518. *The Synthesis of Thyroxine and Related Compounds. Part XV.*[1] *The Preparation of Thyronines from Iodonium Salts and Derivatives of 3,5-Disubstituted Tyrosines.*

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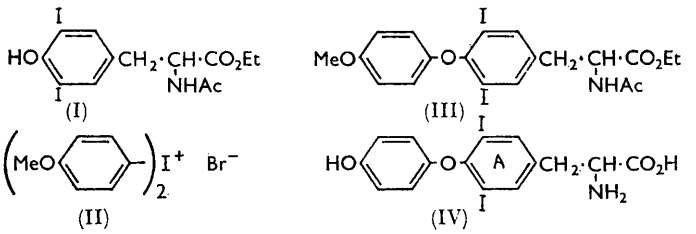
Hillmann's method [2] for preparing 3,5-di-iodo-L-thyronine has been extended to other 3,5-disubstituted thyronines and to a 4-*p*-hydroxyphenoxyacetic acid. The reaction is improved by using soluble di-*p*-methoxyphenyliodonium salts and methods for preparing these are described. The reaction is also suitable for preparing thyronines containing two different halogens in ring A, one of which may be fluorine.

Interest in the biochemical behaviour of 3,5-dihalogenothyronines has led us to examine the scope of Hillmann's method [2] for preparing 3,5-di-iodo-L-thyronine. Hillmann [2b] refluxed *N*-acetyl-3,5-di-iodo-L-tyrosine ethyl ester (I) for 80 hr. with two equivalents of the sparingly souble di-*p*-methoxyphenyliodonium bromide (II) in methanol containing one equivalent of magnesium methoxide; he isolated *N*-acetyl-3,5-di-iodo-4-*p*-methoxyphenoxy-L-phenylalanine ether ester (III) which, when decomposed with hydrobromic acid, gave 3,5-di-iodo-L-thyronine (IV) in 40% overall yield.



Iodonium halides decompose on prolonged heating.[3] We therefore studied the preparation of alcohol-soluble di-*p*-methoxyphenyliodonium salts, which we expected to react more quickly than the bromide. Treating the bromide [4] or iodide [5] with silver sulphate gave the soluble iodonium sulphate almost quantitatively, and from this we obtained the chloride, which is more soluble than the bromide. The soluble trifluoroacetate was prepared by known methods,[6,7] which, slightly modified,[8] gave di-*p*-methoxyphenyliodonium trichloroacetate in 58% yield at less cost.

Di-*p*-methoxyphenyliodonium trichloroacetate is soluble in boiling methanol, in which it quickly decomposes. It is unsuitable for use in the condensation, but when heated in benzene it rapidly decomposes, giving almost pure di-*p*-methoxyphenyliodonium chloride in 92% yield. This provides a convenient route to a compound ideal for use in the condensation. Although we have not investigated the mechanism of the decomposition, we think it very probable that the trichloroacetate ion undergoes decarboxylation and the intermediate CCl_3^- ion decomposes into chloride ion and dichlorocarbene. It has been shown [9] that the decomposition of sodium trichloroacetate in non-protonic solvents and in the presence of a dichlorocarbene acceptor follows this course. We were not able to

[1] Part XIV, *J.*, 1960, 2711.
[2] Hillmann, (*a*) *Z. Naturforsch.*, 1956, **11**b, 419; (*b*) U.S.P. 2,886,592.
[3] Beringer and Mausner, *J. Amer. Chem. Soc.*, 1950, **80**, 4535.
[4] Plati, U.S.P. 2,839,583.
[5] Mastropaolo, *Anales Asoc. quim. argentina*, 1940, **28**, 101; Beringer, Brierley, Drexler, Gindler, and Lumpkin, *J. Amer. Chem. Soc.*, 1953, **75**, 2708.
[6] Beringer, Bachofer, Falk, and Leff, *J. Amer. Chem. Soc.*, 1958, **80**, 4279.
[7] Beringer, Falk, Karniol, Lillian, Masulo, Mausner, and Sommer, *J. Amer. Chem. Soc.*, 1959, **81**, 342.
[8] Fichter and Stern, *Helv. Chim. Acta*, 1928, **11**, 1256.
[9] Wagner, *Proc. Chem. Soc.*, 1959, 229.

detect carbonyl or oxalyl chloride which would have been formed in two other methods of decomposition.

