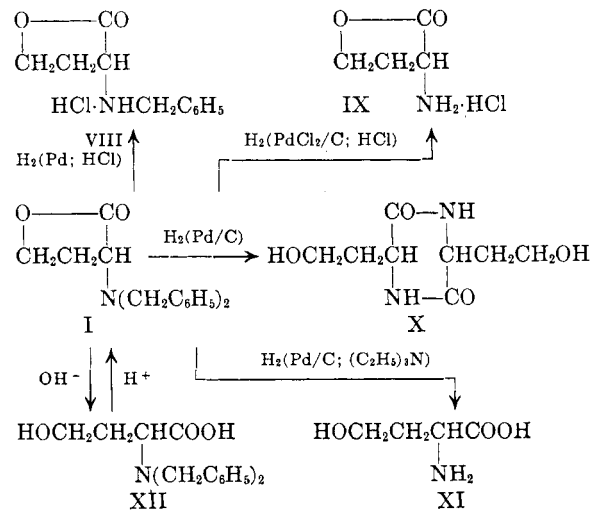
While the α-acylamino-γ-butyrolactone suffered amidic ring opening by ammonia or benzylamine, α-substitution by the dibenzylamino group in γ-butyrolactone led to the inactivation of the lactone ring. I did not react at all with ammonia and its reaction with benzylamine was very slow. As expected, no reaction occurred between I and dibenzylamine.

In accordance with the inertness of dibenzylamine towards lactones, this base was found to be unreactive also towards linear esters. Thus, the reaction of α-benzamido-γ-halogenobutyric acid esters[6] with dibenzylamine resulted in γ-amination only, while reaction of the same esters with benzylamine led to γ-amination and to amide formation.

The inertness of α-dibenzylamino-γ-butyrolactone (I) becomes apparent also in its stability towards hydrogen halides; while α-benzamido-,[8] and α-phthalimido-γ-butyrolactone[7b]) were opened by concentrated hydroiodic acid to the corresponding γ-iodo acids, or by alcoholic hydrogen halides to the corresponding γ-halogeno esters,[6] I was found to be unaffected by these reagents.

This stability of α-dibenzylamino-γ-butyrolactone (I) reveals itself also in the failure to react with aqueous alkali, the lactone I being opened only by hot alcoholic alkali solution.

By controlling the degree of debenzylation and by varying the hydrogenation conditions, I served for the preparation of homoserine and of its lactonic and dimeric forms. These compounds are also intermediates in the syntheses of other natural amino acids.[5,9]



Catalytic hydrogenation of I with the aid of palladium black in ethanol containing hydrochloric acid, gave α-monobenzylamino-γ-butyrolactone hydrochloride (VIII). When a palladium chloride catalyst was used in the presence of hydrochloric acid both benzyl groups were removed, giving α-amino-γ-butyrolactone hydrochloride (IX). Hydrogenation in neutral medium, with

(6) Y. Knobler and M. Frankel, *J. Chem. Soc.*, 1629 (1958).

(7) (a) G. Talbot, R. Gaudry, and L. Berlinguet, *Canad. J. Chem.*, **36**, 593 (1958); (b) M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Res. Counc. Israel*, **7A**, 173 (1958).

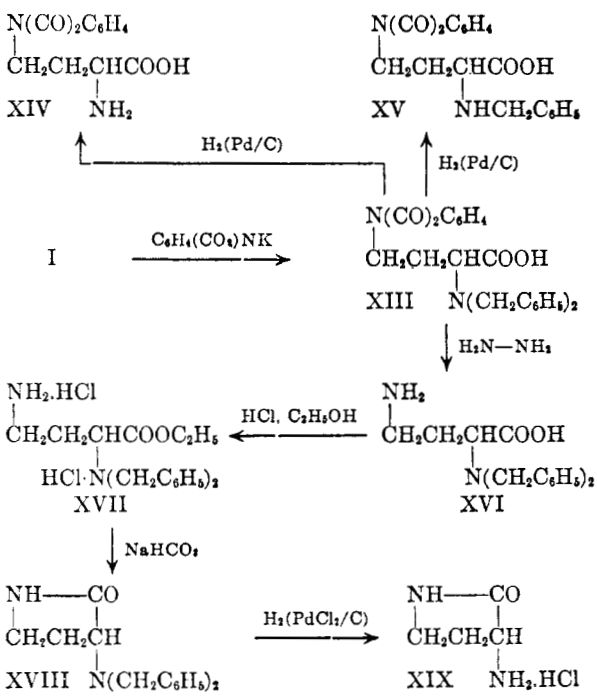
(8) M. Frankel and Y. Knobler, *J. Am. Chem. Soc.*, **80** 3147 (1958).

