556. *The Synthesis of Thyroxine and Related Compounds. Part XVII.*[1] *The Preparation of Some Additional Compounds related to Thyroxine.*

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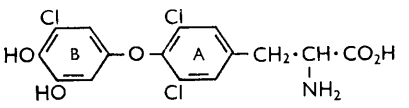
3,5,3′-Trichloro-5′-hydroxy-D- and -L-thyronine (I) have been prepared by the pyridinium salt method. 4-*p*-Hydroxyphenoxy-3,5-di-iodoacetophenone (III) has been prepared from 3,5-di-iodo-4-*p*-methoxyphenoxycinnamic acid. 2-(4-*p*-Hydroxyphenoxy-3,5-di-iodophenyl)ethanol (IV) has been prepared from the corresponding phenylacetic acid.

3,5-Di-iodo-*NN*-dimethyl-D-thyronine has been prepared by a modification of Elks and Waller's method.[2] Some diphenyl sulphides [*e.g.*, (VIII)] related to D-thyronine have been prepared by the pyridinium salt method, and some biphenyls have been obtained from 4-hydroxy-3,5-dinitrobenzoic acid and converted into derivatives of phenylacetic acid [*e.g.*, (XI)].

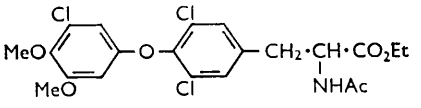
Several substituted D- and L-thyronines and some carboxylic acids related to thyroxine are described.

During the past three years we have prepared many compounds related to thyroxine for testing as depressants of blood cholesterol. We now report the preparation of several of these compounds. We have been interested particularly in derivatives of D-phenylalanine, for in many instances such compounds have a greater effect on fat and steroid metabolism than would have been expected from their action on the heart and on basal metabolic rate.[3]

3,5,3′-Trichloro-5′-hydroxy-D- and -L-thyronine (I) were prepared by the pyridinium salt method [4] from 6-chloro-4-hydroxyveratrole and *N*-acetyl-3,5-dinitro-D- and -L-tyrosine ethyl ester. The phenol was obtained from 5-chloroveratraldehyde *O*-acetyloxime: conversion into the nitrile, then hydrolysis, hypobromite degradation, diazotization, and decomposition of the diazonium salt with aqueous sulphuric acid gave the phenol in 30% overall yield (9% from vanillin). *N*-Acetyl-4-(3-chloro-4,5-dimethoxyphenoxy)-3,5-dinitrophenylalanine ethyl ester was reduced by hydrogen in the presence of platinum to the diamine (reduction in the presence of palladium caused loss of chlorine), which was tetrazotized and converted into the trichloro-compound (II). Acid-hydrolysis of this and demethylation of the amino-acid gave the thyronine (I), but special precautions against oxidation had to be taken while the amino-acid was in solution. Treating the ester (II) with hydriodic acid gave a much lower yield of the thyronine.



(I)



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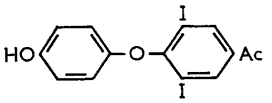


(III)

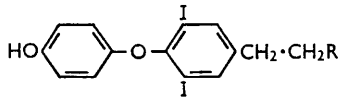
3,5,3′-Trichloro-5′-hydroxy-L-thyronine has little if any thyroactivity,[5] although 3,5,3′-trichloro-L-thyronine is demonstrably active.[6] It has been suggested that normal thyroactivity is due to an *o*-quinonoid compound derived initially from 3,5,3′-tri-iodo-L-thyronine

[1] Part XVI, *J.*, 1961, 2651.
[2] Elks and Waller, *J.*, 1952, 2366.
[3] (*a*) Boyd and Oliver, *J. Endocrinol.*, 1960, **21**, 25, 33; (*b*) Cuthbertson, Elcoate, Ireland, Mills, and Shearley, *ibid.*, pp. 45, 69.
[4] Chalmers, Dickson, Elks, and Hems, *J.*, 1949, 3424.
[5] Boyd, unpublished results.
[6] Cuthbertson, Elcoate, Ireland, Mills, and Shearley, unpublished results.

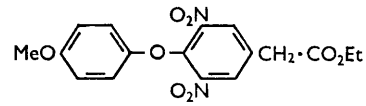
by 5'-hydroxylation (the postulated tri-iodocatechol has not yet been obtained, although 3'-hydroxy-3,5-di-iodo-L-thyronine has now been prepared [7]). The low activity of 3,5,3'-trichloro-5'-hydroxy-L-thyronine does not support the hydroxylation theory.

Cookson and Green [8] obtained the oxime of 3,5-di-iodo-4-*p*-methoxyphenoxyacetophenone as a by-product from the preparation of β-thyroxine. We have improved the preparation of this oxime and converted it into the hydroxy-ketone (III) by successive treatment with hydrochloric and hydriodic acid.

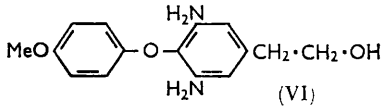
2-(4-*p*-Hydroxyphenoxy-3,5-di-iodophenyl)ethanol (IV) was prepared from ethyl 3,5-dinitrophenyl-4-methoxyphenoxyacetate (V). Reduction of the ester, first with hydrogen and then with lithium aluminium hydride, gave the diamino-alcohol (VI), which was tetrazotized; the tetrazonium salt was then treated with iodine. Acetylation of the resulting di-iodo-alcohol to facilitate chromatographic separation, then treatment with hydriodic acid, gave the substituted alkyl iodide (VII), and hydrolysis with sodium carbonate gave the alcohol (IV).



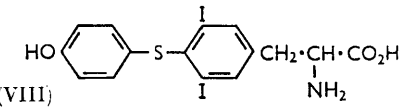
(IV: R = OH)
(VII: R = I)



(V)

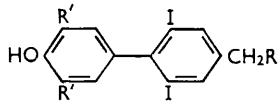


(VI)



(VIII)

The metabolic rôle of the amino-group in iodinated thyronines is still not clear; [9] we therefore prepared 3,5-di-iodo-*NN*-dimethyl-D-thyronine. The selective *N*-methylation of 3,5-di-iodo-D-thyronine was not attempted. Total methylation with diazomethane and subsequent hydrolysis of the methoxy-group were unsuccessful, but treating α-bromo-β-(4-hydroxy-3,5-dinitrophenyl)propionic acid [2] with dimethylamine gave a dimethylamino-acid that we assume, from its mode of formation and optical activity, to be of the D-series. The amino-acid was esterified and converted by known methods [4] into 3,5-di-iodo-*NN*-dimethyl-D-thyronine, but during the tetrazotization and introduction of iodine much of the product was lost in the acid medium (in the synthesis of di-iodothyronine the corresponding amino-group is already acetylated). The dimethylamino-acid has little or no thyroactivity.[6]



