[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Stereochemically Pure Peptide Derivatives by the Phthaloyl Method

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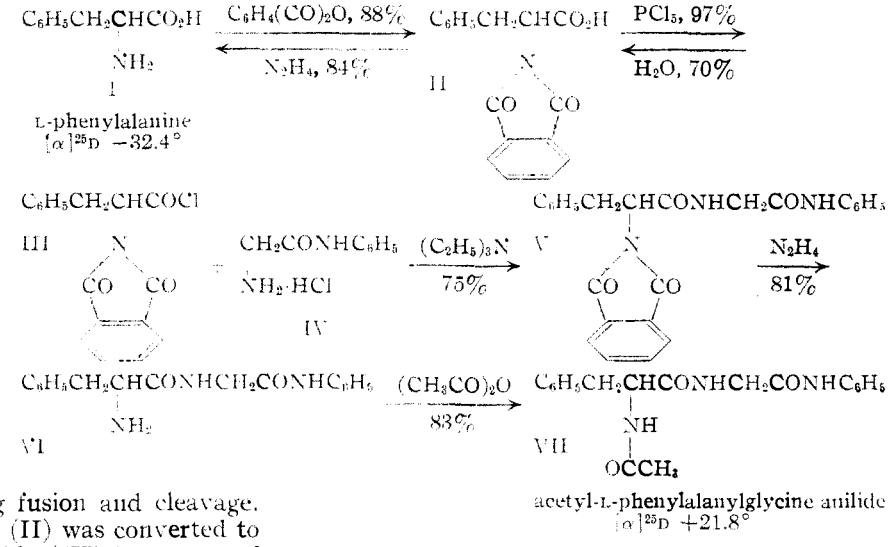
A careful investigation of the various steps in the phthaloyl synthesis of peptides has demonstrated that the method can be used to prepare optically pure peptide derivatives. Fusion of L-phenylalanine with phthalic anhydride afforded phthaloyl-L-phenylalanine, from which L-phenylalanine of unchanged optical rotation was recovered by hydrazine treatment. Phthaloyl-L-phenylalanine was converted to the acid chloride and regenerated by hydrolysis with no significant change in rotatory power. As further evidence for the retention of optical configuration during the synthesis, acetyl-L-phenylalanylglycine anilide and benzoyl-L-leucine anilide were prepared by the phthaloyl method and found to have the same optical rotation as when prepared by an enzymatic method. Glycylglycine and L-phenylalanylglycine were synthesized by an improved procedure involving acylation of the amino acid ester followed by dilute acid hydrolysis to the phthaloyl dipeptide in good yield.

In view of the importance of avoiding racemization during peptide synthesis we have investigated carefully each step in the phthaloyl[2-5] procedure and have determined that optical integrity is maintained under controlled conditions in certain typical examples. Preparations of phthaloyl derivatives of optically active amino acids by direct fusion procedures have been reported,[6-9] but experimental evidence was lacking that the products were optically pure.[10] When phthalic anhydride and D-phenylalanine were fused together at 180°, the resulting product was found to be optically inactive. However, active material was obtained when the reaction was carried out at 145–150°. By cleavage of phthaloyl-L-phenylalanine with alcoholic hydrazine hydrate, the L-phenylalanine so obtained exhibited the same optical rotation as the amino acid used as starting material, thus proving complete retention of configuration both during fusion and cleavage.



Phthaloyl-L-phenylalanine (II) was converted to the corresponding acid chloride (III) by means of phosphorus pentachloride. Hydrolysis of the acid chloride yielded phthaloyl-L-phenylalanine of unchanged rotation. Phthaloyl-L-phenylalanyl chloride was allowed to react with glycine anilide in an inert medium, and the phthaloyl-L-phenylalanylglycine anilide (V) thus obtained was subjected to cleavage with ethanolic hydrazine hydrate, producing L-phenylalanylglycine anilide (VI). The physical constants (including specific rotation) of the acetyl derivative (VII), prepared by acetylation with acetic anhydride, compared very favorably with those reported by Bergmann and Behrens,[11] who obtained the compound by an enzymatic process. In a similar manner, parallel syntheses in the D- and L-series were carried out for the purpose of comparison, the compounds so prepared being phthaloylphenylalanine, the corresponding acid chloride and anilide, and phenylalanine anilide hydrochloride. The relatively small discrepancy between the specific rotation values for the two series is presumably due to different degrees of purity of starting materials. Interest in derivatives of D-phenylalanine has been heightened by the presence of this unnatural form of the amino acid in gramicidin S.[12]