(9) J. A. Stekol, *J. Biol. Chem.*, **173**, 153 (1948); H. R. Snyder and G. W. Cannon, *J. Am. Chem. Soc.*, **66**, 511 (1944).

palladium on charcoal, gave free α-amino-γ-butyrolactone which dimerized on further heating to the diketopiperazine of homoserine (X). Hydrogenation of I using palladium on charcoal in aqueous ethanolic solution in the presence of triethylamine to prevent relactonization, gave α-amino-γ-hydroxybutyric acid (homoserine) (XI).

Ring opening of I by hot alcoholic alkali yielded *N,N*-dibenzylhomoserine (XII). Ring closure back to the lactone I was achieved by prolonged heating in acidic medium.

For the preparation of α,γ-diaminobutyric acid derivatives, I was opened by potassium phthalimide in boiling dimethylformamide. γ-Amination occurred with introduction of the phthalimido group, and α-dibenzylamino-γ-phthalimidobutyric acid (XIII) was obtained.

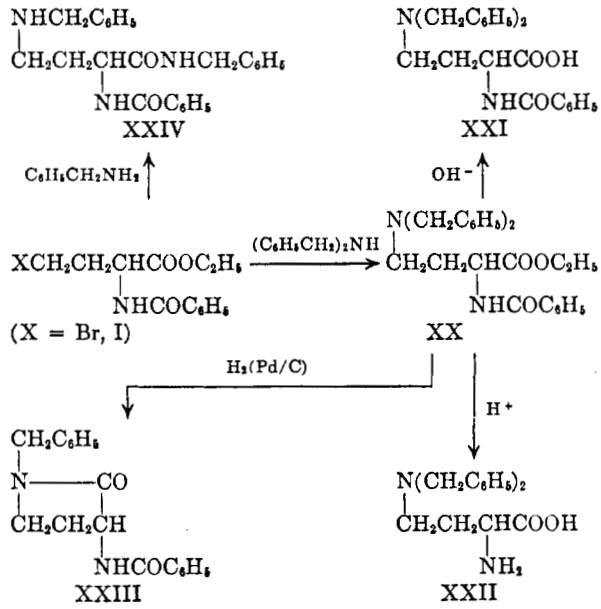


To set free the α-amino group only, XIII was hydrogenated with palladium on charcoal. α-Amino-γ-phthalimidobutyric acid (XIV) resulted as the final hydrogenation product, while on shortening the hydrogenation time the partially hydrogenated intermediate, α-monobenzylamino-γ-phthalimidobutyric acid (XV), was obtained.

For the liberation of the γ-amino group only, the removal of the phthalyl group was carried out by hydrolysis of XIII with concentrated hydrobromic acid or by treating with hydrazine, giving α-dibenzylamino-γ-aminobutyric acid (XVI).

The amino acid XVI was esterified to ethyl α-dibenzylamino-γ-aminobutyrate dihydrochloride (XVII), and the freed ester cyclized to 3-dibenzylaminopyrrolidin-2-one (XVIII), which upon hydrogenation yielded 3-aminopyrrolidin-2-one hydrochloride (XIX).

On attempting to prepare α-amino-γ-phthalimidobutyric acid (XIV), by treating α-amino-γ-butyrolactone hydrobromide with potassium phthalimide,[7b] a transfer of the phthalyl group to the α-amino group of the lactone occurred. Thus, with one mole of potassium phthalimide, α-phthalimido-γ-butyrolactone, and with two moles, α,γ-diphthalimidobutyric acid, were obtained, although in low yields. This transfer did not occur with the free amino acids.