Experiments with several iodonium salts and equivalent quantities of *N*-acetyl-3,5-dichloro-L-tyrosine ethyl ester and sodium methoxide showed the advantage of using a soluble iodonium salt. Under the same conditions the yields of pure dichloro-, dibromo-, and di-iodo-thyronine were similar, but *N*-acetyl-3-fluoro-5-iodo-DL-tyrosine ethyl ester, even with an excess of the iodonium salt, gave a lower yield (36%) of the *O*-methyl-thyronine, and *N*-acetyltyrosine ethyl ester and its 3-nitro- and 3,5-dinitro-derivatives gave no thyronine. Hillmann [2a] reported poor yields from *N*-acetyl-3-iodo-L-tyrosine ethyl ester and the unsubstituted compound. We obtained a 4% yield of 3,5-dimethyl-DL-thronine, under forcing conditions, from the disodium salt of *N*-acetyl-3,5-dimethyl-DL-tyrosine and di-*p*-methoxyphenyliodonium bromide in dimethylformamide (in which the bromide is soluble). This low yield is probably due in part to the low reactivity of the phenol and in part to destruction of the iodonium salt. In the thyronine series, therefore, the iodonium-salt route is at present virtually limited to the preparation of 3,5-dihalogeno-thyronines, but it is the only convenient method for making thyronines with fluorine, or with two different halogen atoms, in ring A, and by this route the optical activity of the tyrosine is fully preserved.[2a]

The reaction was less satisfactory in the absence of an amino-acid side-chain. 2,6-Dimethylphenol with di-*p*-methoxyphenyliodonium sulphate gave small amounts of unidentified compounds that, separated by chromatography, showed carbonyl absorption (1714 and 1704 cm.$^{-1}$) and formed derivatives with 2,4-dinitrophenylhydrazine. In the 4-*p*-hydroxyphenoxyacetic acid series the reaction gave a lower yield than does the pyridinium salt method;[10] 3,5-dichloro-4-*p*-hydroxyphenoxyphenylacetic acid was obtained in only 23% yield from ethyl 3,5-dichloro-4-hydroxyphenylacetate, and the reaction failed completely with the corresponding dibromo-compound.

The preparation of 3-chloro-5-iodo-D-thyronine (the first thyronine with different halogens in ring A to be described) is of interest. We thought it unlikely that 3-chloro-5-iodo-L-thyronine would undergo inversion in the usual way, for 3,5-dichloro-L-thyronine, when treated with nitrosyl bromide, gave an α-bromo-acid from which 3,5-dichloro-L-thyronine was obtained on ammonolysis.[11] We therefore started with D-tyrosine. Partial chlorination with sulphuryl chloride and then iodination with iodine monochloride gave the chloro-iodo-tyrosine which was converted into the thyronine in good yield.

3-Fluoro-DL-tyrosine was prepared by chloromethylating *o*-fluoroanisole and treating the benzyl chloride produced with diethyl acetamidomalonate, with final decarboxylation and hydrolysis. With iodine in ethylamine it gave 3-fluoro-5-iodo-DL-tyrosine, which was converted into the corresponding thyronine. 3,5-Dimethyl-DL-tyrosine was obtained by chloromethylating 2,6-dimethylanisole and condensing the product with diethyl acetamidomalonate, then refluxing the ester with hydriodic acid. We were not able to chloromethylate 2,6-dimethylphenyl carbonate. Other methylated phenol carbonates have, however, been chloromethylated.[12]

Experimental

M. p.s are corrected.

*Di-*p*-methoxyphenyliodonium Sulphate.*—Di-*p*-methoxyphenyliodonium bromide [4] (8·40 g.) was moistened with ethanol and suspended in water (50 ml.), then shaken for 1¼ hr. with silver sulphate (3·12 g.). Silver bromide was removed and the filtrate evaporated under reduced pressure, leaving the *sulphate* (7·61 g., 92%) as a colourless, amorphous mass (Found: C, 42·45; H, 3·6; I, 30·0. $C_{28}H_{28}I_2O_8S,H_2O$ requires C, 42·2; H, 3·8; I, 30·6%).

*Di-*p*-methoxyphenyliodonium Chloride.*—Treatment of the sulphate (5·0 g.) in water (15 ml.)

[10] Meltzer, Lustgarten, and Fischman, *J. Org. Chem.*, 1957, **22**, 1577.
[11] Warburton, following paper.
[12] Sommelet and Marszah, *Compt. rend.*, 1934, **198**, 2256.

with sodium chloride (0·75 g.) in water (10 ml.) gave the chloride as colourless needles (3·8 g., 79%), m. p. 190—191°. One crystallization from ethanol gave needles, m. p. 198—199° (Found: C, 45·0; H, 4·0; Hal., 43·1. Calc. for $C_{14}H_{14}ClIO_2$: C, 44·45; H, 3·75; Hal., 43·1%).