Phthaloyl-L-leucine was converted to the anilide *via* the acid chloride. Cleavage with hydrazine hydrate followed by benzoylation of the crude free base yielded benzoyl-L-leucine anilide, which was found to be identical in properties with the enzymatically prepared compound.[13]

It is preferable to employ excess hydrazine hy-

(1) Swift Amino Acid Fellow, 1950–1951. Presented at the American Chemical Society Meeting in New York, N. Y., September, 1951.

(2) J. C. Sheehan and V. S. Frank, THIS JOURNAL, **71**, 1856 (1949).

(3) D. A. A. Kidd and F. E. King, *Nature*, **162**, 776 (1948).

(4) F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, **1949**, 3315.

(5) O. H. Emerson, U. S. Patent 2,498,665 (1950); *C. A.*, **44**, 4926 (1950).

(6) L. Reese, *Ann.*, **242**, 1 (1887).

(7) M. Fling, F. N. Minard and S. W. Fox, THIS JOURNAL, **69**, 2466 (1947).

(8) J. H. Billman and W. F. Harting, *ibid.*, **70**, 1473 (1948).

(9) J. C. Sheehan and W. E. Bolhofer, *ibid.*, **72**, 2470 (1950).

(10) For example, it was claimed recently (ref. 4) that direct fusion of L-glutamic acid and phthalic anhydride produced racemic phthaloylglutamic acid; a lengthy indirect method was used to obtain the optically active form.

(11) M. Bergmann and O. K. Behrens, *J. Biol. Chem.*, **124**, 7 (1938).

(12) R. L. M. Synge, *Biochem. J.*, **39**, 363 (1945).

(13) M. Bergmann and H. Fraenkel-Conrat, *J. Biol. Chem.*, **119**, 707 (1937).

drate during the cleavage in some cases. As a result, to avoid possible difficulties in purification due to the presence of hydrazine hydrochloride, the free bases of the amino acid or peptide anilides were isolated in most cases and later converted to the hydrochlorides if so desired. The fact that L-leucine anilide, as well as phthaloyl-L-leucyl chloride, was obtained as an oil was not unexpected, in consideration of the melting points of L-leucine derivatives as compared with those of D- and L-phenylalanine and glycine.

In the conventional coupling of a phthaloyl-amino acid chloride with a second amino acid or peptide in buffered aqueous solution hydrolysis of the acyl halide is frequently a competing reaction. The use of low temperatures, very efficient stirring, and prolonged addition times can usually improve the yields of peptide derivative, but in many instances a modified acylation procedure has proven advantageous.

Phthalylglycyl chloride and glycine methyl ester hydrochloride interact in chloroform solution in the presence of triethylamine to produce phthaloylglycylglycine methyl ester in 90% yield. The acylation may also be conducted (in slightly lower yield) in dioxane–water with potassium bicarbonate as the acid acceptor. Although the phthaloyl group is very susceptible to alkaline hydrolysis it is surprisingly resistant to dilute acid hydrolysis. Treatment of the peptide ester with dilute hydrochloric acid afforded phthaloylglycylglycine in 95% yield, from which the free dipeptide was readily obtained (90%).

A similar series was carried out using phthaloyl-L-phenylalanyl chloride and glycine ethyl ester hydrochloride. Phthaloyl-L-phenylalanylglycine ethyl ester (59% yield) gave phthaloyl-L-phenylalanylglycine (83% yield), from which L-phenylalanylglycine was obtained in 99% yield by hydrazine cleavage. The crystalline L-phenylalanylglycine hydrate thus obtained has a much higher rotation than the previously recorded value.[14]

The acid hydrolysis of phthaloyl peptide esters was first carried out in this Laboratory by Mr. Harry Johnson.