On treating dibenzylamine with ethyl α-benzamido-γ-halogenobutyrate (prepared from α-benzamido-γ-butyrolactone in ethanolic hydrogen halide solution),[6] exclusive γ-dibenzylamination occurred, yielding ethyl α-benzamido-γ-dibenzylaminobutyrate (XX). Mild alkaline hydrolysis of the ester XX gave α-benzamido-γ-dibenzylaminobutyric acid (XXI) while acid hydrolysis yielded α-amino-γ-dibenzylaminobutyric acid (XXII).

Hydrogenation of the α-benzamido-γ-dibenzylamino ester XX gave 1-benzyl-3-benzamidopyrrolidin-2-one (XXIII). This result indicates that the cyclization reaction took place before the second benzyl group was removed. The lactamic *N*-benzyl, now attached to an amidic nitrogen, became resistant towards further hydrogenation.

Reaction of α-benzamido-γ-halogenobutyric acid esters with benzylamine resulted in γ-amination as well as in aminolysis of the ester group yielding α-benzamido-γ-benzylamino-*N*-benzylbutyramide (XXIV).

EXPERIMENTAL

α-Dibenzylamino-γ-butyrolactone (I). A mixture of 82.5 g. (0.5 mole) of α-bromo-γ-butyrolactone[8] and 227 g. (1.15 moles) of dibenzylamine was allowed to stand at room temperature for 1 week. Ether was added, separated dibenzylamine hydrobromide was filtered off and the ethereal solu-

tion concentrated *in vacuo* until semisolid. Another portion of ether was added, a second crop of the salt was filtered off, and the lactone I separated on concentration of the ethereal solution; weight 92 g., m.p. 80°. The mother liquor was concentrated *in vacuo* and the residue dissolved in ethyl acetate. Traces of the salt were removed and the solution concentrated *in vacuo* to give an additional 6 g. of I.

Further amounts of I may be obtained either by repeating the above procedure and prolonged extraction with petroleum ether of the dark crude mass, left from the concentration of the mother liquor, or advantageously by alcoholic alkaline hydrolysis and relactonization, as described for the preparation of *N,N*-dibenzylhomoserine (XII), giving an additional 21 g. of I. The overall yield was 85%. After crystallization from acetone-water it melted at 82°.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0. Found: C, 77.0; H, 6.9; N, 4.9.

Slow crystallization from large amount of petroleum ether (b.p. 40–60°) provided star-shaped crystals, m.p. 90°.

Anal. Found. C, 76.9; H, 6.9; N, 5.0.

Elevation of the reaction temperature to 100° did not affect the course of the reaction. In this case the reaction time was shortened to a few hours, but work at room temperature was preferred because of easier isolation and purification of the product.

α-Benzylamino-γ-hydroxy-N-benzylbutyramide (II). α-Bromo-γ-butyrolactone[5] (33 g., 0.2 mole) and benzylamine (107 g., 1 mole) were mixed at 0° and left at room temperature for 5 days. Water was added and the mixture was stirred at 100°, then allowed to cool with stirring. The semicrystalline mass solidified when kept in the cold and was collected. Crystallization from benzene–petroleum ether afforded 36 g. (60%) of the amide II, m.p. 82°.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$. C, 72.5; H, 7.9; N, 9.4. Found: C, 72.2; H, 7.4; N, 9.4.

α-Benzamido-γ-hydroxybutyramide (III). α-Benzamido-γ-butyrolactone[6] (Ia) (4.1 g.) was dissolved by shaking in 50 ml. of 24% ammonia solution. A voluminous precipitate separated out in a few minutes. After 24 hr. it was collected and recrystallized from water to give the amide III (4 g., 90%), m.p. 180°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.5; H, 6.3; N, 12.6. Found: C, 59.8; H, 6.4; N, 12.5.

α-Benzamido-γ-hydroxy-N-benzylbutyramide (IV). A solution of 4.1 g. (0.02 mole) of α-benzamido-γ-butyrolactone[6] (Ia) in 10.7 g. (0.1 mole) of benzylamine was kept at room temperature for 24 hr. Ether and petroleum ether were added and the precipitated amide IV, (5.9 g., 90%), m.p. 131°, was collected.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.4; N, 9.0. Found: C, 69.4; H, 6.6; N, 9.1.

α-Carbobenzoxyamino-γ-hydroxybutyramide (V). The procedure was the same as described for III, using 4.7 g. (0.02 mole) of α-carbobenzoxyamino-γ-butyrolactone[6] (Ib) and 75 ml. of 24% ammonia solution. The product V, (4.2 g., 78%) melted at 137°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.1; H, 6.3; N, 11.1. Found: C, 57.3; H, 6.6; N, 11.1.

