CXVI.—*Synthesis of an Isomeride of Thyroxine, and of Related Compounds.*

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THE elucidation of the constitution of thyroxine (Harington, *Biochem. J.*, 1926, **20**, 293; Harington and Barger, *ibid.*, 1927, **21**, 169) affords an opportunity for the investigation of the effects of various groups on the physiological action of this compound. It has been found that thyronine (deiodothyroxine; compare

Harington, *Biochem. J.*, 1928, **22**, 1430, footnote) is devoid of physiological activity, whereas 3 : 5-di-iodothyronine exhibits the characteristic action of thyroxine but in a much lower degree (Gaddum, *J. Physiol.*, 1927, **64**, 246); the same applies to 3 : 5 : 3′ : 5′-tetrabromothyronine (Gaddum, unpublished observation). Attempts to prepare tetraiodo-derivatives of thyronine other than thyroxine itself having failed, attention was directed to the synthesis of ββ-*di*(3 : 5-*di-iodo*-4-*hydroxyphenyl*)-α-*aminopropionic acid*, $(OH{\cdot}C_6H_2I_2)_2CH{\cdot}CH(NH_2){\cdot}CO_2H$, a substance isomeric with thyroxine and retaining the characteristic *o*-di-iodophenolic group of the latter, but differing from it in that the benzene rings are linked through carbon instead of through oxygen.

Di(4-methoxyphenyl)methyl chloride was brought into reaction with ethyl potassiophthalimidomalonate, and the product hydrolysed with potassium hydroxide; the resulting acid, when heated, passed into the *anhydride* of α-*o*-carboxybenzamido-ββ-di(4-methoxyphenyl)propionic acid, $(OMe{\cdot}C_6H_4)_2CH{-}\begin{matrix}CH{\cdot}CO{\cdot}O{\cdot}CO\\ |\\ NH{\cdot}CO{-}C_6H_4\end{matrix}$, which, on boiling with hydriodic acid and acetic anhydride, gave α-*amino*-ββ-*di*(4-*hydroxyphenyl*)*propionic acid*; this, with iodine and ammonia, yielded the desired isomeride of thyroxine.

Neither this compound, nor the amine derived from it by elimination of carbon dioxide, showed any trace of the type of physiological activity characteristic of thyroxine; further, the pressor effect of the amine, as also that of its iodine-free precursor, was negligible (Gaddum, private communication). Below are also described the synthesis of α-*amino*-ββ-*diphenylpropionic acid* by a method precisely similar to that outlined above, and the preparation of 3′ : 5′-*dibromo*-3 : 5-*di-iodothyronine*, a compound which might be expected to have a physiological effect intermediate between those of 3 : 5-di-iodothyronine and thyroxine.

Experimental.

Ethyl Di(4-*methoxyphenyl*)*methylphthalimidomalonate*.—Di(4-methoxyphenyl)methyl chloride (Straus and Dützmann, *J. pr. Chem.*, 1921, **103**, 47) (1 mol.), dissolved in dry xylene, and freshly prepared ethyl potassiophthalimidomalonate (1 mol.) were heated together at 145° for 4 hours with occasional shaking (compare Stephen and Weizmann, J., 1914, **105**, 1152). The cooled solution was shaken with water, and the precipitate filtered off and washed with cold dilute potassium hydroxide solution and water; a further amount was obtained by drying the xylene solution, removing the solvent under diminished pressure, and rubbing the residual syrup with a little alcohol. The *ester* formed colourless prisms, m. p.

106°, from alcohol; yield, 75% (Found : C, 67·7; H, 5·5; N, 2·4. $C_{30}H_{29}O_8N$ requires C, 67·8; H, 5·8; N, 2·6%).

Anhydride of α-o-*Carboxybenzamido*-ββ-*di*(4-*methoxyphenyl*)*propionic Acid.*—The above ester (29·5 g.) was moistened with alcohol and heated on the steam-bath for 1 hour, with frequent stirring, with a solution of potassium hydroxide (37 g.) in water (75 c.c.). The mixture was cooled, and the potassium salt filtered off, washed with alcohol, and dissolved in warm water. The solution, after cooling as far as possible without separation of the salt, was acidified by addition first of acetic and then of hydrochloric acid; the precipitated acid was collected, dried (crude yield, 22 g.), and, without further purification, heated at 180—200°/13 mm. for 1 hour. As decarboxylation proceeded, the material first became soft and then hardened again; a small amount of phthalic anhydride sublimed into the neck of the flask. The solid cake remaining was dissolved in the minimum boiling glacial acetic acid, and the hot solution slightly diluted with water; on cooling, the *anhydride* separated in colourless prisms. After two further crystallisations it had m. p. 209—210°; yield, 75% (Found : C, 69·4; H, 4·8; N, 2·9. $C_{25}H_{21}O_6N$ requires C, 69·4; H, 4·9; N, 3·1%).