[IX: R = CH(NH$_2$)·CO$_2$H; R' = I]
(X: R = Cl; R' = H)
(XI: R = CO$_2$H; R' = H)

We prepared ethyl 3,5-dinitro-4-phenylthiophenylacetate in 60% yield by treating the pyridinium salt derived from ethyl 4-hydroxy-3,5-dinitrophenylacetate with benzenethiol. The same diphenyl sulphide was obtained, but only in 24% yield, by treating ethyl 4-chloro-3,5-dinitrophenylacetate with benzenethiol in alcoholic potassium hydroxide. The nitro-groups were catalytically reduced with hydrogen, despite the presence of sulphur in the molecule, and from the diamine we obtained 3,5-di-iodo-4-phenylthiophenylacetic acid in reasonable overall yield. The way was therefore clear for making the sulphur analogue (VIII) of 3,5-di-iodo-D-thyronine; it was indeed obtained, although the final demethylation

[7] Doskotch and Lardy, *J. Amer. Chem. Soc.*, 1958, **80**, 6230.
[8] Cookson and Green, *J.*, 1952, 827.
[9] Pitt-Rivers and Tata, "The Thyroid Hormones," Pergamon Press, London, 1959, p. 156.

gave only a 51% yield. The corresponding tri- and tetra-iodo-compounds were also prepared. Harington [10] made the DL-di- and tetra-iodo-compounds from *p*-methoxybenzenethiol and 3,4,5-tri-iodo-1-nitrobenzene by the acetamidomalonic ester method.

The biphenyl (IX) corresponding to DL-thyroxine was prepared by Barnes, Cookson, Dickson, Elks, and Poole [11] from 3,5-di-iodo-4-*p*-methoxyphenylbenzyl chloride (X); the benzyl chloride was made by treating the corresponding alcohol with thionyl chloride and was not isolated. We have obtained the pure benzyl chloride in 71% yield by treating the same alcohol with phosphorus pentachloride and have converted it into 3,5-di-iodophenyl-4-*p*-hydroxyphenylacetic acid (XI). The benzyl chloride, when treated with potassium cyanide, gave a nitrile that was converted into the demethylated phenylacetic acid by hydriodic acid. The corresponding dichloro-acid was prepared similarly; the di-iodo-acid was also converted into the tri- and the tetra-iodo-acid.

We were not able to obtain methyl 3,5-dinitrophenyl-4-*p*-methoxyphenylacetate by treating *p*-iodoanisole with methyl 4-chloro-3,5-dinitrophenylacetate, nor were we able to lengthen the side-chain of the corresponding benzoic acid by the Arndt–Eistert method.

We prepared 3,5-di-iodo-4-isopropoxyphenylacetic acid, a compound that contains a large part of the *p*-phenoxyphenylacetic acid skeleton, in order to establish whether or not the whole biphenyl ether system was essential. The compound, prepared by treating the hydroxy-acid with isopropyl bromide, proved to be inactive.

3,5-Di-iodo-3′,5′-dimethylthyronine is probably resistant to changes in oxidation state at the 3′- and the 5′-position. The L- and the DL-compound have been described.[11,12] We have now prepared the D-isomer. Our yields in the later stages (unlike those reported earlier) were particularly good, probably because we worked on a larger scale and so were able to carry out the critical tetrazotization and Sandmeyer reactions without excessive dilution.

Almost all the compounds that have been tested for thyroactivity contain a 4-hydroxy-group in ring B. We prepared 3,5-di-iodo-4-phenoxy-D-phenylalanine, a compound in which this group is absent, by the pyridinium salt method, but using phenol instead of *p*-methoxyphenol. The compound is effective in lowering blood cholesterol.[6]

3,5-Dichloro-4-(3-chloro-4-hydroxyphenoxy)benzoic acid and the corresponding 3,5,3′-tri-iodo-compound were prepared by partial halogenation of the dichloro- and di-iodo-compounds. 3,5-Dibromo-4-(*p*-hydroxyphenoxy)phenylacetic acid was prepared by the pyridinium salt method and converted into the tri- and tetra-bromo-compounds; similarly prepared were the corresponding tri- and tetra-chloro-acids and also 3,5-di-iodo-4-phenoxyphenylacetic acid.

An extensive study has been made in these laboratories of the effect on blood cholesterol of halogenated thyronines, particularly in the D-series. The nineteen D-thyronines and six L-thyronines shown in the Table have been prepared; some of these are already known in the DL-form. An account of some biological effects of the compounds described in this and earlier papers will be submitted for publication elsewhere.[6]

Series	Substituents				Series	Substituents			
	3	5	3′	5′		3	5	3′	5′
D and L	Cl	Cl	Cl	H	D and L	Br	Br	Br	H
D and L	Cl	Cl	Cl	Cl	D and L	Br	Br	Br	Br
D	Cl	Cl	Cl	I	D	Br	Br	Br	I
D	Cl	Cl	Br	H	D	Br	Br	I	H
D	Cl	Cl	Br	Br	D	Br	Br	I	I
D	Cl	Cl	I	H	D	I	I	Cl	H
D	Cl	Cl	I	I	D	I	I	Cl	Cl
D and L	Cl	I	I	I	D	I	I	Br	H
D and L	Br	Br	H	H	D	I	I	Br	Br
D	Br	Br	Cl	H					

[10] Harington, *Biochem. J.*, 1948, **43**, 434.
[11] Barnes, Cookson, Dickson, Elks, and Poole, *J.*, 1953, 1448.
[12] Bruice, Kharasch, and Winzler, *J. Org. Chem.*, 1953, **18**, 83.

Experimental

M. p.s are corrected. Rotations, except where stated otherwise, refer to 1 : 1 (v/v) N-HCl–EtOH solutions (*c* 1). Chromatography was carried out as described earlier.[13] Presence of solvent of crystallization indicated in molecular formulæ was confirmed by infrared spectroscopy.