Di-p-*methoxyphenyliodonium Trichloroacetate.*—Nitric acid (5·4 ml.; *d* 1·5) was added to stirred acetic anhydride (14 ml.) at −20°. Trichloroacetic acid (20 g.) and iodine (5·0 g.) were added at room temperature. The mixture was shaken for 1 hr., then evaporated at <50° under reduced pressure. Acetic anhydride (30 ml.) was added to the residue at room temperature, followed, at −10°, by anisole (17·4 ml.), trichloroacetic acid (20 g.), and acetic anhydride (70 ml.). The mixture was kept at 0° overnight, then at room temperature for 2 days. Most of the solvent was removed under reduced pressure and ether (250 ml.) added. The yellow solid (13 g.) which separated was stirred with warm ether, leaving di-*p*-methoxyphenyliodonium trichloroacetate as colourless crystals (11·9 g., 58%), m. p. 92—93°. The compound was not obtained analytically pure. It did not give a precipitate with silver nitrate and showed strong absorption in Nujol at 1660 cm.$^{-1}$ (trichloroacetate).

Decomposition of Di-p-*methoxyphenyliodonium Trichloroacetate.*—The trichloroacetate (1·0 g.) was refluxed in benzene (35 ml.) for 5 min., giving the colourless chloride (0·69 g., 92%), m. p. 195—197° (decomp.). Recrystallization from ethanol gave well-formed crystals, m. p. and mixed m. p. 197—198°, identical (infrared) with an authentic sample (Found: C, 44·7; H, 3·8; Hal, 42·8. Calc. for $C_{14}H_{14}ClIO_2$: C, 44·45; H, 3·75; Hal, 43·1%). There was no absorption at 1660 cm.$^{-1}$ in Nujol, and the compound gave a precipitate with silver nitrate. Addition of potassium iodide gave the iodonium iodide, identical (infrared) with a sample prepared by known methods.[5]

Reaction of Di-p-*methoxyphenyliodonium Sulphate with* N-*Acetyl*-3,5-*dichloro*-L-*tyrosine Ethyl Ester.*—*N*-Acetyl-3,5-dichloro-L-tyrosine ethyl ester (2·00 g.), di-*p*-methoxyphenyliodonium sulphate (2·43 g.), sodium methoxide (0·338 g.), and dry methanol (30 ml.) were refluxed for 1¼ hr. *p*-Iodoanisole was removed by steam-distillation and the residue extracted with warm benzene. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure, leaving an oil (2·54 g., 95%). This was refluxed for 2 hr. with acetic acid (27 ml.), constant-boiling hydriodic acid (85 ml.), and red phosphorus (2·0 g.). The mixture was filtered hot through kieselguhr and evaporated to dryness under reduced pressure. The residue was dissolved in a small volume of hot water containing a little ethanol, and a hot solution of sodium acetate containing a little sodium hydrogen sulphite was added to the boiling solution until the pH was about 5. The mixture was cooled and 3,5-dichloro-L-thyronine separated as colourless needles (1·11 g., 52%), m. p. 247—248° (decomp.) identical (infrared) with a specimen prepared by the pyridinium salt method.[11]

The effect of varying the iodonium salt is shown in the following Table; other details are as just described.

Iodonium salt	Yield of crude ester (%)	Yield of pure amino-acid (%)	Iodonium salt	Yield of crude ester (%)	Yield of pure amino-acid (%)
Iodide	0	—	Trifluoroacetate...	80	45
Bromide	Trace	—	Chloride	85	41
Sulphate	95	52	Trichloroacetate	13	Not prepared

Overall yields are not increased by purifying the ester. In dimethylformamide, under the same conditions, the bromide gave a 9% yield of the ester, but the iodide did not react.

Reaction of the N-*Acetyltyrosine Ethyl Esters with Di*-p-*methoxyphenyliodonium Sulphate.*—A series of experiments (iodonium sulphate in methanol) in which the *N*-acetyl-ester was varied is shown in the next Table; other details are as just described:

N-Acetyltyrosine Et ester	Yield of crude ester (%)	Yield of pure amino-acid (%)	*N*-Acetyltyrosine Et ester	Yield of crude ester (%)	Yield of pure amino-acid (%)
3,5-Dichloro	95	52	3-Fluoro-5-iodo ...	>100	36 *
3,5-Dibromo	96·5	58·5	3-Nitro	0	—
3,5-Di-iodo	95	47	3,5-Dinitro	0	—
3-Chloro-5-iodo ...	—	54·5	Unsubst.....	0	—

* *O*-Methylamino-acid; excess of iodonium salt used.