α-*Amino*-ββ-*di*(4-*hydroxyphenyl*)*propionic Acid.*—The anhydride (1 part) was boiled for 2 hours under reflux with a mixture of constant-boiling hydriodic acid (5 parts) and acetic anhydride (5 parts); the solution was evaporated to dryness under diminished pressure, the evaporation being repeated after addition of water. The residue was dissolved in boiling water, the cooled solution filtered and extracted twice with ether, the aqueous layer made faintly alkaline with ammonia and evaporated to dryness under diminished pressure, and the residue dissolved in the minimum boiling alcohol. On standing in the cold, the *amino-acid* separated slowly; the crystals were recrystallised from water (charcoal); further crops were obtained by concentration of the mother-liquors. The compound forms fine colourless needles which soften at 190—200° and melt at 241° (decomp.). When pure, it is fairly readily soluble in water and sparingly soluble in alcohol. The air-dried substance always contains some water, but does not appear to form a definite hydrate; for analysis it was dried in a vacuum over sulphuric acid (Found : C, 65·7; H, 5·7; N, 5·0. $C_{15}H_{15}O_4N$ requires C, 65·9; H, 5·5; N, 5·1%).

ββ-*Di*(3 : 5-*di-iodo*-4-*hydroxyphenyl*)-α-*aminopropionic Acid.*—The above-described amino-acid was dissolved in the minimum amount of ammonia (*d* 0·880), and the ice-cold solution treated with the calculated amount of iodine in potassium iodide (2·54*N*), the rate of addition being slackened in the later stages. The solution was

evaporated to dryness under diminished pressure, and the residue collected, washed with dilute acetic acid, and dissolved in boiling dilute aqueous-alcoholic hydrochloric acid. This solution was boiled with charcoal, filtered, and treated with sodium acetate until it was no longer acid to Congo-red; immediate separation of the product ensued; after one similar recrystallisation it formed a colourless sphaero-crystalline powder, m. p. 218° (decomp.); yield, 60%. The *compound* is very sparingly soluble in water or alcohol; the acidic salts also are sparingly soluble in water, but readily soluble in dilute alcohol (Found: N, 1·8; I, 65·1. $C_{15}H_{11}O_4NI_4$ requires N, 1·8; I, 65·3%).

ββ-*Di*(4-*hydroxyphenyl*)*ethylamine*.—α-Amino-ββ-di(4-hydroxyphenyl)propionic acid was heated in portions of 0·5 g. in a sublimation apparatus at 290—315°/2 mm.; rapid decarboxylation occurred and a crust of the impure amine formed on the condenser. The *product* was collected, washed with boiling ethyl acetate, and crystallised from a large volume of hot water, from which it separated in colourless needles, m. p. 207—208°; yield, 55% (Found: C, 73·3; H, 6·6; N, 6·1. $C_{14}H_{15}O_2N$ requires C, 73·4; H, 6·6; N, 6·1%). The base is readily soluble in methyl and ethyl alcohol, but almost insoluble in other organic solvents. The hydrochloride, which is very soluble in water, was obtained by addition of ether to a solution of the base in saturated alcoholic hydrogen chloride; recrystallised from a small volume of alcohol, it had m. p. 275°. The *tribenzoyl* derivative crystallised from alcohol in clusters of fine needles, m. p. 200° (Found: N, 2·6. $C_{35}H_{27}O_5N$ requires N, 2·7%).

ββ-*Di*(3 : 5-*di-iodo*-4-*hydroxyphenyl*)*ethylamine*.—The above-described base (1 g.) was dissolved in ammonia solution (*d* 0·880; 150 c.c.) and the theoretical amount of iodine in potassium iodide (2·54*N*) was run in slowly, without cooling; the product began to separate after about half the iodine had been added. After standing for a few hours, the solution was diluted and the product collected. It was suspended in a large volume of dilute sulphuric acid, traces of free iodine were removed by addition of a little bisulphite, an equal volume of alcohol was added, and the solution heated to boiling and filtered. The filtrate was further diluted with water containing a little sulphuric acid, freed from alcohol by boiling, and again rapidly filtered to remove some tar. The final filtrate, on cooling, deposited the sulphate of the new base. The crystals were collected and dissolved in boiling 50% alcohol and the solution was treated with a slight excess of ammonia and concentrated by boiling until the *base* began to separate. The product was purified by re-solution in ammonia, followed by evaporation of the

excess of the latter; it then separated in clusters of colourless needles, m. p. 232—233° (decomp. with liberation of iodine); yield, 30% (Found: N, 1·9. $C_{14}H_{11}O_2NI_4$ requires N, 1·9%. The results of the iodine analyses of this compound were consistently about 1% low for a reason at present unexplained; there seemed to be no question as to its purity). The base is insoluble in water and alcohol and readily soluble in dilute aqueous sodium hydroxide and in dilute aqueous-alcoholic hydrochloric or sulphuric acid.