5-Chloroveratronitrile.—5-Chloroveratraldehyde[14] (50·1 g.) in warm absolute ethanol (100 ml.) was treated with a warm solution of hydroxylamine hydrochloride (21 g.) in water (25 ml.), then with a solution of sodium hydroxide (15 g.) in water (20 ml.), and the mixture was set aside for 2½ hr. Ice (130 g.) was added and the mixture saturated with carbon dioxide. The white solid was washed with water, drained nearly dry, and warmed with acetic anhydride (150 ml.) for 30 min. The solution was poured into cold water (400 ml.), and the precipitated white solid washed with water and recrystallized from ethanol, giving needles of *5-chloroveratronitrile* (39·0 g., 79%), m. p. 101—102·5°. A second crop (6·4 g., 13%), m. p. 99·5—100·5°, was obtained from the mother-liquors. Further crystallization from ethanol gave needles, m. p. 101·5—102·5° (Found: C, 54·5; H, 3·8; Cl, 18·2; N, 6·6. $C_9H_8ClNO_2$ requires C, 54·7; H, 4·1; Cl, 17·9; N, 7·1%).

5-Chloroveratramide.—5-Chloroveratronitrile (72·5 g.) was added to a stirred mixture of hydrogen peroxide (100-vol.; 390 ml.) and water (1·3 l.). Then 10N-sodium hydroxide (46 ml.) was added and the mixture was heated slowly to 80° and stirred at that temperature for about 20 min. After it had cooled, the white solid was filtered off. Recrystallization from aqueous ethanol gave the *amide* (64·0 g., 81%), m. p. 144—145°. Further crystallization from 30% ethanol gave needles, m. p. 144—145° (Found: C, 50·3; H, 4·8; Cl, 16·4; N, 6·4. $C_9H_{10}ClNO_3$ requires C, 50·1; H, 4·7; Cl, 16·4; N, 6·5%).

3-Chloro-4,5-dimethoxyaniline.—Bromine (49·7 g.) was added to a stirred solution of sodium hydroxide (75·5 g.) in water (475 ml.) containing crushed ice (300 g.). The foregoing amide (64·0 g.) was added, with stirring, and the mixture heated at 75° for 30 min., then a solution of sodium hydroxide (151 g.) in water (150 ml.) was added and the solution kept at 80—90° for 1 hr. The solid *amine* which separated on cooling recrystallized from aqueous ethanol giving brown needles (42·2 g., 76%), m. p. 96·5—97·5°. Two more recrystallizations from aqueous ethanol gave needles, m. p. 97—97·5° (Found: C, 51·7; H, 5·7; Cl, 18·9; N, 7·3. $C_8H_{10}ClNO_2$ requires C, 51·2; H, 5·4; Cl, 18·9; N, 7·5%).

3-Chloro-4,5-dimethoxyphenol.—The preceding amine (25·4 g.) was diazotized. The reaction mixture was stirred for 15 min. and the yellow suspension poured into a stirred, boiling mixture of concentrated sulphuric acid (94 ml.) and water (80 ml.). The whole was cooled and the dark red solid which separated was boiled with ethanol (charcoal), then the solution was filtered, diluted with a little water, and set aside overnight. A little dark red gum was filtered off and the filtrate evaporated to dryness under reduced pressure. The solid residue was stirred with a little benzene and dried, leaving material (11·7 g., 46%) of m. p. 150°. A sample recrystallized from carbon tetrachloride gave off-white needles of the *phenol*, m. p. 148—149° (Found: C, 51·0; H, 5·0; Cl, 18·8; OMe, 32·4. $C_8H_9ClO_3$ requires C, 50·1; H, 4·8; Cl, 18·8; OMe, 32·9%).

*Ethyl Ester of N-Acetyl-4-(5-chloro-3,4-dimethoxyphenoxy)-3,5-dinitro-*D- *and* -L-*phenylalanine.*—The ethyl ester of *N*-acetyl-3,5-dinitro-D-tyrosine (30·7 g.) was warmed for 30 min. on the steam-bath with toluene-*p*-sulphonyl chloride (19·1 g.) and dry pyridine (155 ml.). The phenol mentioned above (8·8 g.) was added and the mixture refluxed for 1½ hr., cooled, acidified with 2N-hydrochloric acid, and extracted with chloroform. The extracts were washed with water, 2N-sodium hydroxide, and water, then dried ($CaCl_2$). The chloroform was distilled off leaving a dark red oil which was passed, in acetone, through an alumina column. The orange-yellow solution obtained was evaporated to dryness, leaving a yellow solid which crystallized from ethanol as yellow needles (16·9 g., 71%), m. p. 156—157°. Further crystallization gave pale yellow needles of the *ester*, m. p. 157—157·5°, $[\alpha]_D^{19}$ −29·8° (*c* 0·87 in chloroform) (Found: C, 49·0; H, 4·3; Cl, 6·8; N, 8·0. $C_{21}H_{22}ClN_3O_{10}$ requires C, 49·3; H, 4·3; Cl, 6·9; N, 8·2%). The L-*isomer*, prepared similarly, had m. p. 157—158°, $[\alpha]_D^{22}$ +30·0° (Found: C, 49·0; H, 4·3; Cl, 7·3; N, 8·5%).

*Ethyl Ester of N-Acetyl-3,5-diamino-4-(5-chloro-3,4-dimethoxyphenoxy)-*D- *and* -L-*phenylalanine.*—The preceding D-compound (22·3 g.) was reduced in methanol (2 l.) with hydrogen in the presence of 5% platinum–carbon (4·5 g.). Removal of the methanol left crystals, a small

[13] Varcoe and Warburton, *J.*, 1960, 2711.
[14] Raiford and Parry, *J. Org. Chem.*, 1942, **7**, 354.

portion of which, recrystallized from aqueous methanol, gave the D-*diamine* as colourless needles, m. p. 104—105° (Found: C, 53·7; H, 6·1; Cl, 7·7; N, 8·7. $C_{21}H_{26}ClN_3O_6,H_2O$ requires C, 53·7; H, 6·0; Cl, 7·6; N, 8·9%). The corresponding L-diamine did not crystallize; its *diacetyl derivative* had m. p. 185—186° (Found: C, 55·7; H, 6·0; Cl, 6·8; N, 8·0. $C_{25}H_{30}ClNO_8$ requires C, 56·0; H, 5·6; Cl, 6·6; N, 7·8%).

Ethyl Ester of N-*Acetyl*-3,5-*dichloro*-4-(5-*chloro*-3,4-*dimethoxyphenoxy*)-D- *and* -L-*phenylalanine*.—The D-diamine (from 22·3 g. of the dinitro-compound) was tetrazotized, and the tetrazonium salt decomposed with cuprous chloride. The combined chloroform solutions were washed with water, 2N-sodium hydroxide, and water, dried ($MgSO_4$), evaporated to asmall volume, and passed through a column of "Florisil." Evaporation of the eluate gave the D-trichloro-compound as an orange gum (15·1 g., 71%). The L-*trichloro-compound* was obtained in the same way, but with m. p. 140·5—141° (Found: C, 51·6; H, 4·7; Cl, 21·3; N, 2·7. $C_{21}H_{22}Cl_3NO_6$ requires C, 51·4; H, 4·5; Cl, 21·7; N, 2·8%).