We wish to express our appreciation to Swift and Co. for the support of a fellowship for one of us (D.W.C.).

Experimental[15]

Phthaloyl-L-phenylalanine (II).—The following procedure is a modification of the general method of Fling, Minard and Fox.[7] An intimate mixture of 9.90 g. (0.06 mole) of L-phenylalanine and 8.95 g. (0.06 mole) of finely ground phthalic anhydride was heated for 30 minutes with stirring in an oil-bath at 145–150°. After cooling, the solid material was dissolved in 40 ml. of hot methanol, the filtered solution was diluted with water (40 ml.), and the product was allowed to crystallize slowly. The yield was 15.53 g. (88%) of fine colorless needles; m.p. 183–185°, $[\alpha]_D$ −212° (0.0288 g. in 1.50 ml. of absolute ethanol). In numerous separate preparations, the observed rotation has been the same within 0.5%.

Anal. Calcd. for $C_{17}H_{13}O_4N$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.15; H, 4.78; N, 5.01.

(14) E. Fischer and W. Schoeller, *Ann.*, **357**, 18 (1907).

(15) All melting points are corrected unless otherwise stated. We are indebted to Dr. S. M. Nagy and associates for the microanalytical data.

Cleavage of Phthaloyl-L-phenylalanine.—A solution of 1.41 g. (0.0048 mole) of phthaloyl-L-phenylalanine in 15 ml. of ethanol containing 0.70 ml. of *M* alcoholic hydrazine hydrate (0.012 mole) was heated under reflux for 2 hours. The solvent was removed under reduced pressure, 10 ml. of water was added and the solution was acidified to *p*H 6 with acetic acid. After digestion for one hour on a steam-bath, the suspension was diluted with 30 ml. of water, cooled to room temperature and filtered. Concentration of the filtrate afforded 0.655 g. (84.4%) of L-phenylalanine, $[\alpha]^{26}_D$ −32.4° (0.0287 g. in 1.50 ml. of water). A sample of L-phenylalanine used as starting material had a specific rotation $[\alpha]^{25}_D$ −32.2°.

Phthaloyl-D-phenylalanine.—A mixture of D-phenylalanine (0.825 g., 0.005 mole) and phthalic anhydride (0.74 g., 0.005 mole) was heated in an oil-bath at 150° for 20 minutes. The crystalline product was isolated as described for the L-isomer; yield 1.19 g. (81%), m.p. 180–180.5° (uncor.). $[\alpha]_D$ +207° (0.0578 g. in 2.00 ml. of absolute ethanol).

Anal. Calcd. for $C_{17}H_{13}O_4N$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.89; H, 4.55; N, 4.78.

When the above reaction was carried out by heating for 30 minutes in an oil-bath at 170–180°, the resulting product was found to be optically inactive.

Phthaloyl-L-phenylalanyl Chloride (III).—A mixture of phthaloyl-L-phenylalanine (5.90 g., 0.02 mole) and phosphorus pentachloride (4.5 g., 0.022 mole) in 75 ml. of dry benzene was heated in a water-bath at 50–55° for one hour. The slightly yellowish solution was separated from the remaining phosphorus pentachloride by filtration. After concentrating to dryness under reduced pressure and flushing twice with dry toluene, the solid was crystallized from benzene–petroleum ether and dried under reduced pressure over paraffin shavings. The yield of fine, colorless needles was 6.09 g. (97%); m.p. 82–83°, $[\alpha]^{25.5}_D$ −197° (0.0338 g. in 1.50 ml. of benzene). A sample was recrystallized twice for analysis from benzene–petroleum ether; m.p. 83–84°.

Anal. Calcd. for $C_{17}H_{12}O_3NCl$: C, 65.08; H, 3.86; N, 4.47. Found: C, 65.30; H, 4.14; N, 4.70.