Ethyl Diphenylmethylphthalimidomalonate. — Diphenylmethyl bromide (Claisen, *Annalen*, 1925, **442**, 245, footnote) was condensed with ethyl potassiophthalimidomalonate precisely as described above for the corresponding *p*-dimethoxy-compound. The *product* remained in the xylene layer, when the xylene solution was mixed with water, and was obtained by drying the layer over calcium chloride, evaporating the xylene under diminished pressure, and crystallising the residue from a little alcohol; it formed colourless prisms, m. p. 117°; yield, 57% (Found: C, 70·9; H, 5·3; N, 3·0. $C_{28}H_{25}O_6N$ requires C, 71·3; H, 5·3; N, 3·0%).

Anhydride of α-o-Carboxybenzamido-ββ-diphenylpropionic Acid.— The crude acid, obtained by hydrolysis of the above ester with potassium hydroxide, when heated under diminished pressure at 180—200°, gave the *anhydride*, which formed colourless prisms, m. p. 214—215°, from acetic acid; yield, theoretical (Found: C, 74·2; H, 4·7; N, 3·8. $C_{23}H_{17}O_4N$ requires C, 74·4; H, 4·6; N, 3·8%).

α-Amino-ββ-diphenylpropionic Acid.—The anhydride was boiled for 2 hours with a mixture of equal volumes of constant-boiling hydriodic acid and acetic anhydride (10 parts). After evaporation to dryness under diminished pressure, the residue was dissolved in water and the solution neutralised with ammonia, whereupon immediate precipitation of the *amino-acid* took place. For purification it was dissolved in hot water with the aid of a little ammonia and the solution was neutralised with acetic acid; the amino-acid formed large colourless prisms, m. p. 236° (decomp.); yield, 77% (Found: C, 74·6; H, 6·3; N, 5·6. $C_{15}H_{15}O_4N$ requires C, 74·7; H, 6·2; N, 5·8%). The compound is sparingly soluble in water and alcohol.

ββ-Diphenylethylamine.—This compound, which had already been prepared (Lipp, *Annalen*, 1926, **449**, 24; Rupe and Gisiger, *Helv. Chim. Acta*, 1925, **8**, 340), was obtained in improved yield by heating ββ-diphenylalanine with diphenylamine (compare Johnson and Daschavsky, *J. Biol. Chem.*, 1924—1925, **62**, 725; Abderhalden and Gebelein, *Z. physiol. Chem.*, 1926, **152**, 125). ββ-Diphenyl-

alanine (2 g.), mixed with diphenylamine (40 g.), was heated in a metal-bath, the air being displaced from the reaction flask by a current of hydrogen which was afterwards led through a wash-bottle containing dilute sulphuric acid; the temperature of the bath was raised from 200° to 250° in the course of an hour, by which time decarboxylation was complete. The reaction mixture was cooled and dissolved in benzene, the latter being then extracted with the dilute sulphuric acid which had been employed in the wash-bottle. The acid extract was treated with excess of sodium hydroxide, the precipitated oil collected with ether (crude yield, 75%), and the base purified by distillation; it had b. p. 180°/15 mm., m. p. 39—40°. The hydrochloride had m. p. 259° and the picrate m. p. 216—217°. The chloroaurate and the chloroplatinate also coincided in properties with those described by the above-mentioned workers.

3′ : 5′-*Dibromo*-3 : 5-*di-iodothyronine*.—3 : 5-Di-iodothyronine (0·53 g.) was suspended in glacial acetic acid (1·7 c.c.), and bromine (0·1 c.c.) in acetic acid (0·3 c.c.) added drop by drop; the addition was accompanied by evolution of heat and the amino-acid passed into solution. On keeping over-night in the ice-chest a crystalline precipitate separated; this was collected and dissolved in 50% alcoholic *N*-ammonium hydroxide. The ammoniacal solution was filtered, heated to boiling, and acidified with acetic acid; immediate crystallisation of the product ensued. The *compound* had m. p. 244·5° (decomp.); yield, 45% (Found: N, 2·1; I, 37·4. $C_{15}H_{11}O_4NBr_2I_2$ requires N, 2·1; I, 37·2%). In solubilities the substance closely resembled thyroxine.

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