hydride. Crystallization from aqueous alcohol at room temperature gave 2.5 g. of *meso*-9,10-octadecanediol, m.p. 129.8–131.0° (reported[5] 127°,[3] 127.5–128°); on admixture it did not change the melting point of *meso*-9,10-octadecanediol reference compound. The infrared spectrum of this compound measured on a KBr disk was also superimposable upon that of the reference compound.

After the mother liquor had stood at 0°, a second crop of 5.4 g. of *meso*-9,10-octadecanediol was obtained of m.p. 129.2–131.0°. The total yield of the *meso*-diol was 7.9 g. (42%).

The filtrate from crop 2 on standing at −20° afforded 10.5 g. (56% yield) of *dl*-9,10-octadecanediol, m.p. 76.8–78.0° (reported[13] >70°,[3] 76–77°); on admixture with *dl*-9,10-octadecanediol reference compound the melting point was unchanged. The infrared spectra of this substance measured both on a KBr disk and on a CS_2 solution were superimposable on those of the reference compound.

meso-9,10-Octadecanediol, reference compound. Following the procedure of Woodward *et al*,[6] 1.2 g. of *cis*-9-octadecene[7] was *cis*-hydroxylated by treatment in ether solution for 48 hr. with hydrogen peroxide and a little osmium tetroxide. Crystallization at −20° yielded 0.541 g. of the impure product and, after recrystallization from 95% ethyl alcohol and from ligroin at −20°, 0.185 g. of *meso*-9,10-octadecanediol, m.p. 127.4–129.0° (reported[5] 127°,[3] 127.5–128°).

dl-9,10-Octadecanediol, reference compound. Following the procedure of Swern,[8] 1.07 g. of *cis*-9,10-epoxyoctadecane,[7] heated 1 hr. at 100° in 25 ml. of anhydrous formic acid, yielded after saponification and two recrystallizations at −20° from ethanol 0.35 g. of *dl*-9,10-octadecanediol, m.p. 75.8–77.6° (reported[13] >70°,[3] 76–77°).

Solubility determinations. Twenty-five ml. portions of saturated solutions of the 9,10-octadecanediols, dihydroxystearic acids, and dichlorooctadecanols were freed of solvent by evaporation under an air jet and heating for 1.5 hr. at 50° and 1 mm. pressure. The weights of the residues permitted calculation of the solubilities reported in Table I.

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Preparation of *O*-Phenyl-DL-homoserine and of DL-Homoserine from α-Phthalimido-γ-butyrolactone

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In previous studies[1,2,3] it was shown, that α-amino-γ-butyrolactone, in its free and masked forms, can be converted into the corresponding γ-substituted α-amino acids.

As polymerization of *O*-phenyl-DL-homoserine resulted in high molecular, fiber-forming polypeptides,[4] it was of interest to obtain the starting material by a simpler method than hitherto[5] known. The easy availability of α-phthalimido-γ-butyrolactone[3] renders this compound a useful intermediate in the synthesis of *O*-phenyl-DL-homoserine. As direct opening of α-phthalimido-γ-butyrolactone proved successful, the following procedure has been worked out: by reaction of α-phthalimido-γ-butyrolactone with sodium phenoxide α-phthalimido-γ-phenoxybutyric acid (I) was prepared. Removal of the phthaloyl group was carried out by hydrolysis with 18% hydrochloric acid and α-amino-γ-phenoxybutyric acid hydrochloride isolated, from which the free *O*-phenyl-DL-homoserine (II) was obtained by treatment with triethylamine. Overall yield based on α-phthalimido-γ-butyrolactone was 42–45%, on γ-butyrolactone 27–29%.

Previously[2] we have described the synthesis of α-amino-γ-iodobutyric acid hydroiodide from α-bromo-γ-butyrolactone and aqueous ammonia. Some difficulties are encountered in the removal of the admixed salts from the intermediate α-amino-γ-butyrolactone hydroiodide. These are avoided in the present synthesis by employing α-phthalimido-γ-butyrolactone, which reacts with 55% hydroiodic acid, yielding α-amino-γ-iodobutyric acid hydroiodide (III) without any opportunity of its contamination by inorganic salts. From α-benzamido-γ-butyrolactone,[1] the hydroiodide (III) was prepared in a similar manner.