N-*Acetyl*-3,5-*dichloro*-L-*tyrosine.*—A solution of 3,5-dichloro-L-tyrosine [13] (25·0 g.) in 2N-sodium hydroxide (200 ml.) was treated with acetic anhydride (12·5 ml.) with stirring at 20°.

[13] Zeynek, *Z. physiol. Chem.*, 1921, **114**, 275.

The solution was stirred for 1 hr., then heated at 40° for 30 min. to decompose the excess of acetic anhydride. 5N-Hydrochloric acid was added until the solution was acid to Congo Red, and the solid (18·7 g.) recrystallized from water. N-*Acetyl*-3,5-*dichloro*-L-*tyrosine* separated as needles (16·1 g., 55%), m. p. 136—139°, $[\alpha]_D^{20}$ +83·0° (*c* 5·6 in dioxan) (Found: C, 44·1; H, 4·0; N, 4·65; Cl, 23·65. $C_{11}H_{11}Cl_2NO_4,\frac{1}{2}H_2O$ requires C, 44·0; H, 4·0; N, 4·7; Cl, 23·7%).

N-*Acetyl*-3,5-*dichloro*-L-*tyrosine Ethyl Ester*.—*N*-Acetyl-3,5-dichloro-L-tyrosine (9·0 g.), toluene-*p*-sulphonic acid (0·85 g.), ethanol (6 ml.), and chloroform (280 ml.) were refluxed under an automatic water separator for 17 hr. The cold solution was extracted with 2N-sodium carbonate, and the extract acidified, giving the pale grey *ester* (7·3 g., 74%), m. p. 138—139°. Two recrystallizations from aqueous ethanol gave m. p. 140—141° (Found: C, 48·95; H, 4·8; N, 4·3; Cl, 21·8. $C_{13}H_{15}Cl_2NO_4$ requires C, 48·8; H, 4·7; N, 4·4; Cl, 22·1%).

N-*Acetyl*-3,5-*dibromo*-L-*tyrosine Ethyl Ester*.—*N*-Acetyl-3,5-dibromo-L-tyrosine [14] was esterified as above, giving the *ester* (65%), m. p. 141—143° (Found: C, 38·2; H, 3·6; Br, 38·7. $C_{13}H_{15}Br_2NO_4$ requires C, 38·2; H, 3·7; Br, 39·0%).

N-*Acetyl*-3-*nitro*-L-*tyrosine*.—3-Nitro-L-tyrosine [15] was acetylated as described above, giving the *acetyl derivative*, m. p. 189—192° (from water) (Found: C, 49·4; H, 4·6; N, 10·5. $C_{11}H_{12}N_2O_6$ requires C, 49·3; H, 4·5; N, 10·45%).

N-*Acetyl*-3-*nitro*-L-*tyrosine Ethyl Ester*.—Esterification of the preceding compound as described above gave the *ester*, m. p. 95—97° (from ethanol) (Found: C, 52·8; H, 5·4; N, 9·75. $C_{13}H_{16}N_2O_6$ requires C, 52·7; H, 5·4; N, 9·5%).

4-*Chloromethyl*-2,6-*dimethylanisole*.—A stirred mixture of 2,6-dimethylanisole (40 g.), 38% aqueous formaldehyde (20 ml.), concentrated hydrochloric acid (10 ml.), zinc chloride (6 g.), and ether (120 ml.) was saturated with hydrogen chloride at 20—25°, then kept at room temperature for 5 days. The solution was poured into ether (200 ml.) and ice (500 g.), and the organic layer washed with 2N-sodium hydrogen carbonate and water and dried ($MgSO_4$). The ether was removed at room temperature and the residue distilled as quickly as possible from an oil-bath previously heated to 80—90°. The following fractions were collected: (i) 3·5 g., b. p. 40—80°/1 mm., n_D^{24} 1·5190, mainly 2,6-dimethylanisole; (ii) 6·2 g., b. p. 80—83°/1 mm., n_D^{24} 1·5350; (iii) 30·2 g., b. p. 83—85°/1 mm., n_D^{20} 1·5375. Fractions (ii) and (iii) were 4-chloromethyl-2,6-dimethylanisole (infrared).

Ethyl α-*Acetamido*-α-(4-*methoxy*-3,5-*dimethylbenzyl*)*malonate*.—Sodium (5·50 g.) was dissolved in ethanol (250 ml.), and diethyl acetamidomalonate (52·0 g.) added to the cooled solution. 4-Chloromethyl-2,6-dimethylanisole (43·5 g.) in ethanol (150 ml.) was added, and the solution refluxed with stirring for 6 hr. The filtrate was taken to dryness under reduced pressure and the residue dissolved in ethyl acetate (500 ml.), washed with water, dried ($MgSO_4$), and again taken to dryness. The almost colourless gum solidified and was recrystallized from aqueous methanol below 40°. The *product* (69 g., 79%) separated as plates, m. p. 97—99° (Found: C, 62·4; H, 7·7; N, 4·1. $C_{19}H_{27}NO_6$ requires C, 62·45; H, 7·4; N, 3·8%).