α-Carbobenzoxyamino-γ-hydroxy-N-benzylbutyramide (VI). VI was prepared as described for IV, from Ib (4.7 g., 0.02 mole) and benzylamine (10.7 g., 0.1 mole), giving 6 g. (88%) of the amide VI, m.p. 133°.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.7; H, 6.4; N, 8.2. Found: C, 66.7; H, 6.7; N, 8.3.

α-Dibenzylamino-γ-hydroxy-N-benzylbutyramide (VII). The lactone I (1.4 g., 0.005 mole) was dissolved in 5 g. (0.05 mole) of benzylamine and left at room temperature for 1 week. Water was added and the separated oil was washed with portions of water and left in the cold. The semisolid was dissolved in acetone, precipitated by adding water, kept again in the cold and this procedure repeated until crystallization. The amide VII (1.7 g. 88%) melted at 76–78°.

Anal. Calcd. for $C_{25}H_{28}N_2O_2$. C, 77.3; H, 7.2; N, 7.2. Found. C, 77.3; H, 7.4; N, 7.2.

Attempted reaction of α-dibenzylamino-γ-butyrolactone (I) *with hydroiodic acid.* The lactone I (2.8 g.) was suspended in 20 ml. of 55% hydroiodic acid and the mixture was stirred at 50–60° during 10 hr. The solid was filtered off, washed with ethanol, followed by ether and then by petroleum ether. The compound (3.7 g., 90%) melted at 175°.

Anal. Calcd. for $C_{18}H_{20}NO_2I$: C, 52.8; H, 4.9; N, 3.4; I, 31.1. Found: C, 52.5; H, 4.8; N, 3.4; I, 31.2.

The analytical data are the same for the expected α-dibenzylamino-γ-iodobutyric acid and for the hydroiodide of the unchanged starting material I. But as the infrared spectrum of the product was identical with that of I, showing the specific γ-lactone band at 5.6 μ, it can be assumed that I could not be opened by concentrated hydriodic acid and that the product is its hydroiodide. Moreover, the product did not dissolve in alkali, the free lactone I, m.p. 82°, being recovered.

α-Benzylamino-γ-butyrolactone hydrochloride (VIII). The lactone I (2.8 g.) was dissolved in 100 ml. of ethanol containing 1 ml. of concd. hydrochloric acid, palladium black (0.2 g.) was added, and the mixture hydrogenated for 5 hr. at 3 atm. The catalyst was filtered off and the filtrate evaporated *in vacuo*. Water was added and the undissolved, unchanged I was removed. The aqueous solution was concentrated *in vacuo* and an additional amount of I which separated was filtered off (total 1.5 g., 54% recovery). The filtrate was evaporated *in vacuo*, and the crude residue of VIII was dissolved in a little ethanol and precipitated with ether, yielding a crystalline substance (0.75 g., 30%), m.p. 205–215°. Recrystallized from ethanol-ether, m.p. 220°.

Anal. Calcd. for $C_{11}H_{14}NO_2Cl$: C, 58.0; H, 6.2; N, 6.2; Cl, 15.6. Found: C, 58.2; H, 6.1; N, 6.2; Cl, 15.3.

α-Amino-γ-butyrolactone hydrochloride (IX). The lactone I (1.4 g.) was dissolved in 50 ml. of ethanol containing 0.5 ml. of concd. hydrochloric acid, 0.5 g. of 25% palladium chloride on charcoal was added and the mixture was hydrogenated for 5 hr. at 3 atm. The catalyst was filtered off and washed with water, the filtrate evaporated *in vacuo* and the residue purified by washing with ethanol. The crystals (0.3 g.) melted at 202–203°. Concentration of the washing solution and precipitation with ether yielded additional 0.3 g. of IX, m.p. 202°, (over-all yield 85%).

Anal. Calcd. for $C_4H_8NO_2Cl$: N, 10.2; Cl, 25.8. Found: N, 10.2; Cl, 25.5.