Hydrolysis of Phthaloyl-L-phenylalanyl Chloride.—To 0.3 g. (0.003 mole) of potassium bicarbonate in 5 ml. of water containing a trace of pyridine, there was added with swirling a solution of 0.313 g. (0.001 mole) of phthaloyl-L-phenylalanyl chloride in 5 ml. of dioxane. Acetone (5 ml.) was then added to effect complete solution and the mixture was allowed to stand for one hour at 25°. After acidification to *p*H 2 with 2 *N* hydrochloric acid, followed by concentration to dryness under reduced pressure, the residual solid was extracted with 10 ml. of methanol. The methanolic extract was concentrated to dryness and the material was allowed to crystallize from 4 ml. of 50% aqueous methanol. The yield was 0.205 g. (70%); m.p. 182–184°, $[\alpha]^{25}_D$ −213° (0.0364 g. in 1.20 ml. of absolute ethanol).

Phthaloyl-L-phenylalanylglycine Anilide (V).—Glycine anilide hydrochloride (0.36 g., 1.93 millimoles) was suspended in 25 ml. of methylene chloride containing 0.55 ml. (4.05 millimoles) of triethylamine. A short period of stirring brought about complete solution. To this cooled (0–5°) solution was added with stirring during 45 minutes 0.606 g. (1.92 millimoles) of phthaloyl-L-phenylalanyl chloride in 25 ml. of methylene chloride. After one hour, the solvent was removed under reduced pressure and the residual solid was crystallized from 20 ml. of ethanol. The product was obtained as colorless needles, 0.55 g., m.p. 203–208°. Concentration of the mother liquor, washing with dilute potassium bicarbonate solution, and crystallization from 5 ml. of ethanol yielded a second crop, 0.07 g., m.p. 211–212°. The combined materials represented a yield of 75%; $[\alpha]^{26}_D$ −196° (0.0374 g. in 2.00 ml. of glacial acetic acid).

Anal. Calcd. for $C_{25}H_{21}O_4N_3$: C, 70.25; H, 4.95; N, 9.83. Found: C, 69.91; H, 4.97; N, 10.04.

L-Phenylalanylglycine Anilide (VI).—A mixture of 0.427 g. (0.001 mole) of phthaloyl-L-phenylalanylglycine anilide in 30 ml. of ethanol containing 5 ml. of *M* alcoholic hydrazine hydrate (0.005 mole), was heated under reflux for one hour. The solvent was removed under reduced pressure and the residue was taken up in 20 ml. of water and acidified to *p*H 5 with glacial acetic acid. After cooling in an ice-bath and filtering, the filtrate was concentrated to dryness under reduced pressure. The oily material remaining was

dissolved in 8 ml. of hot water, filtered, and slowly basified to *p*H 8 with concentrated ammonium hydroxide. The yield of fine, colorless needles was 0.24 g. (81%); m.p. 169–170°, $[\alpha]^{26}D$ +67° (0.0344 g. in 1.50 ml. of glacial acetic acid). A portion was recrystallized from 35% ethanol; m.p. 172–173°.

Anal. Calcd. for $C_{17}H_{19}O_2N_3$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.98; H, 6.46; N, 14.09.

In a similar experiment employing only a twofold excess of hydrazine hydrate the yield was 77%; this was increased to 79% by an additional hour under reflux.

Acetyl-L-phenylalanylglycine Anilide (VII).—Acetic anhydride (1.0 ml.) was added with swirling to a suspension of 0.10 g. (0.337 millimole) of L-phenylalanylglycine anilide in 10 ml. of ice-water. After five minutes a second 1.0-ml. portion of acetic anhydride was added similarly. After standing at room temperature for one hour, 3 ml. of glacial acetic acid was added, solution was completed on a steam-cone, and the product was allowed to crystallize from the cooled solution. The yield of colorless needles was 0.095 g. (83%); m.p. 212.5–213°, reported[11] 208–209°; $[\alpha]$ +21.8° (0.0510 g. in 1.20 ml. of glacial acetic acid) (Bergmann and Behrens[11] reported +21.3°). A sample was twice recrystallized from acetic acid–water mixture for analysis.

