## 245. *New Syntheses of* dl-*Thiolhistidine.*

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Any new method for the preparation of thiolhistidine, which has already been synthesised by Harington and his collaborators (J., 1930, 2586; *Biochem. J.*, 1933, **27**, 338), may have a possible significance for the ultimate synthesis of ergothioneine, to which it bears a close constitutional relationship. Two new methods for the preparation of *dl*-thiolhistidine are now recorded.

*Ethyl αδ-diphthalimido-γ-keto-α-carbethoxyvalerate* (II) obtained in poor yield by condensing *phthalo-ω-iodoacetonylimide* (I, X = I) with ethyl sodiophthalimidomalonate, on hydrolysis with concentrated hydrobromic acid gave the *dihydrobromide* of αδ-diamino-γ-ketovaleric acid, which when condensed with sodium thiocyanate formed *dl*-thiolhistidine:

$$\underset{\text{(I.)}}{R\cdot CH_2\cdot CO\cdot CH_2X} + CRNa(CO_2Et)_2 \longrightarrow \underset{\text{(II.)}}{R\cdot CH_2\cdot CO\cdot CH_2\cdot CR(CO_2Et)_2} \longrightarrow$$

$$NH_2\cdot CH_2\cdot CO\cdot CH_2\cdot CH(NH_2)\cdot CO_2H,2HBr \longrightarrow \textit{dl}\text{-thiolhistidine}$$

$$(R = C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N;\ X = I, Br, \text{or } Cl.)$$

The same ester (II) was obtained, but in even smaller yield, when the corresponding chloro- or bromo-derivative (I, X = Br or Cl) was substituted for the iodo-compound.

In the second method, *δ-phthalimido-α-carbethoxy-γ-valerolactone* (III), obtained from phthalo-βγ-epoxypropylimide and ethyl sodiomalonate, was brominated, and the product hydrolysed and decarboxylated, giving the *bromo-lactone* (IV): this condensed with potassiophthalimide to furnish *αδ-diphthalimido-γ-valerolactone*, which on hydrolysis with potassium hydroxide gave αδ-bis-(*o*-carboxybenzamido)-γ-hydroxyvaleric acid (V). The corresponding keto-acid obtained by oxidation of the hydroxy-acid (V) with dilute potassium permanganate solution was hydrolysed with hydrochloric acid, and the resulting

dihydrochloride (VI) of αδ-diamino-γ-ketovaleric acid condensed with sodium thiocyanate, furnishing *dl*-thiolhistidine.

$$\underset{\text{(III.)}}{R\cdot CH_2\cdot \underset{\displaystyle O\text{———}CO}{CH}\cdot CH_2\cdot CH\cdot CO_2Et} \longrightarrow \underset{\text{(IV.)}}{R\cdot CH_2\cdot \underset{\displaystyle O\text{———}CO}{CH}\cdot CH_2\cdot CHBr} \longrightarrow$$

$$\text{(V.)}\quad T\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CHT\cdot CO_2H \longrightarrow NH_2\cdot CH_2\cdot CO\cdot CH_2\cdot CH(NH_2)\cdot CO_2H,2HCl \quad \text{(VI.)}$$

$$(R = C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle N;\ T = CO_2H\cdot C_6H_4\cdot CO\cdot NH.)$$

αδ-Diphthalimido-γ-valerolactone on hydrolysis with concentrated hydrochloric acid gave an almost quantitative yield of αδ-diamino-γ-valerolactone dihydrochloride, which has been obtained by other workers only in small yields (Traube, Johow, and Tepohl, *Ber.*, 1923, **56**, 1861; Tomita, *Z. physiol. Chem.*, 1926, **158**, 58; Hammerstein, *Centr.*, 1916, I, 1811).

## Experimental.

*Phthalo-ω-iodoacetonylimide* (I, X = I).—A mixture of phthalo-ω-chloroacetonylimide (23·5 g.) (Gabriel, *Ber.*, 1917, **50**, 819), sodium iodide (17 g.), and acetone (100 c.c.) was refluxed for 4 hours. *Phthalo-ω-iodoacetonylimide*, which separated on cooling, was washed with water, dilute sulphurous acid, and alcohol and dried; a further quantity was obtained by pouring the mother-liquor into cold water. It crystallised from acetone or alcohol in white needles, m. p. 184°, sparingly soluble in most organic solvents (yield, 80%) (Found : C, 40·0; H, 2·4; I, 38·4. $C_{11}H_8O_3NI$ requires C, 40·1; H, 2·4; I, 38·6%).