3,6-Bis(β-hydroxyethyl)-2,5-diketopiperazine (X). The lactone I (1.4 g.) was dissolved in 50 ml. of ethanol, 0.7 g. of 10% palladium on charcoal was added and the mixture was hydrogenated at 60° for 10 hr. (3 atm.). The catalyst was filtered off, the filtrate refluxed for 12 hr. and then evaporated *in vacuo*. Crystallization of the semisolid residue from alcohol-ether afforded 0.35 g. (70%) of X, m.p. 184–186°.

Anal. Calcd. for $C_8H_{14}N_2O_4$: N, 13.9; N (Van Slyke), 0.0. Found: N (Kjeldahl), 13.6; N (Van Slyke), 0.0.

Homoserine (α-amino-γ-hydroxybutyric acid) (XI). The lactone I (1.4 g.) was dissolved in 200 ml. of ethanol-water 1:1. Triethylamine (2 ml.) and 0.125 g. of 10% palladium on charcoal were added and the mixture was hydrogenated for 10 hr. at 60–65° (3 atm.). The catalyst was filtered off and the solvent removed *in vacuo*. The residue was dissolved in a small amount of water, ethanol was added, followed by an excess of acetone. The precipitated acid XI (0.45 g. 75%) was recrystallized from water-ethanol-acetone, m.p. 185°.

Anal. Calcd. for $C_4H_9NO_3$: N, 11.8. Found: N (Van Slyke), 11.7.

N,N-Dibenzylhomoserine (α-dibenzylamino-γ-hydroxybutyric acid) (XII). The lactone I (2.8 g., 0.01 mole) was dissolved in 40 ml. of ethanol and a solution of 1 g. (0.025 mole) of sodium hydroxide in 40 ml. of water was added. The mixture was refluxed for 10 hr. with slow dissolution of the reprecipitated I. The solution was purified with Norit

and evaporated *in vacuo*. The residue was dissolved in 100 ml. of water and acidified with acetic acid. The crude mass which separated was recrystallized from its precipitation solution and washed with water and acetone. The acid XII obtained (1 g.) melted at 153–154°. On concentrating the mother solution an additional amount (0.8 g.) of pure XII was obtained, m.p. 154°. The over-all yield was 60%.

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.0; N, 4.7. Found: C, 72.2; H, 6.9; N, 4.8.

On heating the acid XII for 4 hr. in water containing a little acetic acid or a few drops of hydrochloric acid, relactonization to I, m.p. 82°, occurred. (Found: C, 76.8; H, 7.0; N, 5.0).

α-Dibenzylamino-γ-phthalimidobutyric acid (XIII). α-Dibenzylamino-γ-butyrolactone (I) (14 g., 0.05 mole) and potassium phthalimide (9.3 g., 0.05 mole) in dimethylformamide (250 ml.) were refluxed for 5 hr. Most of the solvent was distilled off *in vacuo* and 500 ml. of water was added. On acidification with 18% hydrochloric acid (Congo Red) the acid XIII separated as an oil which solidified immediately. Recrystallization from alcohol gave 15.5 g. (72%) of XIII, m.p. 185°.

Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.9; H, 5.6; N, 6.5. Found: C, 72.7; H, 5.7; N, 6.5.

α-Amino-γ-phthalimidobutyric acid (XIV). The acid XIII (2.15 g.) was dissolved in 100 ml. of ethanol, 1 g. of 10% palladium on charcoal was added, and the mixture hydrogenated at 40–50° for 12 hr. at a pressure of 3 atm. During hydrogenation the acid XIV separated out. Water (400 ml.) was added, the acid dissolved in the boiling solution and the catalyst was removed by rapid filtration in the hot. Evaporation of the filtrate gave 1.1 g. (88%) of XIV, m.p. 200° dec.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$. N (Kjeldahl), 11.3; N (Van Slyke), 5.6. Found: N (Kjeldahl), 11.4; N (Van Slyke), 5.5.

α-Benzylamino-γ-phthalimidobutyric acid (XV). The acid XIII (2.15 g.) was dissolved in 100 ml. of ethanol, 1 g. of 10% palladium on charcoal was added, and the mixture hydrogenated for 2 hr. at room temperature (3 atm.). The catalyst was removed by filtration and the solution was concentrated *in vacuo* to a small volume. Upon addition of water, the α-monobenzylamino acid XV precipitated (1.5 g. 80%), m.p. 215° dec.; recrystallized from ethanol, m.p. 219° dec.