Hydrolysis of α-phthalimido-γ-butyrolactone with 24% hydrobromic acid gave α-amino-γ-butyrolactone hydrobromide (IV), as expected,[2] without opening of the lactone ring.

The convenient preparation of α-phthalimido-γ-butyrolactone and its ready hydrolysis by sulphuric acid renders this compound also an advantageous intermediate for a smooth synthesis of DL-homoserine. Overall yield was 50–55% of recrystallized homoserine based on γ-butyrolactone.

EXPERIMENTAL

α-Phthalimido-γ-phenoxybutyric acid (I). Clean sodium (4.6 g., 0.2 mole) was cautiously added in portions, and with occasional shaking, to an excess of molten phenol, placed in a flask fitted with an air condenser and a drying tube containing calcium chloride, the rate of addition being sufficient to keep the phenol molten. The mixture was finally heated until the sodium was dissolved, then gently refluxed for 5 min., and allowed to cool. After addition of α-phthalimido-γ-butyrolactone[3] (46 g., 0.2 mole), heating to reflux for ½ hr., and subsequent cooling, the solidified mixture was triturated with 250–300 ml. of ether, and the crude sodium

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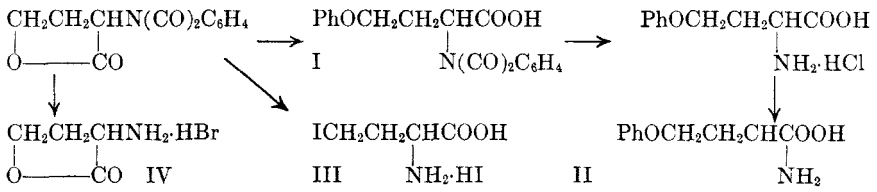

salt filtered off as a dark hygroscopic mass, which was dissolved in water and purified by repeated treatments with Norit and filtrations. 18% hydrochloric acid was introduced dropwise under cooling and stirring within two hours into the filtrate, to acidic reaction. The reaction mixture containing an oily, heavy precipitate was kept in the refrigerator for 1 day. After decantation, the semisolid acid (I) was purified by solution in boiling acetic acid, addition of a small amount of water, and treatment with Norit. To the cooled, vigorously stirred filtrate water was added slowly, causing precipitation of the acid (I). The dried crystals weighed 40 g. (62%), m.p. 122°. On recrystallisation from benzene–petroleum ether, m.p. 124°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 66.5; H, 4.6; N, 4.3. Found: C, 66.6; H, 4.7; N, 4.3.

*O-Phenyl-*DL*-homoserine hydrochloride (α-amino-γ-phenoxybutyric acid hydrochloride).* 300 ml. of 18% hydrochloric acid was added to a solution of α-phthalimido-γ-phenoxybutyric acid (I) (13 g., 0.04 mole) in 10 ml. of acetic acid, and the mixture refluxed for 3 hr. After concentration and cooling, phthalic acid was filtered off and the solution purified by treating with Norit. The crude hydrochloride, obtained on evaporation in vacuo, was dissolved in a small amount of water, freed from the rest of the phthalic acid by filtration and the solution concentrated again in vacuo. The dry residue was dissolved in water-ethanol, precipitated with ether, and dried in vacuo (P_2O_5). The almost colourless crystals (7 g., 76%) melted at 214°.

Anal. Calcd. for $C_{10}H_{14}NO_3Cl$: C, 51.7; H, 6.1; N, 6.1; Cl, 15.3. Found: C, 51.5; H, 6.3; N, 6.2; Cl, 15.5.

*O-Phenyl-*DL*-homoserine (α-amino-γ-phenoxybutyric acid) (II).* Triethylamine was added dropwise to a solution of O-phenyl-DL-homoserine hydrochloride (1 g., 0.0043 mole) in 10 ml. of 50% aqueous ethanol until *p*H 7–8. The precipitated free acid (II) was filtered off and washed with portions of ethanol. After drying in vacuo (P_2O_5), the crystals (0.8 g., 95%) melted at 230°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2. Found: C, 61.3; H, 6.9; N, 7.2.