Anal. Calcd. for $C_{19}H_{21}O_3N_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.27; H, 6.38; N, 12.70.

Phthaloyl-L-phenylalanine Anilide.—Phthaloyl-L-phenylalanine (1.00 g., 0.0034 mole) was converted to the corresponding acid chloride in benzene solution by reaction with phosphorus pentachloride (0.71 g., 0.0034 mole). The solvent was removed under reduced pressure and the reaction vessel and contents flushed twice with dry toluene.

The solid residue was taken up in 5 ml. of dioxane and the resulting solution was added during 15 minutes to a stirred, ice-cooled solution of 0.34 g. (0.0037 mole) of aniline and 0.85 g. (0.01 mole) of sodium bicarbonate in 20 ml. of water. After stirring for ten minutes, the suspension was acidified with 2 *N* hydrochloric acid and concentrated to dryness under reduced pressure. Crystallization from an acetic acid–water mixture yielded 0.95 g. (76%) of colorless needles; m.p. 203–205°, $[\alpha]^{28}D$ −104° (0.0303 g. in 1.50 ml. of chloroform). A portion was recrystallized from ethanol for analysis.

Anal. Calcd. for $C_{23}H_{18}O_3N_2$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.83; H, 5.12; N, 7.59.

Phthaloyl-D-phenylalanine Anilide.—To a cooled (5°) benzene solution of phthaloyl-D-phenylalanyl chloride (1.1 g., 0.004 mole, prepared as described for the L-isomer), 5 ml. of a 2 *M* solution of aniline (0.01 mole) in benzene was added. The product was removed by filtration and recrystallized from methanol, yielding 1.06 g. (78%); m.p. 207–208°, $[\alpha]^{25}D$ +105° (0.0187 g. in 3.00 ml. of chloroform).

Anal. Calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.88; H, 4.96; N, 7.78.

L-Phenylalanine Anilide.—To a solution of 0.74 g. (0.002 mole) of phthaloyl-L-phenylalanine anilide in 40 ml. of ethanol, there was added 6 ml. of *M* ethanolic hydrazine hydrate (0.006 mole). After heating one hour under reflux, the solvent was removed under reduced pressure. Water (20 ml.) was added and the suspension was acidified to *p*H 5 with glacial acetic acid. After cooling in an ice-bath, the phthalhydrazide was removed by filtration and washed with 30 ml. of water. The combined filtrates were concentrated to dryness under reduced pressure. The residue was dissolved in 15 ml. of 65% ethanol, basified with concentrated ammonium hydroxide to *p*H 8 and set aside to crystallize. The yield of colorless leaflets was 0.34 g.; m.p. 72–74°. A second crop of 0.21 g. (m.p. 72–74°) was obtained from 9 ml. of 65% ethanol; the combined products represent a yield of 72%. The specific rotation was determined in absolute ethanol; $[\alpha]^{26}D$ +19° (0.0374 g. in 2.00 ml.).

A portion was recrystallized from 65% ethanol for analysis.

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.72; N, 11.66. Found: C, 74.95; H, 6.65; N, 11.79.

The free base dissolved in ether was converted to the corresponding hydrochloride by saturation with hydrogen chloride; m.p. 218–221°, $[\alpha]^{26}D$ +111° (0.0277 g. in 2.00 ml. of absolute ethanol). An analytical sample, m.p. 223–224°, was prepared by recrystallization from absolute ethanol–*n*-butyl ether.

Anal. Calcd. for $C_{15}H_{17}ON_2Cl$: C, 65.09; H, 6.19; N, 10.12. Found: C, 64.64; H, 6.20; N, 9.79.