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.5; H, 5.3; N, 8.3. Found: C, 67.4; H, 5.1; N, 8.3.

α-Dibenzylamino-γ-aminobutyric acid (XVI). (A) *By treating with hydrazine.* A solution of 4.3 g. of XIII and 1 ml. of 80% hydrazine hydrate in 100 ml. of ethanol was refluxed for 1 hr. The solvent was removed *in vacuo*, 50 ml. of 18% hydrochloric acid was added and the mixture heated on a water bath for 30 min. After filtration and evaporation of the filtrate, the hygroscopic residue was dissolved in a little water and some insoluble material was filtered off. Treatment with sodium bicarbonate solution precipitated the free γ-amino acid XVI (2.5 g. 83%), m.p. 192–193° dec.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.5; H, 7.4; N (Kjeldahl), 9.4; N (Van Slyke), 4.7. Found: C, 72.6; H, 7.7; N (Kjeldahl), 9.2; N (Van Slyke), 4.5.

(B) *By hydrolysis with hydrobromic acid.* The acid XIII (2.15 g.) in 50 ml. of 48% hydrobromic acid was refluxed for 4 hr., during which time it dissolved completely. The solution was cooled, filtered from phthalic acid, and washed with ether. Then the hydrobromic acid was removed *in vacuo*, to give the dihydrobromide of XVI (2 g., 77%) as a light brown very hygroscopic solid.

Anal. Calcd. for $C_{18}H_{24}N_2O_2Br_2$: C, 47.0; H, 5.2; N (Kjeldahl), 6.1; N (Van Slyke), 3.0; Br, 34.8. Found: C, 45.8; H, 5.2; N (Kjeldahl), 5.8; N (Van Slyke), 2.8; Br, 33.9.

Treatment of an aqueous solution of the dihydrobromide with aqueous sodium bicarbonate gave a quantitative yield of the free acid XVI, m.p. 192° dec.

Anal. Found: N (Kjeldahl), 9.1; N (Van Slyke), 4.5.

α-Dibenzylamino-γ-benzamidobutyric acid. Benzoylation of XVI was carried out in the usual way with benzoyl chloride in 2*N* sodium hydroxide solution. The benzoyl derivative was recrystallized from alcohol and melted at 120–121°.

Anal. Calcd. for $C_{25}H_{26}N_2O_3$: C, 74.6; H, 6.5; N, 7.0. Found: C, 74.4; H, 6.3; N, 6.8.

Ethyl α-dibenzylamino-γ-aminobutyrate dihydrochloride (XVII). The acid XVI (2.15 g.) was suspended in 50 ml. of absolute ethanol and dry hydrogen chloride was passed through the suspension. Dissolution occurred in a few minutes. The solution was refluxed for 5 hr. under continued hydrogen chloride introduction. The solvent was removed *in vacuo*, another portion of ethanol was added and evaporated. The ester XVII (4 g., 100%) remained as an hygroscopic solid, m.p. 100–105°.

Anal. Calcd. for $C_{20}H_{28}N_2O_2Cl_2$: N (Kjeldahl), 7.0; N (Van Slyke), 3.5; OC_2H_5, 11.3. Found: N (Kjeldahl), 6.7; N (Van Slyke), 3.3; OC_2H_5, 11.0.

3-Dibenzylaminopyrrolidin-2-one (XVIII). A solution of 2 g. of the ester XVII in 30 ml. of water was made alkaline with aqueous sodium bicarbonate and the free ester taken up in benzene. The aqueous layer was extracted with benzene and the combined benzene solution was washed with water, dried over sodium sulfate, and then refluxed for 1 hr. Some high melting material (the probable product of intermolecular reaction) which separated upon concentration was filtered off. Final removal of the benzene and crystallization of the oily residue from ethanol-water yielded the pyrrolidinone XVIII (1.1 g., 80%), m.p. 103–104°.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.1; H, 7.1; N, 10.0. Found: C, 77.1; H, 7.4; N, 9.8.