*N-Benzoyl-O-phenyl-*DL*-homoserine.* The *N*-benzoyl derivative was prepared in the usual way by benzoylation of the acid hydrochloride in 3*N* sodium hydroxide. After recrystallization from ethyl acetate–petroleum ether it melted at 145°.

Anal. Calcd. for $C_{17}H_{17}NO_4$: N, 4.7. Found: N, 4.6.

α-Amino-γ-iodobutyric acid hydroiodide (III). (a) From α-phthalimido-γ-butyrolactone: Powdered α-phthalimido-γ-butyrolactone[3] (23 g., 0.1 mole) was refluxed with 110 ml. of 55% hydroiodic acid during 2 hr. 500 ml. of toluene was added and refluxing continued for 3 hr. The aqueous hydroiodic acid was removed from the stirred mixture by azeotropic distillation. After cooling, the toluenic layer, containing the phthalic acid, was removed by decantation and the residue of crude, dark hydroiodide (III) was washed with ether. White yellow crystals (35 g., 98%) were obtained by extraction with dry ether in a Soxhlet apparatus, m.p. 195–198°.

Anal. Calcd. for $C_4H_9NO_2I_2$: N, 3.9; I, 71.1; Found: N, 4.0; I, 71.2. Since hydrolysis and γ-iodination of α-phthalimido-γ-butyrolactone proceeds quantitatively, the yield of the hydroiodide (III) equalled that of α-phthalimido-γ-butyrolactone (75–80%), prepared from α-bromo-γ-butyrolactone. Uncrystallized lactone could be used giving similar yield; overall yield based on γ-butyrolactone *via* α-bromo-γ-butyrolactone and α-phthalimido-γ-butyrolactone was 64–72%. (*b*) *From α-benzamido-γ-butyrolactone:* α-benzamido-γ-butyrolactone[1] (20.5 g., 0.1 mole) was refluxed with 110 ml. of 55% hydroiodic acid. The mixture was worked up as described above, yielding 95% of the hydroiodide (III); based on γ-butyrolactone via α-bromo-γ-butyrolactone and α-benzamido-γ-butyrolactone the yield was 48–51%.

Anal. Found: N, 4.0; I, 71.3.

α-Amino-γ-butyrolactone hydrobromide (IV). Powdered α-phthalimido-γ-butyrolactone (2.3 g., 0.01 mole) was refluxed with 50 ml. of 24% hydrobromic acid for 3 hr. The solution was cooled and the phthalic acid which separated out was filtered off. The mother liquor was evaporated in vacuo; the dry residue was dissolved in 10 ml. of water and freed from traces of phthalic acid by filtration. Water was distilled off and the product washed with ethanol-ether. After drying in vacuo (P_2O_5), the crystals (1.7 g., 93%) melted at 225°.

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.7; Br, 43.9. Found: N, 7.6; Br, 44.1.

DL*-Homoserine (α-amino-γ-hydroxybutyric acid).* Powdered α-phthalimido-γ-butyrolactone (9.2 g., 0.04 mole) was dispersed in 50 ml. of 50% sulphuric acid, and the mixture refluxed for 3 hr. to dissolution of the lactone. The solution was left to cool to room temperature, then in ice-water. The phthalic acid was filtered off and the solution, containing the α-amino-γ-butyrolactone sulphate, was diluted, treated with Norit and filtered. 45 g. of calcium hydroxide was added and the mixture stirred on a steam bath for 1 hr. Calcium sulphate was filtered off and the solution, containing the calcium salt of DL-homoserine, concentrated to 20–25 ml. Diluted sulphuric acid was dropped in until neutral, and precipitated calcium sulphate filtered off. The solution was purified with Norit, the filtrate concentrated in vacuo to 10–15 ml., 20 ml. of ethanol, followed by 100 ml. of acetone were added and the mixture was kept in the freezer until complete separation of crude DL-homoserine (4.3 g., 91%). When recrystallized from a small amount of water and an excess of 1:5 ethanol-acetone, the crystals (3.8 g., 80%) melted at 182–183°.

Anal. Calcd. for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.8. Found: C, 40.1; H, 7.6; N, 11.7.

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The Synthesis of Nitroestradiols[1,2]

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As part of an investigation concerned with the relationship of molecular structure to estrogenic activity, new compounds are being synthesized by introducing substituents at various positions

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