3,5-*Dichloro*-4-(5-*chloro*-3,4-*dimethoxyphenoxy*)-D-*phenylalanine*.—The preceding crude D-ester (11·8 g.) was refluxed in acetic acid (60 ml.) and 5N-hydrochloric acid (120 ml.) for 2½ hr. A solid crystallized from the cooled solution and was collected. Its solution in pyridine was filtered and diluted at the b. p. with water. Crystals of 3,5-*dichloro*-4-(5-*chloro*-3,4-*dimethoxyphenoxy*)-D-*phenylalanine* separated (4·3 g.; m. p. 190—200°). A further 1·0 g. (total yield 50%) was obtained from the mother-liquors (Found: C, 45·9; H, 4·2; Cl, 24·1; N, 3·3. $C_{17}H_{16}Cl_3NO_5,H_2O$ requires C, 46·6; H, 4·1; Cl, 24·3; N, 3·2%).

3,5,3′-*Trichloro*-5′-*hydroxy*-D-*thyronine*.—The preceding compound (2·0 g.) was refluxed for 3 hr. with glacial acetic acid (40 ml.) and constant-boiling hydrobromic acid (40 ml.), and the solution was diluted with hot water (80 ml.), treated with charcoal, filtered, and brought to pH 4 with solid sodium carbonate. On cooling, 3,5,3′-*trichloro*-5′-*hydroxy*-D-*thyronine* crystallized as colourless needles (1·1 g., 59%), m. p. 204° (decomp.). Recrystallization from aqueous acetic acid gave needles, m. p. 215°. After drying at 155°/0·2 mm. this compound still contained some acetic acid (infrared) and was redissolved in 0·5N-hydrochloric acid and brought to pH 2 at the b. p. with N-sodium hydroxide, giving off-white needles, m. p. 222° (decomp.), $[\alpha]_D^{20}$ −28·2° (Found: C, 44·4; H, 3·1; Cl, 26·1. $C_{15}H_{12}Cl_3NO_5,H_2O$ requires C, 43·9; H, 3·4; Cl, 25·9%).

3,5,3′-*Trichloro*-5′-*hydroxy*-L-*thyronine*.—The ethyl ester of *N*-acetyl-3,5-dichloro-4-(5-chloro-3,4-dimethoxyphenoxy)-L-phenylalanine (1·8 g.) was refluxed for 4 hr. with acetic acid (18 ml.) and constant-boiling hydriodic acid (18 ml.). Removal of the acids under reduced pressure left a dark residue which was dissolved in water and treated with a little "Versene" and sodium hydrogen sulphite. The pH was adjusted to 4 with sodium acetate; a dark gum separated and later solidified. The solid was dissolved in 2N-hydrochloric acid, the solution boiled with charcoal and filtered, and the filtrate neutralized as before. The dark solid was redissolved in hydrochloric acid, and the solution again treated with "Versene" and sodium hydrogen sulphite, then neutralized. 3,5,3′-Trichloro-5′-hydroxy-L-thyronine was obtained as a dark grey solid (450 mg., 31%), m. p. 221—223° (decomp.) (Found: C, 45·7; H, 3·5; Cl, 24·4; N, 3·4. Calc. for $C_{15}H_{12}Cl_3NO_5$: C, 45·9; H, 3·1; Cl, 27·1; N, 3·6%). This compound, which was not quite pure, had an infrared spectrum similar to that of the D-compound, but its rotation could not be determined.

3,5-*Di-iodo*-4-p-*methoxyphenoxyacetophenone Oxime* (with Dr. A. C. RITCHIE).—Hydroxylamine hydrochloride (10·25 g.) in water (19·6 ml.) was added to a solution of sodium (3·36 g.) in ethanol (280 ml.). The precipitated sodium chloride was filtered off, and 3,5-di-iodo-4-*p*-methoxyphenoxycinnamic acid [8] (35 g.) added, then dioxan (84 ml.). The mixture was refluxed for 24 hr., then cooled, and the precipitate washed with water and alcohol, then dried at 60°, giving β-amino-β-(3,5-di-iodo-4-*p*-methoxyphenoxyphenyl)propionic acid (8·63 g., 24%), m. p. 230—232° (decomp.). The yellow filtrate from the reaction with hydroxylamine was concentrated under reduced pressure. Water (1·5 l.) was added and the mixture heated on the steam-bath under reduced pressure until all the alcohol had been removed. Filtration gave a pale yellow solid (24·7 g.), m. p. 156—160° (decomp.). This material, dissolved in benzene containing 5% of dioxan, was passed through a column of alumina and eluted with benzene containing 20% of ethanol. Evaporation of the eluate left a brown solid (14 g.). This crystallized from methanol (charcoal), giving almost colourless needles of 3,5-di-iodo-4-*p*-methoxyphenoxyacetophenone oxime (10·23 g., 36·5%), m. p. 180—182°. Cookson and Green [8] report m. p. 179—181°.

3,5-*Di-iodo*-4-p-*methoxyphenoxyacetophenone* (with Dr. A. C. RITCHIE).—The preceding

compound (12 g.) was refluxed with ethanol (120 ml.) and 10N-hydrochloric acid (24 ml.) for 1 hr. and the mixture cooled to room temperature, then refrigerated for 2½ hr. The solid was collected and washed with methanol, then with water until neutral, leaving the ketone (9·38 g., 81%), m. p. 138—143°. Cookson and Green [8] report m. p. 141—142°.

4-p-*Hydroxyphenoxy*-3,5-*di-iodoacetophenone* (with Dr. A. C. RITCHIE).—The preceding compound (9·25 g.) was refluxed in glacial acetic acid (36 ml.) and constant-boiling hydriodic acid (27 ml.) for 30 min., then cooled to room temperature and refrigerated for 1 hr. The yellow solid was collected, washed with a little acetic acid, then with water, and dissolved in methanol (170 ml.) containing a little benzene. Treatment with charcoal, filtration, and reduction of volume gave a solid, which was washed with methanol, leaving colourless 4-p-*hydroxyphenoxy*-3,5-*di-iodoacetophenone* (7·18 g.), m. p. 217—221° (Found: C, 34·7; H, 1·8; I, 51·9. $C_{14}H_{10}I_2O_3$ requires C, 35·0; H, 2·1; I, 52·8%).