*Ethyl αδ-Diphthalimido-γ-keto-α-carbethoxyvalerate* (II).—Phthalo-ω-iodoacetonylimide (33 g.) was added to a suspension of ethyl sodiophthalimidomalonate in benzene (prepared from ethyl phthalimidomalonate, 35 g., and sodium, 2·3 g.; Sörensen, *Z. physiol. Chem.*, 1905, **44**, 454) containing a few c.c. of alcohol. The mixture was warmed on a water-bath for 4 hours, cooled, and poured into water; the solid that separated was filtered off and repeatedly digested with small quantities of hot alcohol. From the combined alcoholic filtrates, on cooling, long needles of the *ester* (II) separated, m. p. 184° after recrystallisation from alcohol (yield, 3 g.; 7%) (Found : C, 61·4; H, 4·0; N, 5·7. $C_{26}H_{22}O_9N_2$ requires C, 61·7; H, 4·4; N, 5·5%).

*αδ-Diamino-γ-ketovaleric Acid Dihydrobromide.*—The ester (II) was refluxed with hydrobromic acid (5 parts) for 12 hours, the solution cooled, the phthalic acid removed, the filtrate extracted several times with ether to remove traces of phthalic acid, and the aqueous solution evaporated under reduced pressure. The residue was extracted with small quantities of methyl alcohol; the *dihydrobromide* of αδ-diamino-γ-ketovaleric acid, which remained as a white powder, m. p. 231°, was recrystallised from alcohol (Found : Br, 51·8. $C_5H_{10}O_3N_2,2HBr$ requires Br, 51·9%).

dl-*Thiolhistidine.*—A solution of the above dihydrobromide (3·1 g.) in water (10 c.c.) was warmed on a water-bath, and sodium thiocyanate (1 g.) added during 1 hour. The mixture was heated for another hour, cooled, and a concentrated solution of sodium acetate added. The precipitated *dl*-thiolhistidine was washed and dried; it did not melt even at 320° (Found : C, 38·3; H, 4·7; N, 22·5. Calc. for $C_6H_9O_2N_3S$ : C, 38·5; H, 4·8; N, 22·4%). On oxidation with ferric sulphate it gave *dl*-histidine (cf. Pyman, J., 1911, **99**, 681).

*δ-Phthalimido-α-carbethoxy-γ-valerolactone* (III).—Ethyl malonate (80 g.) and phthalo-βγ-epoxypropylimide (105 g.) were added to a solution of sodium ethoxide (sodium, 11·5 g.; alcohol, 140 c.c.); the mixture was cautiously warmed till the vigorous reaction was over and then boiled for 2½ hours. The alcohol was removed under reduced pressure, and the residue poured into dilute hydrochloric acid and ice. The viscous mass that separated, after solidifying, was washed, dried, and recrystallised from dilute alcohol (norit), giving colourless crystals, m. p. 114° (yield, 60%) (Found : C, 60·4; H, 4·5; N, 4·5. $C_{16}H_{15}O_6N$ requires C, 60·6; H, 4·7; N, 4·4%).

*α-Bromo-δ-phthalimido-α-carbethoxy-γ-valerolactone.*—A solution of the above ester (31·7 g.) in chloroform (150 c.c.) was mixed with bromine (16·6 g.) and exposed to sunlight (5—6 hours in bright sunlight; 1—3 days in dull light). The solution was repeatedly washed with water, decolourised with sulphurous acid, dried, and evaporated. The viscous residue solidified in contact with water and had m. p. 122° after crystallisation from alcohol. For analysis it was dissolved in the minimum quantity of ether, precipitated with an excess of light petroleum,

and dried in a vacuum desiccator for several days (yield, theoretical) (Found: Br, 19·8. $C_{16}H_{14}O_6NBr$ requires Br, 20·2%).

*α-Bromo-δ-phthalimido-α-carboxy-γ-valerolactone.*—The above bromo-ester (10 g.), when shaken with hydrobromic acid (*d* 1·78; 50 c.c.) in a strong glass-stoppered bottle for 48 hours, gradually dissolved and granular crystals of the corresponding lactonic acid separated. The mixture was warmed at 50—60° in an open flask for 1 hour to remove ethyl bromide and the excess of hydrobromic acid; it was then cooled, mixed with an equal volume of cold water, and cooled with ice; *α-bromo-δ-phthalimido-α-carboxy-γ-valerolactone* separated in almost colourless crystals (7·2 g.), m. p. 132° (Found: C, 45·4; H, 2·7; N, 3·9; Br, 21·5. $C_{14}H_{10}O_6NBr$ requires C, 45·7; H, 2·7; N, 3·8; Br, 21·7%).