D-Phenylalanine Anilide Hydrochloride.—A mixture of phthaloyl-D-phenylalanine anilide (0.978 g., 0.0026 mole) and hydrazine hydrate (0.137 g., 0.0027 mole) in 70 ml. of ethanol was heated under reflux for one hour. The solution was evaporated to dryness under reduced pressure, and the solid residue was treated with 10 ml. of 2 *N* hydrochloric acid and 20 ml. of water. After heating for several minutes at 60°, the phthalhydrazide was removed by filtration at room temperature and the filtrate was evaporated to dryness. The crystalline solid, after washing with acetone, yielded 0.70 g. (96%), m.p. 203–206°, $[\alpha]^{25}D$ −94° (0.0404 g. in 2.00 ml. of ethanol).

Crystallization from absolute ethanol–*n*-butyl ether afforded an analytical sample; m.p. 226–227°, $[\alpha]^{25}D$ −105° (0.0266 g. in 2.00 ml. of absolute ethanol).

Anal. Calcd. for $C_{15}H_{17}ON_2Cl$: C, 65.09; H, 6.19; N, 10.12. Found: C, 64.93; H, 6.30; N, 10.26.

Phthaloyl-L-leucine.—A mixture of 2.50 g. (0.019 mole) of L-leucine and 2.81 g. (0.019 mole) of phthalic anhydride was heated for 25 min. in an oil-bath at 150°. After cooling, the glassy solid was heated under reflux with 15 ml. of dry ether. The solution was filtered and the filtrate was treated with 15 ml. of *n*-hexane (b.p. 60–70°). There was obtained two crops of colorless needles: 1.97 g., m.p. 118.5–119.5° (uncor.), and 1.31 g., m.p. 114–119° (uncor.) (total yield 66%). The specific rotation was determined in absolute ethanol; $[\alpha]^{26.5}D$ −24° (0.0435 g. in 1.50 ml.) (Fling, Minard and Fox[7] reported $[\alpha]^{17}D$ −22 ± 1.0°).

Phthaloyl-L-leucine Anilide.—To a solution of 2.61 g. (0.01 mole) of phthaloyl-L-leucine in 50 ml. of benzene there was added 2.29 g. (0.011 mole) of phosphorus pentachloride and the suspension heated for one hour in a water-bath at 55–60°. The solution was filtered, the solvent removed under reduced pressure, and the vessel flushed with two 25-ml. portions of dry toluene. The acid chloride was obtained as an uncrystallizable oil.

A solution of the acid chloride in 20 ml. of dry chloroform was added during 30 minutes to a stirred solution of 1.90 ml. (0.01 mole) of aniline and 2.78 ml. (0.02 mole) of triethylamine in 25 ml. of dry chloroform. After one hour, the solvent was removed under reduced pressure. The residual heavy oil was washed with 10-ml. portions of water, dilute hydrochloric acid and water. Crystallization from 17 ml. of 60% acetic acid (Norit) yielded 2.00 g. (60%) of colorless needles; m.p. 154.5–156°, $[\alpha]^{26}D$ −21° (0.0322 g. in 1.50 ml. of glacial acetic acid).

Recrystallization from benzene–petroleum ether produced an analytical sample.

Anal. Calcd. for $C_{20}H_{20}O_3N$: C, 71.39; H, 5.99; N, 8.33. Found: C, 71.30; H, 6.01; N, 8.32.

Benzoyl-L-leucine Anilide.—A solution of 1.68 g. (0.005 mole) of phthaloyl-L-leucine anilide in 40 ml. of ethanol containing 10 ml. of *M* ethanolic hydrazine hydrate (0.01 mole) was heated under reflux for one hour. The solvent was removed under reduced pressure and 20 ml. of water containing 1.06 g. (0.01 mole) of sodium carbonate was added. The sirupy oil which separated was removed by extracting with two 20-ml. portions of ether. The extract was dried over sodium carbonate prior to evaporation of the solvent.

The non-crystalline amino acid anilide was dissolved in 10 ml. of dry ether. To this ice-cooled solution was added 1.40 ml. (0.01 mole) of triethylamine, followed by 1.39 ml. (0.01 mole) of benzoyl chloride in 10 ml. of dry ether. After 15 minutes, the excess acid chloride was decomposed with water.