3,5-*Di-iodo*-4-*isopropoxyphenylacetic Acid* (with Dr. A. C. RITCHIE).—4-Hydroxy-3,5-di-iodophenylacetic acid (9·95 g.) was dissolved in a solution of potassium hydroxide (12 g.) in water (48 ml.) and ethanol (100 ml.). Isopropyl bromide (40 ml.) was added and the mixture refluxed for 2 hr. Most of the ethanol was removed under reduced pressure and the solution diluted to about 400 ml. with water, extracted with ether, then acidified to pH 1. The oil which separated solidified in the refrigerator overnight and the solid was filtered off, washed well with water, then recrystallized from benzene and light petroleum (b. p. 60—80°) (charcoal), giving 3,5-*di-iodo*-4-*isopropoxyphenylacetic acid* (8·4 g., 76%), m. p. 129—133° (Found: C, 29·6; H, 2·75; I, 56·7. $C_{11}H_{12}I_2O_3$ requires C, 29·5; H, 2·7; I, 56·7%).

2-(3,5-*Diamino*-4-p-*methoxyphenoxyphenyl*)*ethanol*.—Ethyl 3,5-diamino-4-*p*-methoxyphenoxyphenyl acetate [15] (14 g.) was reduced in tetrahydrofuran with lithium aluminium hydride, giving the *alcohol* (8·5 g., 69%), m. p. 127·5—129° (from chloroform) (Found: C, 66·1; H, 6·7; N, 9·6. $C_{15}H_{18}N_2O_3$ requires C, 65·7; H, 6·6; N, 10·2%). The NN′-*diacetyl derivative* had m. p. 181—182·5° (Found: N, 7·5. $C_{19}H_{22}N_2O_5$ requires N, 7·8%).

3,5-*Di-iodo*-4-p-*methoxyphenoxyphenethyl Acetate*.—The preceding diamine (8·7 g.) was tetrazotized, and the tetrazonium salt decomposed with iodine in potassium iodide solution,[4] giving a gum, which was warmed for 1 hr. with acetic acid (50 ml.) and acetic anhydride (10 ml.). The cooled solution was poured into water and the *acetyl compound* separated (12·3 g., 72%; m. p. 95·5—98·5°) (Found: C, 38·5; H, 3·1; I, 47·4. $C_{17}H_{16}I_2O_4$ requires C, 37·9; H, 3·0; I, 47·2%).

4-p-*Hydroxyphenoxy*-3,5-*di-iodophenethyl Iodide*.—Demethylation of the preceding compound (12·3 g.) with hydriodic acid gave the *iodide* (11·8 g., 87%), m. p. 157·5—160·5° (Found: C, 28·8; H, 1·9; I, 64·5. $C_{14}H_{11}I_3O_2$ requires C, 28·4; H, 1·9; I, 64·3%).

4-p-*Hydroxyphenoxy*-3,5-*di-iodophenethyl Alcohol*.—The preceding compound was refluxed for 15 hr. with 10% sodium carbonate solution (150 ml.) and ethanol (190 ml.). The mixture was cooled and extracted three times with ether. The ether extracts were combined, washed with water, and dried (Na_2SO_4). Removal of the ether left an oil, which crystallized from benzene on addition of light petroleum (b. p. 40—60°). The *alcohol* (5·6 g., 69%) had m. p. 112—116° (Found: I, 53·7. $C_{14}H_{12}I_2O_3$ requires I, 52·7%).

NN-*Dimethyl*-3,5-*dinitro*-D-*tyrosine*.—α-Bromo-β-(4-hydroxy-3,5-dinitrophenyl)propionic acid [1] (10·0 g.) was dissolved in 25% (w/v) aqueous dimethylamine and left for 3 days. Most of the dimethylamine was then removed under reduced pressure and the solution cooled and made just acid with 2N-hydrochloric acid. The orange solid was dissolved in 0·4N-sodium hydroxide and the solution filtered, cooled, and brought to pH 4·5 with sodium acetate. NN-*Dimethyl*-3,5-*dinitro*-D-*tyrosine* separated as orange crystals (6·50 g., 73%), m. p. 250° (explodes) (Found: C, 43·6; H, 4·3; N, 13·8. $C_{11}H_{13}N_3O_7$ requires C, 44·1; H, 4·4; N, 14·0%).

The acid (41·0 g.) was refluxed for 6 hr. in ethanol while hydrogen chloride was passed in. The ethanol was removed and the residue dissolved in water (600 ml.) and ethanol (150 ml.). The solution was treated with charcoal and filtered, then neutralized with sodium acetate at the b. p. The *ethyl ester* separated as orange crystals (32·0 g., 76%), m. p. 193—197° (decomp.), $[\alpha]_D^{20}$ −72° (*c* 1 in dioxan containing 10% of 2N-hydrochloric acid) (Found: C, 46·9; H, 5·1; N, 12·2. $C_{13}H_{17}N_3O_7,\frac{1}{2}H_2O$ requires C, 46·5; H, 5·4; N, 12·5%).

Ethyl Ester of 4-p-*Methoxyphenoxy*-NN-*dimethyl*-3,5-*dinitro*-D-*phenylalanine*.—The preceding ester (5·00 g.) was warmed with toluene-*p*-sulphonyl chloride (3·26 g.) and pyridine (25 ml.) on the steam-bath for 30 min. *p*-Methoxyphenol (5·6 g.) was added and the mixture refluxed for

[15] Meltzer, Lustgarten, and Fischman, *J. Org. Chem.*, 1957, **22**, 1577.

1 hr. After cooling, the solution was treated with 2N-hydrochloric acid, then extracted with chloroform several times. The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated, leaving a residue which recrystallized from aqueous ethanol. The *diphenyl ether* separated as pale yellow needles (2·9 g., 44%), m. p. 87·5—89°, $[\alpha]_D^{20}$ −27° (*c* 1 in dioxan containing 10% of 2N-hydrochloric acid) (Found: C, 55·3; H, 5·0. $C_{20}H_{23}N_3O_8$ requires C, 55·4; H, 5·3%).