3,5-*Dimethyl*-DL-*tyrosine*.—The preceding ester (69 g.), acetic acid (450 ml.), and constant-boiling hydriodic acid (350 ml.) were refluxed for 7 hr., then evaporated to dryness under reduced pressure. The red oil was dissolved in water (150 ml.) and extracted with ether, which removed most of the colour. The aqueous layer was brought to pH 8 with concentrated ammonia solution, washed with ethyl acetate, and concentrated under reduced pressure. 3,5-Dimethyl-DL-tyrosine was collected after refrigeration [23·1 g., 58%; m. p. 242—248° (decomp.) (lit.,[16] 250—253°)].

N-*Acetyl*-3,5-*dimethyl*-DL-*tyrosine*.—3,5-Dimethyl-DL-tyrosine (22 g.) in 2N-sodium hydroxide (500 ml.) was treated dropwise with acetic anhydride (30 ml.) at 16—20° during 2 hr. with stirring and kept overnight. The solution was then heated to 40° for 45 min., and acidified with 10N-hydrochloric acid at below 15°, giving a colourless solid (12·0 g.), m. p. 182—184°. The mother-liquors were made strongly alkaline with 40% sodium hydroxide solution and the acetylation repeated with acetic anhydride (50 ml.). A second crop of N-*acetyl*-3,5-*dimethyl*-DL-*tyrosine* (11·0 g., total yield 86%) separated. Recrystallization from acetonitrile gave rosettes, m. p. 183—185° (Found: C, 61·9; H, 6·5; N, 5·45. $C_{13}H_{17}NO_4$ requires C, 62·1; H, 6·8; N, 5·6%).

N-*Acetyl*-3,5-*dimethyl*-DL-*tyrosine Ethyl Ester*.—Esterification of the preceding compound as

[14] De Witt and Ingersoll, *J. Amer. Chem. Soc.*, 1951, **73**, 5782.
[15] Städeler, *Annalen*, 1896, **116**, 77.
[16] Steiner and Sorkin, *Helv. Chim. Acta*, 1952, **35**, 2486.

described above gave the *ester*, m. p. 101—102° (from ethyl acetate and di-isopropyl ether) (Found: C, 64·0; H, 7·5; N, 4·8. $C_{15}H_{21}NO_4$ requires C, 64·5; H, 7·6; N, 5·0%).

3,5-*Dimethyl*-DL-*thyronine*.—*N*-Acetyl-3,5-dimethyl-DL-tyrosine (1·69 g.) was dissolved in 1·17N-methanolic sodium methoxide (11·0 ml.), the methanol removed under reduced pressure, and the residue dried at 40° for 3 hr. Anhydrous dimethylformamide (20 ml.) and di-*p*-methoxyphenyliodonium bromide (2·6 g.) were added, and the mixture was heated on the steam-bath for 4 hr. with occasional shaking. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was extracted with 2N-sodium hydroxide, and the extract, combined with the original aqueous layer, acidified and extracted with ethyl acetate. Concentration of the ethyl acetate extract gave a light brown foam (1·80 g.), which, dissolved in ethyl acetate (10 ml.) and stored overnight at 5°, gave unchanged *N*-acetyl-3,5-dimethyl-DL-tyrosine (0·40 g., 24%). The mother-liquors were taken to dryness and the residue refluxed for 2 hr. with acetic acid (10 ml.) and constant-boiling hydriodic acid (10 ml.). Evaporation left a residue, which was dissolved in water (15 ml.). The solution was partly decolorized by treatment with sodium hydrogen sulphite solution and extraction with ether, then neutralized with ammonia and concentrated under reduced pressure until crystallization started. 3,5-*Dimethyl*-DL-*thyronine* separated as pale grey crystals (80 mg., 3·8%), m. p. 210—212° (decomp.) after drying at 80° in a vacuum (Found: C, 64·4; H, 6·6; N, 4·4. $C_{17}H_{19}NO_4,H_2O$ requires C, 63·9; H, 6·6; N, 4·4%). The acid was chromatographically pure.

When two equivalents of the iodonium bromide were added in successive portions, the yield was 4·3%. Ester hydrolysis made it impossible to condense *N*-acetyl-3,5-dimethyl-DL-tyrosine ethyl ester with the iodonium bromide under forcing conditions.