The insoluble residue and the concentrate from the ethereal solution were combined and crystallized from 20 ml. of absolute ethanol. Two crops of colorless platelets were obtained; 0.79 g., m.p. 214–215.5°, and 0.10 g., m.p. 212–215° (total yield 57%). The specific rotation was determined in glacial acetic acid; $[\alpha]^{25}D$ +8.9° (0.0661 g. in 1.50 ml.) (Bergmann and Fraenkel-Conrat[13] reported m.p. 213°; $[\alpha]^{23}D$ +9.2° and $[\alpha]^{22}D$ +9.0° on separate preparations.)

Phthaloylglycylglycine Methyl Ester.—To a mixture of 2.50 g. (0.02 mole) of glycine methyl ester hydrochloride and 4.48 g. (0.02 mole) of phthaloylglycyl chloride in 60 ml. an-

hydrous chloroform maintained at a temperature of −25° was added 4.04 g. (0.04 mole) of triethylamine in 40 ml. of chloroform over a period of 40 minutes with vigorous stirring. After completion of the addition, the temperature was maintained at −25° for 10 minutes (with continued stirring) and then slowly raised to 0° and held at that temperature for another 10 minutes. After a final holding period of 20 minutes at room temperature, the solvent was removed under reduced pressure, the residue was washed with cold water to remove the triethylamine hydrochloride, and the product was crystallized from water. The phthaloylglycylglycine methyl ester was obtained in the form of colorless needles, m.p. 203–204°, yield 5.10 g. (90%). The recorded[16] m.p. is 205°.

Phthaloylglycylglycine.[2]—Phthaloylglycylglycine methyl ester (2.76 g., 0.01 mole) was heated with 25 ml. of 2 *N* hydrochloric acid on a steam-cone for one hour; upon cooling, the crude phthaloylglycylglycine crystallized from the solution. The crude product was recrystallized from ethyl alcohol; 2.50 g. (95%) of colorless needles was obtained, m.p. 230–231°. Hydrazinolysis[2] afforded glycylglycine in 90% yield.

Phthaloyl-L-phenylalanylglycine Ethyl Ester.—To a solution of phthaloyl-L-phenylalanyl chloride (prepared from 1.48 g. (0.005 mole) of phthaloyl-L-phenylalanine and used without purification) in 20 ml. of dry methylene chloride there was added 0.70 g. (0.005 mole) of glycine ethyl ester hydrochloride. The solution was cooled in a bath at −45° and, with stirring, a solution of 2.10 ml. (0.015 mole) of triethylamine in 20 ml. of methylene chloride was added over a period of 20 minutes. The mixture was stirred further for 100 minutes as the bath came to room temperature, then stored overnight. After extraction with dilute aqueous bicarbonate solution, the organic layer was evaporated to dryness. Crystallization from 20 ml. of ethanol yielded two crops of colorless needles; 1.01 g., m.p. 160–161.5°, and 0.11 g., m.p. 154–157° (total yield 59% over-all), $[\alpha]^{29.5}D$ −146° (0.0320 g. in 3.00 ml. absolute ethanol).

A portion was twice crystallized from ethanol for analysis, m.p. 160.6–161.4°.

Anal. Calcd. for $C_{21}H_{20}O_5N_2$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.19; H, 5.30; N, 7.62.

(16) E. Drechsel, *J. prakt. Chem.*, [II] **27**, 418 (1883).

Phthaloyl-L-phenylalanylglycine.—To 4.6 g. (0.0121 mole) of phthaloyl-L-phenylalanylglycine ethyl ester was added a solution of 50 ml. of acetone, 35 ml. of water and 15 ml. of concentrated hydrochloric acid. After heating for 2 hours under reflux, the clear solution was evaporated to dryness under reduced pressure, and the residue was dissolved in 50 ml. of water containing 6 g. of potassium bicarbonate. The solution was filtered and acidified to congo red with concentrated hydrochloric acid. Ethanol (25 ml.) was added and solution was attained by heating. On cooling, very fine, colorless needles separated. The product was collected, and washed with 50 ml. of water; yield 3.55 g. (83%), m.p. 183–185°, $[\alpha]^{28}D$ −148.5° (0.0311 g. in 2.00 ml. of absolute ethanol).