3,5,-*Di-iodo*-NN-*dimethyl*-D-*thyronine*.—The preceding compound (9·0 g.) was reduced in acetic acid (50 ml.) with hydrogen in the presence of 5% palladium–charcoal (1 g.), and the diamine solution tetrazotized and treated with iodine in potassium iodide.[4] The chloroform solutions were combined and washed with water containing sodium hydrogen sulphite, then dried ($MgSO_4$) and passed through a short column of " Florisil." The eluate was taken to dryness and the residue rechromatographed in 1 : 1 benzene–chloroform on " Florisil." The dark brown oil remaining after removal of the solvent was dissolved in benzene. Addition of light petroleum caused more dark material to separate. The solution was decanted and evaporated to dryness. The oil remaining did not crystallize and was demethylated with hydriodic acid, giving the *amino-acid* (1·43 g., 12·5%) as colourless needles, m. p. 255—260° (decomp.), $[\alpha]_D^{20}$ −18° (Found: C, 36·4; H, 3·3; N, 2·4. $C_{17}H_{17}I_2NO_4$ requires C, 37·0; H, 3·1; N, 2·5%).

Ethyl 4-*Chloro*-3,5-*dinitrophenylacetate*.—Diethylaniline (45 ml.) was added dropwise to a solution of ethyl 4-hydroxy-3,5-dinitrophenylacetate [15] (25 g.) in phosphoryl chloride (54 ml.), and the solution heated on the steam-bath for 1¼ hr., then cooled. Unchanged phosphoryl chloride was destroyed with ethanol. The mixture was evaporated under reduced pressure and the residue extracted with chloroform. The chloroform was washed with 2N-hydrochloric acid, then with water, dried (Na_2SO_4), and evaporated, leaving a dark gum which was passed in benzene through alumina. Evaporation left an oil which was crystallized from ethanol, giving *ethyl* 4-*chloro*-3,5-*dinitrophenylacetate* (12·0 g., 41%), m. p. 71—73° (Found: C, 41·6; H, 2·9; Cl, 12·3; N, 9·6. $C_{10}H_9ClN_2O_6$ requires C, 41·8; H, 3·1; Cl, 12·0; N, 9·7%).

Ethyl 3,5-*Dinitro*-4-*phenylthiophenylacetate*.—(a) *From ethyl* 4-*chloro*-3,5-*dinitrophenylacetate*. The chloro-compound (1·0 g.) was refluxed for 30 min. with benzenethiol (0·36 ml.) and potassium hydroxide (214 mg.) in 95% ethanol (15 ml.). The mixture was cooled, diluted with water, and extracted with benzene. The benzene extract was washed with 2N-sodium hydroxide (30 ml.), then with water, dried, and evaporated. The residual oil was chromatographed on alumina. Elution with benzene gave first a dark red oil, then a pale yellow oil. The latter crystallized from 95% ethanol to give 300 mg. (24%) of a product, m. p. 51—53·5°, identical (infrared) with that described in (b).

(b) *From ethyl* 3,5-*dinitro*-4-*toluene*-p-*sulphonyloxyphenylacetate*. This sulphonate [15] (9·8 g.) in dry benzene (40 ml.) was refluxed for 30 min. with dry pyridine (6 ml.), the mixture cooled, and the benzene decanted. The residual gum, dissolved in chloroform (50 ml.) and pyridine (6 ml.), was refluxed for 16 hr. with benzenethiol (8·1 ml.). The mixture was diluted with chloroform and the solution washed with 2N-hydrochloric acid, 2N-sodium hydroxide, and water, dried (Na_2SO_4), and evaporated. The residual gum was dissolved in light petroleum (b. p. 60—80°) containing a trace of benzene and chromatographed on alumina (23 × 3 cm.). Elution with light petroleum containing 15% of benzene gave diphenyl disulphide, m. p. 57—59°. Further elution with benzene gave an orange oil (5·3 g.), which crystallized from alcohol giving *ethyl* 3,5-*dinitro*-4-*phenylthiophenylacetate* (5·0 g., 60%), m. p. 53—55° (Found: C, 52·7; H, 3·5; N, 8·4; S, 9·4. $C_{16}H_{14}N_2O_6S$ requires C, 53·0; H, 3·9; N, 7·9; S, 8·8%).

Ethyl 3,5-*Diamino*-4-*phenylthiophenylacetate*.—The preceding ester (3·0 g.) in acetic acid (25 ml.) was shaken in hydrogen in the presence of 5% palladium–charcoal (400 mg.). No hydrogen was taken up, so more catalyst (400 mg.) was added and shaking resumed. Hydrogenation was then complete in 12 hr. The catalyst was filtered off in nitrogen and the filtrate evaporated to dryness under reduced pressure. The residual gum crystallized from alcohol, giving the diamine, m. p. 87—89°, which rapidly darkened. The *diacetyl derivative* had m. p. 176—177° (Found: C, 62·9; H, 5·7; N, 7·1; S, 8·4. $C_{20}H_{22}N_2O_4S$ requires C, 62·3; H, 5·7; N, 7·3; S, 8·3%).

Ethyl 3,5-*Di-iodo*-4-*phenylthiophenylacetate*.—The diamine prepared from ethyl 3,5-dinitro-4-phenylthiophenylacetate (10 g.) was tetrazotized and the tetrazonium solution treated with iodine in potassium iodide solution.[4] The combined chloroform extracts were washed with sodium hydrogen sulphite solution, then with water, dried (Na_2SO_4), and evaporated. The

residual gum was twice chromatographed in benzene on alumina and eluted with benzene. Removal of the benzene gave a pale yellow gum (9·05 g.) which crystallized from alcohol, giving *ethyl* 3,5-*di-iodo*-4-*phenylthiophenylacetate* (7·4 g., 50% from the dinitro-compound), m. p. 111—113° (Found: C, 37·0; H, 2·5; S, 6·3. $C_{16}H_{14}I_2O_2S$ requires C, 36·7; H, 2·7; S, 6·1%).

3,5-*Di-iodo*-4-*phenylthiophenylacetic Acid*.—6N-Hydrochloric acid (75 ml.) was added to a hot solution of the preceding ester (5·5 g.) in glacial acetic acid (120 ml.). The mixture was refluxed for 1½ hr. On cooling, the solution deposited 3,5-*di-iodo*-4-*phenylthiophenylacetic acid* (4·6 g., 88%), m. p. 187—189° (Found: C, 33·9; H, 2·0; I, 51·3; S, 6·5. $C_{14}H_{10}I_2O_2S$ requires C, 33·8; H, 2·0; I, 51·2; S, 6·4%).