*α-Bromo-δ-phthalimido-γ-valerolactone* (IV).—The above lactonic acid (50 g.) was heated at 140—150° under reduced pressure until the evolution of carbon dioxide ceased. The oily residue separated from alcohol (charcoal) in colourless crystals, m. p. 140°, which were recrystallised from alcohol (yield, 70%) (Found: C, 48·0; H, 3·1; N, 4·4; Br, 24·6. $C_{13}H_{10}O_4NBr$ requires C, 48·2; H, 3·1; N, 4·3; Br, 24·7%).

*αδ-Diphthalimido-γ-valerolactone.*—A solution of the bromo-lactone (32·4 g.) in xylene (30 c.c.) was heated at 110°, and potassiophthalimide (18·5 g.) added during 1 hour. After a further 3 hours' heating, the xylene was steam-distilled, and the residual solid washed with water and crystallised from acetic acid; m. p. 260° (yield, theoretical) (Found: C, 64·4; H, 3·3; N, 7·0. $C_{21}H_{14}O_6N_2$ requires C, 64·6; H, 3·6; N, 7·2%).

*αδ-Diaminovalerolactone Dihydrochloride.*—The preceding lactone (3 g.) was refluxed with hydrochloric acid (40 c.c.) for 24 hours, the mixture cooled, and the phthalic acid removed; the filtrate was concentrated somewhat, shaken with ether to remove traces of phthalic acid, and evaporated to dryness. The residual αδ-diamino-γ-valerolactone dihydrochloride, crystallised from a little water or, better, from dilute alcohol, had m. p. 240° (Found: C, 27·6; H, 6·0; N, 12·6; Cl, 32·1. Calc. for $C_5H_{10}O_2N_2,2HCl,H_2O$: C, 27·7; H, 6·4; N, 12·9; Cl, 32·1%). With potassium cyanate it gave the diureide, m. p. 206°, described by Traube, Johow, and Tepohl (*loc. cit.*).

The dihydrochloride was also obtained by heating the bromo-lactone (IV) with 25% aqueous ammonia (5 parts), evaporating the liquid under reduced pressure, and hydrolysing the residual solid with hydrochloric acid; the solution was cooled, filtered, and evaporated to dryness, and the residue triturated with small quantities of cold water and recrystallised from dilute alcohol.

*αδ-Diamino-γ-ketovaleric Acid Dihydrochloride* (VI).—αδ-Diphthalimidovalerolactone (20 g.) was warmed with aqueous potassium hydroxide (10 g. in 30 c.c.), the solution cooled, 1% potassium permanganate solution (50 c.c.) added, and the mixture left in ice for a few hours; the manganese dioxide was then removed, and the filtrate strongly acidified. The oily precipitate obtained slowly solidified to a hard resin. This, having been washed, dried, and powdered, was heated at 180° for ½ hour, cooled, and treated with dilute sodium carbonate solution. The residue of αδ-diphthalimidovalerolactone was recrystallised from acetic acid and identified by mixed m. p. The alkaline filtrate on acidification gave a bulky amorphous precipitate. This was washed and then refluxed with hydrochloric acid (20%; 100 c.c.) for 5 hours. The phthalic acid which separated on cooling was removed, and the filtrate extracted with ether and evaporated to dryness at 40—60° under reduced pressure. The mixture of the hydrochlorides of aminoacetic acid and αδ-diamino-γ-ketovaleric acid thus obtained was thrice triturated with concentrated hydrochloric acid (5 c.c.) and the combined filtrates were evaporated under reduced pressure. The residue, consisting mainly of αδ-diamino-γ-ketovaleric acid dihydrochloride, was a syrupy liquid which when left over caustic potash in a vacuum desiccator gave the monohydrochloride described by Harington and Overloff (*Biochem. J.*, **1933**, **27**, 338). This was dissolved in the minimum quantity of alcohol and reprecipitated with excess of ether. The hydrochloride was converted into *dl*-thiolhistidine by condensing it with sodium thiocyanate.

The author thanks Professor J. F. Thorpe for his kindly interest in this work.

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[*Received, February 25th,* 1937.]