Anal. Calcd. for $C_{19}H_{16}O_5N_2$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.71; H, 4.67; N, 7.94.

L-Phenylalanylglycine Monohydrate.—A solution of 3.52 g. (0.01 mole) of phthaloyl-L-phenylalanylglycine in 100 ml. of ethanol containing 3.0 ml. (0.06 mole) of hydrazine hydrate was heated under reflux for one hour. Water (50 ml.) was added to ensure continued solubility of the hydrazine salt of phthalhydrazide. The solvent was removed under reduced pressure. The residue was taken up in 50 ml. of water and the solution was acidified to *p*H 5 with glacial acetic acid. After one hour, the phthalhydrazide was removed by filtration and washed with 50 ml. of water. The combined filtrates were concentrated to dryness under reduced pressure. To the resulting sirup acetone (15 ml.) was added dropwise with swirling. After a short period a further quantity of acetone (35 ml.) was added to the mass of fine, colorless crystals. The product was collected by suction filtration, washed with 20 ml. of acetone, and dried for two hours in a vacuum desiccator at 70°; weight 2.37 g. (99%, calculated as a monohydrate), m.p. 259.5–260.5° with charring, $[\alpha]^{28}D$ +42° (0.0307 g. in 1.50 ml. of acetic acid, $[\alpha]^{28}D$ +84.4°)(0.0299 g. in 1.50 ml. of water). The reported[14] value is $[\alpha]^{20}D$ +54.2° in water.

A portion was recrystallized by the slow addition of acetone to the aqueous solution, m.p. 259.2–260.4°.

Anal. Calcd. for $C_{11}H_{16}O_4N_2$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.13; H, 6.58; N, 11.39.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Teloidinone and 6-Hydroxytropinone

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2,5-Dimethoxy-2,5-dihydrofuran (V) was converted by treatment with potassium permanganate to *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran (VI), the cyclic acetal of *meso*-tartaraldehyde. Interaction of V with hypochlorous acid gave 3-chloro-4-hydroxy-2,5-dimethoxytetrahydrofuran (IX) which was converted by means of potassium hydroxide to 3,4-epoxy-2,5-dimethoxytetrahydrofuran (X), the cyclic acetal of epoxysuccinaldehyde. Reduction of the epoxyacetal X with lithium aluminum hydride gave 3-hydroxy-2,5-dimethoxytetrahydrofuran (XI), the cyclic acetal of malicaldehyde. *meso*-6,7-Dihydroxytropinone (teloidinone) and 6-hydroxytropinone were prepared by condensation of *meso*-tartaraldehyde and malicaldehyde (obtained by hydrolysis of the corresponding tetrahydrofuran derivatives VI and XI) with methylamine and acetonedicarboxylic acid.

The synthesis of tropinone by the effective method of Robinson,[2] as modified by Schöpf and Lehmann,[3] involves the condensation of a γ-dialdehyde with acetonedicarboxylic acid and methylamine hydrochloride to form the tropane skeleton. Because of its remarkable simplicity, this type of reaction has been utilized in a preponderance of the recorded attempts to synthesize various tropane alkaloids. From a practical point of view the major difficulty to be overcome in accomplishing the synthesis of the more complex tropane alkaloids lies with the prerequisite preparation of the appropriate dialdehyde.

Among the tropane alkaloids,[4] scopolamine (I), valeroidine (II) and meteoloidine (III) bear structural resemblance to one another in that they possess oxygen-bearing substituents on the pyrrolidine ring of the bicyclic tropane system, in addition to the acylated 3-hydroxyl group commonly found in this family. Because of these substituents the preparation of the substituted tropinones from which these naturally occurring bases are derived

(1) F. J. Moore Fellow, 1950–1951.

(2) R. Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

(3) C. Schöpf and G. Lehmann, *Ann.*, **518**, 1 (1935).

(4) For an excellent review of the chemistry of the tropane alkaloids, see: R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 271.