3-Aminopyrrolidin-2-one hydrochloride (XIX). The pyrrolidinone XVIII (0.7 g.) was dissolved in 50 ml. of ethanol containing a few drops of hydrochloric acid, 0.5 g. of 10% palladium chloride on charcoal was added and the mixture was hydrogenated for 12 hr. at 3 atm. The catalyst was filtered off and the solvent removed *in vacuo*. The semisolid residue was crystallized from ethanol-ether to give the pyrrolidinone XIX (0.3 g. 85%), m.p. 202°.

Anal. Calcd. for $C_4H_9N_2OCl$: N (Kjeldahl), 20.5; N (Van Slyke), 10.3. Found: N (Kjeldahl), 20.1; N (Van Slyke), 10.1.

Reaction between α-amino-γ-butyrolactone hydrobromide and potassium phthalimide. (A) *With one equivalent of potassium phthalimide.* α-Amino-γ-butyrolactone hydrobromide[10] (1.8 g., 0.01 mole) and potassium phthalimide (1.85 g., 0.01 mole) were dissolved in dimethylformamide (50 ml.) and the solution was refluxed for 7 hr. Precipitated potassium bromide was filtered off and the solvent was removed *in vacuo*. Water was added and the insoluble material then extracted with benzene. Phthalimide was removed by filtration and the benzene was evaporated. The residue was extracted again with benzene and α-phthalimido-γ-butyrolactone (0.35 g., 15%), m.p. 175°, precipitated upon concentration.

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.3; H, 3.9; N, 6.0. Found: C, 62.5; H, 3.7; N, 6.2.

(B) *With two equivalents of potassium phthalimide.* A solution of 3.65 g. (0.02 mole) of α-amino-γ-butyrolactone hydrobromide[10] and of 7.4 g. (0.04 mole) of potassium phthalimide in 80 ml. of dimethylformamide was refluxed for 8 hr. Potassium bromide was filtered off and the solvent was removed *in vacuo*. Water was added and phthalimide was removed by filtration. Acidification of the solution by hydrochloric acid caused the precipitation of α,γ-diphthalimidobutyric acid (0.75 g., 20%), m.p. 195°.

Anal. Calcd. for $C_{20}H_{14}O_6N_2$: C, 63.5; H, 3.7; N, 7.4. Found: C, 63.2; H, 3.7; N, 7.6.

Mixed melting points of α-phthalimido-γ-butyrolactone and α,γ-diphthalimidobutyric acid thus obtained with samples prepared from α-bromo-γ-butyrolactone and potas-

(10) M. Frankel, Y. Knobler, and T. Sheradsky, *J. Chem. Soc.*, 3642 (1959).

sium phthalimide[7b] showed no depression and the infrared spectra were identical.

Ethyl α-benzamido-γ-dibenzylaminobutyrate (XX). Ethyl α-benzamido-γ-iodobutyrate[6] (3.65 g., 0.01 mole) was dissolved in 200 ml. of ether and a solution of 4 g. (0.02 mole) of dibenzylamine in 50 ml. of ether was added with cooling. The mixture was left at room temperature for 4–5 days, and the precipitated dibenzylamine hydroiodide was filtered off. Further amounts of the salts were removed by repeated concentration of the solution, addition of ethyl acetate, and filtration. After final concentration, the semisolid residue was purified by washing with portions of water, then with petroleum ether until crystallization. The ester XX (2.8 g., 65%) melted at 80–82°.

Anal. Calcd. for $C_{27}H_{30}N_2O_3$: N, 6.5; OC_2H_5, 10.5. Found: N, 6.4; OC_2H_5, 10.8.

The same ester (XX) was obtained in an analogous reaction with ethyl α-benzamido-γ-bromobutyrate.[6]

α-Benzamido-γ-dibenzylaminobutyric acid (XXI). The ester XX (1.1 g., 0.025 mole) was dissolved in 50 ml. of methanol containing 25 ml. of 0.5% aqueous sodium hydroxide and the solution refluxed for 6 hr. The methanol was removed *in vacuo*, and the remaining cooled solution acidified with hydrochloric acid. The semisolid precipitate was recrystallized from benzene yielding 0.6 g. (60%) of the acid XXI, m.p. 147°.

Anal. Calcd. for $C_{25}H_{26}N_2O_3$: N, 7.0. Found: N, 6.8.