3-*Chloro*-D-*tyrosine*.—Chlorination of D-tyrosine [17] by the method used by Zeynek [18] in the L-series gave 3-*chloro*-D-*tyrosine* (48%), m. p. 255—256° (decomp.), $[\alpha]_D^{20}$ +26·0° (*c* 0·9 in H_2O) (Found: C, 50·7; H, 4·8; N, 6·3; Cl, 16·1. $C_9H_{10}ClNO_3$ requires C, 50·1; H, 4·7; N, 6·5; Cl, 16·4%). 3-Chloro-L-tyrosine prepared by the same method had $[\alpha]_D^{20}$ −26·2°.

3-*Chloro*-5-*iodo*-D- *and* -L-*tyrosine*.—3-Chloro-D-tyrosine hydrochloride (11·6 g.) was dissolved in water (73 ml.) and cooled to 10°. Iodine monochloride (9·4 g.) was warmed to 40° and a stream of dry air was drawn over it and through the solution of the hydrochloride. After 3 hr. at 10°, the hydrochloride solution was decolorized with sodium hydrogen sulphite. Concentrated hydrochloric acid (73 ml.) was added and the solid which separated overnight in the refrigerator was dissolved in a little 2N-sodium hydroxide. Neutralization with 2N-acetic acid gave 3-*chloro*-5-*iodo*-D-*tyrosine* (12·94 g., 84%), m. p. 197—198° (decomp.). Recrystallized from water it had m. p. 201° (decomp.), $[\alpha]_D^{20}$ +10·7° (*c* 0·5 in H_2O) (Found: C, 30·8; H, 3·1; N, 3·9; I, 36·3. $C_9H_9O_3ClIN,\frac{1}{2}H_2O$ requires C, 30·8; H, 2·9; N, 4·0; I, 36·2%). 3-*Chloro*-5-*iodo*-L-*tyrosine* prepared in the same way had m. p. 201° (decomp.), $[\alpha]_D^{20}$ −10·6° (Found: C, 31·2; H, 2·7; N, 3·8; I, 35·9%).

N-*Acetyl*-3-*chloro*-5-*iodo*-D- *and* -L-*tyrosine*.—Acetylation of the amino-acids as described earlier gave N-*acetyl*-3-*chloro*-5-*iodo*-D-*tyrosine* (92%), m. p. 117—121°, $[\alpha]_D^{20}$ −69° (*c* 0·9 in dioxan) (Found: C, 33·5; H, 3·4; N, 3·5; I, 31·9. $C_{11}H_{11}ClINO_4,\frac{1}{2}H_2O$ requires C, 33·6; H, 3·1; N, 3·6; I, 32·3%), and the corresponding L-*isomer*, m. p. 115—120°, $[\alpha]_D^{20}$ +70° (Found: C, 32·9; H, 3·3; N, 3·6%).

N-*Acetyl*-3-*chloro*-5-*iodo*-D- *and* -L-*tyrosine Ethyl Ester*.—Esterification of the acetates as described above gave N-*acetyl*-3-*chloro*-5-*iodo*-D-*tyrosine ethyl ester* (85%), m. p. 127—129°, $[\alpha]_D^{20}$ −45° (*c* 0·9 in dioxan) (Found: C, 37·9; H, 3·7; N, 3·1; I, 30·8. $C_{13}H_{15}ClINO_4$ requires C, 37·9; H, 3·7; N, 3·4; I, 30·8%), and the corresponding L-isomer, m. p. 129·5—131·5°, $[\alpha]_D^{20}$ +47°.

3-*Chloro*-5-*iodo*-D- *and* -L-*thyronine*.—*N*-Acetyl-3-chloro-5-iodo-D-tyrosine ethyl ester (10·0 g.), di-*p*-methoxyphenyliodonium sulphate (10·6 g.), dry methanol (140 ml.), and sodium methoxide (1·32 g.) were refluxed for 1½ hr. The mixture was steam-distilled and the residue extracted with benzene, giving an oil (12·1 g.). Demethylation and purification, as described earlier, gave 3-*chloro*-5-*iodo*-D-*thyronine* (5·81 g., 54·5%), m. p. 232—234° (decomp.), $[\alpha]_D^{20}$ −27·2° (*c* 0·7 in 1 : 1 EtOH–N-HCl) (Found: C, 39·9; H, 3·3; N, 2·9. $C_{15}H_{13}ClINO_4,\frac{1}{2}H_2O$ requires C, 39·9; H, 3·3; N, 3·1%). The corresponding L-*amino-acid* had m. p. 232—234°, $[\alpha]_D^{20}$ +27·5° (Found: C, 39·6; H, 3·4; N, 3·0%).