Ethyl Ester of N-*Acetyl*-4-p-*methoxyphenylthio*-3,5-*dinitro*-D-*phenylalanine*.—*N*-Acetyl-3,5-dinitro-D-tyrosine ethyl ester (10·0 g.) was converted into the toluene-*p*-sulphonate.[4] This was refluxed in benzene (44 ml.) for 30 min. with pyridine (6·8 ml.), then cooled to 0° and the benzene was decanted. The residual gum, dissolved in chloroform (50 ml.) and pyridine (7·4 ml.), was refluxed for 16 hr. with *p*-methoxybenzenethiol (8·2 g., 2 equiv.). The mixture was diluted with chloroform (150 ml.) and washed with 2N-hydrochloric acid, 2N-sodium hydroxide, and water, dried ($MgSO_4$), and evaporated. The residual solid recrystallized from benzene–light petroleum (b. p. 60—80°), giving the pale yellow *ester* (10·0 g., 74%), m. p. 146—150° (Found: C, 51·8; H, 4·7; N, 9·4; S, 7·1. $C_{20}H_{21}N_3O_8S$ requires C, 51·8; H, 4·5; N, 9·1; S, 6·9%).

Ethyl Ester of N-*Acetyl*-3,5-*diamino*-4-p-*methoxyphenylthio*-D-*phenylalanine*.—Hydrogenation of the preceding ester (15·0 g.) gave the diamine as a pale brown solid (10·8 g., 83%). The *diacetyl derivative* had m. p. 217·5—220·5 (Found: C, 59·0; H, 5·9; N, 9·1; S, 6·1. $C_{24}H_{29}N_3O_6S$ requires C, 59·2; H, 5·9; N, 8·6; S, 6·6%).

Ethyl Ester of N-*Acetyl*-3,5-*di-iodo*-4-p-*methoxyphenylthio*-D-*phenylalanine*.—The preceding diamine (10·0 g.) was tetrazotized and treated with iodine in potassium iodide,[4] giving the *di-iodo-ester* (6·3 g., 41%), m. p. 148—150° (from ethanol) (Found: C, 38·3; H, 3·6; I, 40·0. $C_{20}H_{21}I_2NO_4S$ requires C, 38·4; H, 3·4; I, 40·6%).

4-p-*Hydroxyphenylthio*-3,5-*di-iodo*-D-*phenylalanine*.—The preceding ester (15·4 g.), refluxed for 2 hr. with 6N-hydrobromic acid (300 ml.) in glacial acetic acid (300 ml.), gave 4-p-*hydroxyphenylthio*-3,5-*di-iodo*-D-*phenylalanine* (6·32 g., 51%), m. p. 239—244° (decomp.), $[\alpha]_D^{20}$ −24·5° (*c* 2) (Found: C, 32·8; H, 2·6; I, 45·0. $C_{15}H_{13}I_2NO_3S$ requires C, 33·3; H, 2·4; I, 46·9%).

4-(4-*Hydroxy*-3,5-*di-iodophenylthio*)-3,5-*di-iodo*-D-*phenylalanine*.—The di-iodo-compound (2·0 g.) was dissolved in aqueous 33% ethylamine (50 ml.), and a N-solution of iodine in potassium iodide (22 ml., 50% excess) was added to the stirred solution during 45 min. at 25—30°. The solution was left overnight, then evaporated to dryness under reduced pressure. The residue was treated with charcoal and a little sodium hydrogen sulphite in dilute hydrochloric acid and ethanol and neutralized at the b. p. with sodium acetate. The crystalline *tetra-iodo-acid* was filtered off and washed with ethyl acetate until almost colourless [1·5 g., 51%; m. p. 230—233° (decomp.)] (Found: C, 23·2; H, 1·8; I, 60·2. $C_{15}H_{11}I_4NO_3S$,½EtOH requires C, 23·5; H, 1·7; I, 62·3%).

4-(4-*Hydroxy*-3-*iodophenylthio*)-3,5-*di-iodo*-D-*phenylalanine*.—The di-iodo-compound (2·0 g.) was dissolved in aqueous 33% ethylamine (50 ml.), and a N-solution of iodine in potassium iodide (8·0 ml.) added to the stirred solution during 45 min. at 25—30°. The mixture was worked up as above, giving the tri-iodo-acid (0·5 g., 20%). This contained <3% of the di-iodo- and <2% of the tetraiodo-compound (Found: C, 28·1; H, 2·3; I, 52·1; N, 1·9. Calc. for $C_{15}H_{12}I_3NO_3S$,EtOH: C, 28·6; H, 2·5; I, 53·4; N, 1·9%).

4-*Chloromethyl*-2,6-*di-iodo*-4′-*methoxybiphenyl*.—4-Hydroxymethyl-2,6-di-iodo-4′-methoxybiphenyl [11] (2·34 g.) in chloroform (14 ml.) was cooled to 0°. Phosphorus pentachloride (1·25 g.) was added in small portions with stirring which was continued at room temperature for a further 90 min. The solution was washed with water, dilute sodium hydrogen carbonate solution, then water, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting oil crystallized from alcohol, giving 4-chloromethyl-2,6-di-iodo-4′-methoxybiphenyl (1·75 g., 72%), m. p. 108—109°.

4-*Cyanomethyl*-2,6-*di-iodo*-4′-*methoxybiphenyl*.—The preceding compound (10·32 g.), in ethanol (100 ml.) containing a trace of potassium iodide, was mixed with potassium cyanide (2·5 g.) in water (5 ml.) and refluxed for 4½ hr. The solution was concentrated under reduced pressure and diluted with water, giving 4-cyanomethyl-2,6-di-iodo-4′-methoxybiphenyl (10·0 g., 99%), with no definite m. p. (Found: C, 39·1; H, 2·6. Calc. for $C_{15}H_{11}I_2NO$: C, 38·0; H, 2·3%). This material could not be recrystallized.

3,5-*Di-iodophenyl*-4-p-*hydroxyphenylacetic Acid*.—The preceding compound (10·0 g.) was

refluxed for 1½ hr. with glacial acetic acid (18 ml.) and constant-boiling hydriodic acid (90 ml.). Some of the solvent was removed under reduced pressure and aqueous sodium hydrogen sulphite solution added. The brown product which separated was dissolved in the minimum volume of hot acetone and reprecipitated with dilute aqueous sodium hydrogen sulphite, giving 10·12 g. of pale yellow material. This was dissolved in alcohol (charcoal), filtered, and taken to dryness, then crystallized from benzene containing a little acetone, giving an *acid* (7·2 g., 72%), m. p. 238—242° (Found: C, 35·1; H, 2·2; I, 52·9. $C_{14}H_{10}I_2O_3$ requires C, 35·0; H, 2·1; I, 52·9%).