α-Amino-γ-dibenzylaminobutyric acid (XXII). The ester XX (1.1 g.) was refluxed in 50 ml. of 12% hydrochloric acid for 5 hr., during which time it dissolved completely. The solution was cooled, filtered from benzoic acid, washed with ether, and the solvent was evaporated *in vacuo*. The solid hygroscopic residue was dissolved in water, the solution made alkaline with aqueous sodium bicarbonate and the α-amino acid XXII (0.55 g., 73%), precipitated; recrystallized from water, m.p. 188–190° dec.

Anal. Calcd. for $C_{18}H_{22}N_2O_2$. C, 72.5; H, 7.4; N (Kjeldahl), 9.4; N (Van Slyke), 4.7. Found. C, 72.8; H, 7.6; N (Kjeldahl,) 9.2; N (Van Slyke), 4.6.

1-Benzyl-3-benzamidopyrrolidin-2-one (XXIII). The ester XX (2.15 g.) was dissolved in 100 ml. of ethanol, 3 g. of 5% palladium on charcoal was added and the mixture hydrogenated at 60–70° for 12 hr. (3 atm.). The catalyst was filtered off, the solvent evaporated and the oily residue crystallized from ethanol-water. Recrystallization from benzene–petroleum ether yielded 1.2 g. (80%) of the pyrrolidinone XXIII, m.p. 160–161°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$. C, 73.5; H, 6.1; N, 9.5. Found. C, 73.9; H, 6.4; N, 9.3.

α-Benzamido-γ-benzylamino-N-benzylbutyramide (XXIV). Ethyl α-benzamido-γ-iodobutyrate[6] (3.6 g., 0.01 mole) was dissolved in 50 ml. of benzene, benzylamine (10.7 g., 0.1 mole) was added and the solution was allowed to stand at room temperature for 1 week. Precipitated benzylamine hydroiodide was filtered off, and the filtrate evaporated *n vacuo*. The residue was recrystallized three times from ethanol-water to give the amide XXIV (2 g. 50%), m.p. 165°.

Anal. Calcd. for $C_{25}H_{27}N_3O_2$. C, 75.0; H, 6.7; N, 10.5. Found. C, 74.5; H, 6.8; N, 9.9.

The same amide (XXIV) was obtained in an analogous reaction with ethyl α-benzamido-γ-bromobutyrate.[6]

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Crystalline Complexes of Amino Acids with Alkyl Titanates

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Glycine dissolves on heating in solutions of a titanate ester in an alcohol. A crystalline complex containing the amino acid and titanium ester separates from the cold solution. On further standing, the solution deposits crystals of diketopiperazine. Dipeptides also dissolve in the titanate ester–alcohol solution, and yield a substituted diketopiperazine corresponding to the dipeptide employed.

In preliminary studies of the yellowing of wool by ultraviolet light[2] it was observed that pretreatment of wool with an alkyl titanate, for example, tetra-*n*-butyl titanate, protects wool from yellowing. It was proved that protection was not due to screening of ultraviolet light from wool by the titanate. Other observations suggested that the titanates may react with proteins, peptides, and amino acids. In this investigation, reaction of titanates with amino acids is confirmed by preparation of crystalline complexes of several alkyl titanates with glycine, alanine, and phenylalanine. These complexes were found to lose titanate on standing at room temperature, with conversion of the amino acid moiety to cyclic anhydrides.

Several amino acids were found to react with alkyl titanates in the presence of alcohol. Glycine is typical of these. It is insoluble in butyl titanate but becomes soluble when ethyl alcohol is present. From a solution prepared by warming a mixture of glycine, butyl titanate, and ethyl alcohol, present in the molar ratios 1:2:4 (a glycine concentration of about 8%), crystals deposit on cooling to room temperature. The crystals contain both titanium esters and glycine and appear usually as rhomb-shaped plates. Similar crystals can be obtained from less concentrated solutions of glycine and by precipitation with hexane. Recrystallization is inconvenient because of hydrolysis from atmospheric moisture, which proceeds in a manner similar to that of the alkyl titanates. The crystals of complex are birefringent and exhibit well defined X-ray diffraction patterns differing from those of the constituents. Analysis of the complex indicates an equimolar ratio of glycine and titan-

(1) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) H. P. Lundgren, *Proc. Intern. Wool Textile Research Conf., Melbourne*, 1955C, pp. 374–395.