[17] Sealock, *Biochem. Prep.*, 1949, Vol. I, p. 71.
[18] Zeynek, *Z. physiol. Chem.*, 1925, **144**, 246.

3,5-*Dichloro*-4-*hydroxyphenylacetic Acid*.—*p*-Hydroxyphenylacetic acid (20·0 g.) in acetic acid (750 ml.) was treated with chlorine until the temperature, which had risen to 40°, started to fall. The solution was evaporated to dryness under reduced pressure and left a residue (23·2 g.), m. p. 160°, which was washed with water and dried. Crystallization from aqueous acetic acid, then from water (charcoal), gave 3,5-*dichloro*-4-*hydroxyphenylacetic acid* (8·2 g., 29%), m. p. 176—180° (Found: C, 43·5; H, 2·8; Cl, 31·8. $C_8H_6Cl_2O_3$ requires C, 43·5; H, 2·7; Cl, 32·1%).

Esterification gave the *ethyl ester*, m. p. 78—79° (from light petroleum) (Found: C, 48·3; H, 4·1; Cl, 28·35. $C_{10}H_{10}Cl_2O_3$ requires C, 48·3; H, 4·0; Cl, 28·5%).

3,5-*Dichloro*-4-p-*hydroxyphenoxyphenylacetic Acid*.—(a) *By the iodonium salt method*. Ethyl 3,5-dichloro-4-hydroxyphenylacetate (6·0 g.), di-*p*-methoxyphenyliodonium sulphate (9·9 g.), sodium methoxide (1·41 g.), and dry methanol (90 ml.) were refluxed for 1¼ hr. After steam-distillation the residue was extracted into ether, and the crude, dried product treated with hydriodic acid as above. 3,5-Dichloro-4-*p*-hydroxyphenoxyphenylacetic acid (1·75 g., 23%) separated from ethanol containing a little benzene, had m. p. 192—194°, and was identical (infrared) with the product described below.

(b) *By the pyridinium salt method*. The tetrazonium sulphate solution prepared [10] from 3,5-diamino-4-*p*-methoxyphenoxyphenylacetic acid (13·2 g.) was added slowly to a stirred mixture of cuprous chloride (23 g.), 10N-hydrochloric acid (375 ml.), and chloroform (400 ml.). The mixture was then stirred vigorously for 1 hr. Water (500 ml.) was added, the organic layer separated, and the aqueous layer extracted with more chloroform. The combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in cold benzene. A dark impurity was removed by adding a little light petroleum and decanting the liquid, and evaporation left a solid, which was recrystallized from 90% aqueous acetic acid, giving 3,5-*dichloro*-4-p-*methoxyphenoxyphenylacetic acid* (7·0 g., 52%), m. p. 116·5—117·5° (Found: Cl, 20·8. $C_{15}H_{12}Cl_2O_4$ requires Cl, 21·6%).

The methoxy-compound (10·0 g.) with constant-boiling hydriodic acid (20 ml.) in acetic acid (30 ml.) containing red phosphorus (2 g.) for 16 hr. gave 8·4 g. of a crude product which was recrystallized twice from acetonitrile, giving 3,5-*dichloro*-4-p-*hydroxyphenoxyphenylacetic acid* (3·82 g.), m. p. 192—194° (Found: C, 53·7; H, 3·2; Cl, 22·8. $C_{14}H_{10}Cl_2O_4$ requires C, 53·8; H, 3·2; Cl, 22·7%).

Ethyl α-*Acetamido*-α-(3-*fluoro*-4-*methoxybenzyl*)*malonate*.—Sodium (17·0 g.) was dissolved in dry ethanol (780 ml.). Diethyl acetamidomalonate (180 g.) was added and dissolved, then 3-fluoro-4-methoxybenzyl chloride [19] (129 g.) was added with stirring. The solution was refluxed for 5 hr., then filtered hot. The solution deposited colourless crystals (172 g.), m. p. 123—125°; recrystallized material from the concentrated mother-liquors amounted to 51·0 g. Further recrystallization from ethanol gave the *ester*, m. p. 127—128° (Found: C, 57·7; H, 6·1; N, 4·0. $C_{17}H_{22}FNO_6$ requires C, 57·5; H, 6·2; N, 3·9%).

3-*Fluoro*-DL-*tyrosine*.—The preceding compound (10·0 g.), constant-boiling hydriodic acid (57 ml.), and acetic acid (57 ml.) were refluxed for 3 hr. The solution was evaporated to dryness under reduced pressure and the residue dissolved in a little hot water and decolorized with sodium hydrogen sulphite. The pH was adjusted to 5; 3-fluoro-DL-tyrosine (4·0 g., 72%) slowly separated, having m. p. 283—284° (Found: C, 54·2; H, 5·1; N, 6·6; F, 9·1. Calc. for $C_9H_{10}FNO_3$: C, 54·3; H, 5·0; N, 7·0; F, 9·6%). Kraft [19] reports m. p. 278—280°.

3-*Fluoro*-5-*iodo*-DL-*tyrosine*.—A solution of iodine (25·8 g.) in saturated potassium iodide solution (24 ml.) was added dropwise to a stirred solution of 3-fluoro-DL-tyrosine (20·0 g.) in 33% aqueous ethylamine (50 ml.). The mixture was left overnight, then most of the ethylamine was removed under reduced pressure and the pH brought to 2 with 10N-hydrochloric acid. After 24 hr. the yellow solid was washed with water and dried, giving 3-fluoro-5-iodo-DL-tyrosine (18·4 g., 56%). Recrystallization from 50% aqueous ethanol raised the m. p. to 199—201° (Found: C, 31·9; H, 2·9; I, 37·1. Calc. for $C_9H_9FINO_3,H_2O$: C, 31·5; H, 3·2; I, 37·0%). Kraft and Dergel [20] report m. p. 190—193°. We were not able to prepare this compound by Kraft and Dergel's method.

N-*Acetyl*-3-*fluoro*-5-*iodo*-DL-*tyrosine*.—Acetylation of the amino-acid as above gave an almost quantitative yield of the *acetyl derivative*, m. p. 210—214° (Found: C, 36·2; H, 3·1. $C_{11}H_{11}FINO_4$ requires C, 35·9; H, 3·0%).

[19] Kraft, *Chem. Ber.*, 1951, **84**, 150.
[20] Kraft and Dergel, G.P. 895,292.

Esterification gave the *ethyl ester* (90% yield), m. p. 172—179° (Found: C, 39·7; H, 4·0; I, 31·6. $C_{13}H_{15}FINO_4$ requires C, 39·5; H, 3·8; I, 32·2%).

3-*Fluoro*-5-*iodo*-4-p-*methoxyphenoxy*-DL-*phenylalanine*.—*N*-Acetyl-3-fluoro-5-iodo-DL-tyrosine ethyl ester (10·7 g.), di-*p*-methoxyphenyliodonium sulphate (24·2 g.), sodium methoxide (2·06 g.), and dry methanol (200 ml.) were refluxed for 18 hr. under anhydrous conditions. After steam-distillation the product was extracted into warm benzene, and the benzene extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual red oil (14·2 g.) was refluxed with 2N-hydrochloric acid (100 ml.) and acetic acid (100 ml.) for 2 hr. Charcoal was added and boiling continued for 5 min. The solution was filtered hot, the volume reduced to *ca.* 70 ml., and the solution allowed to cool. The hydrochloride (6·3 g.) which separated was dissolved in 0·5N-sodium hydroxide (100 ml.) and neutralized at the b. p. with glacial acetic acid. 3-*Fluoro*-5-*iodo*-4-p-*methoxyphenoxy*-DL-*phenylalanine* (4·8 g., 36%) separated, having m. p. 225—228° (Found: C, 44·8; H, 3·6; N, 3·1; I, 29·2; F, 4·3. $C_{16}H_{15}FINO_4$ requires C, 44·6; H, 3·4; N, 3·2; I, 29·5; F, 4·4%).

3-*Fluoro*-5-*iodo*-DL-*thyronine*.—*N*-Acetyl-3-fluoro-5-iodo-DL-tyrosine ethyl ester (1·5 g.), di-*p*-methoxyphenyliodonium sulphate (2·0 g.), sodium methoxide (234 mg.), and dry methanol (25 ml.) were refluxed for 2 hr. After steam-distillation the product was extracted into hot benzene and the extracts were evaporated to dryness. The residual oil (1·2 g.) was refluxed for 2 hr. with 48% hydrobromic acid (20 ml.) and acetic acid (20 ml.). The solution was evaporated to dryness under reduced pressure, the residual oil dissolved in hot water, and the solution neutralized with sodium acetate solution. The amino-acid (0·26 g., 14%) recrystallized as its hydrochloride from 2N-hydrochloric acid. The hydrochloride was dissolved in 0·5N-sodium hydroxide and neutralized at the b. p. with glacial acetic acid. 3-*Fluoro*-5-*iodo*-DL-*thyronine* slowly separated as colourless crystals, m. p. 239—242° (Found: C, 41·6; H, 3·5; N, 3·0; I, 32·1; F, 5·1. $C_{15}H_{13}FINO_4$ requires C, 41·4; H, 3·4; N, 3·2; I, 29·2; F, 4·4%).

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