3,5-*Di-iodophenyl*-4-(4-*hydroxy*-3,5-*di-iodophenyl*)*acetic Acid*.—The preceding compound (0·5 g.) was dissolved in 33% (w/v) aqueous ethylamine (10 ml.) and a 0·99N-solution of iodine in potassium iodide (6·3 ml.) was added to the stirred solution during 20 min. at 28—30°. After 1 hr. the solution was made just acid with hydrochloric acid, and the precipitate filtered off, washed with water, dried (0·77 g.), and recrystallized from acetic acid, giving the *tetraiodo-acid* (0·61 g., 80%), m. p. 232—233° (decomp.) (Found: C, 23·3; H, 1·2; I, 69·8. $C_{14}H_8I_4O_3$ requires C, 23·0; H, 1·1; I, 69·4%).

3,5-*Di-iodophenyl*-4-(4-*hydroxy*-3-*iodophenyl*)*acetic Acid*.—The di-iodo-acid (6·0 g.) was dissolved in 33% (w/v) aqueous ethylamine (50 ml.) and a 0·99N-solution of iodine in potassium iodide (29·0 ml.) added during 35 min. at 29°. The solution was worked up as in the last experiment, giving the tri-iodo-acid (2·28 g., 30%), m. p. 210—211° (decomp.) (Found: C, 28·4; H, 1·95; I, 62·0. Calc. for $C_{14}H_9I_3O_3$: C, 27·75; H, 1·5; I, 62·8%). This material contained less than 5% each of di-iodo- and tetraiodo-acid.

4-*Acetoxymethyl*-2,6-*dichloro*-4′-*methoxybiphenyl*.—2,6-Diamino-4-hydroxymethyl-4′-methoxybiphenyl (5·0 g.) was tetrazotized, and the tetrazonium salt decomposed with cuprous chloride, giving a dark red oil. This was heated on the steam-bath for 1 hr. with acetic anhydride. Excess of acetic anhydride was removed under reduced pressure and the residue (5·64 g.) in benzene was chromatographed on " Florisil " (100 g.). Evaporation of the eluate and treatment of the product with charcoal in ethanol gave 5·13 g. of crude solid. 1·5 g. of this material were crystallized from aqueous ethanol, then from isopropyl ether, giving 4-*acetoxymethyl*-2,6-*dichloro*-4′-*methoxybiphenyl* (0·44 g., 22%), m. p. 57—59° (Found: C, 59·3; H, 4·6; Cl, 21·65. $C_{16}H_{14}Cl_2O_3$ requires C, 59·1; H, 4·3; Cl, 21·8%). The product also crystallized from isopropyl ether in 35% yield, giving material of m. p. 52—55°.

2,6-*Dichloro*-4-*hydroxymethyl*-4′-*methoxybiphenyl*.—Alkaline hydrolysis of the preceding compound, m. p. 52—55° (9·3 g.), gave 8·1 g. (100%) of a straw-coloured oil.

2,6-*Dichloro*-4-*chloromethyl*-4′-*methoxybiphenyl*.—Crude 2,6-dichloro-4-hydroxymethyl-4′-methoxybiphenyl (8·0 g.) in chloroform (180 ml.) was stirred, and phosphorus pentachloride (8·0 g., added at 0—5°. The solution was left at room temperature for 1½ hr., then washed with water and dilute sodium hydrogen carbonate solution, dried, and evaporated under reduced pressure. The resulting oil crystallized from ethanol, giving 2,6-*dichloro*-4-*chloromethyl*-4′-*methoxybiphenyl* (5·92 g., 70%), m. p. 82—83°. A sample recrystallized from ethanol had m. p. 86—87° (Found: C, 56·1; H, 3·7; Cl, 35·1. $C_{14}H_{11}Cl_3O$ requires C, 55·75; H, 3·7; Cl, 35·3%).

2,6-*Dichloro*-4-*cyanomethyl*-4′-*methoxybiphenyl*.—The preceding compound (m. p. 82—83°) (1·0 g.) was dissolved in ethanol (10 ml.) containing a trace of potassium iodide and refluxed for 4½ hr. with potassium cyanide (0·36 g.) in water (0·7 ml.). Some of the solvent was removed under reduced pressure, then the solution was diluted with water and extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure; leaving a straw-coloured oil (0·97 g.).

2,6-*Dichloro*-4′-*hydroxy*-4-*biphenylylacetic Acid*.—The preceding compound (5·48 g.), demethylated with hydriodic acid, underwent simultaneous hydrolysis and gave the named *biphenylylacetic acid* (2·89 g., 52%), m. p. 182—186° (Found: C, 56·65; H, 3·4; Cl, 23·9. $C_{14}H_{10}Cl_2O_3$ requires C, 56·6; H, 3·4; Cl, 23·9%).

3,5-*Dichloro*-4-(3-*chloro*-4-*hydroxyphenoxy*)*benzoic Acid*.—3,5-Dichloro-4-*p*-hydroxyphenoxybenzoic acid (5·00 g.) was treated in glacial acetic acid (750 ml.) with a freshly prepared solution of chlorine (1·19 g.) in glacial acetic acid (26 ml.) in one portion with vigorous stirring. After 20 min. (negative starch–iodide reaction) the acid was removed under reduced pressure and the residue dissolved in acetic acid and filtered. Water was added to the hot solution until precipitation started, the solution was cooled, and a little solid was filtered off. The hot filtrate was again diluted with water and cooled. The colourless trichloro-acid separated (4·7 g., 80%), having m. p. 180—184° (Found: C, 46·7; H, 2·3; Cl, 30·9. Calc. for $C_{13}H_7Cl_3O_4$: C, 46·7; H, 2·1; Cl, 31·9%). This material contained <5% each of the dichloro- and tetrachloro-acid.

4-(4-*Hydroxy*-3-*iodophenoxy*)-3,5-*di-iodobenzoic Acid*.—4-*p*-Hydroxyphenoxy-3,5-di-iodobenzoic acid [16] (10·0 g.) was dissolved in aqueous 33% ethylamine (100 ml.) and a N-solution of iodine in potassium iodide (42 ml.) added, with stirring, during 1½ hr. at 25—30°. Ice (200 g.) was then added and the mixture shaken with ethyl acetate. Concentrated hydrochloric acid (60 ml.) was added and the mixture shaken again. The organic layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined extracts (total vol. 300 ml.) were washed with sodium chloride solution, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was dissolved in ethanol (30 ml.), and a solution of diethanolamine (2·65 g.) in ethanol (10 ml.) added. The mixture was refrigerated overnight and the precipitated diethanolamine salt recrystallized from ethanol.

This salt was decomposed in water with hydrochloric acid and the organic acid extracted into ethyl acetate. The extract was washed with sodium chloride solution, dried ($MgSO_4$), and evaporated under reduced pressure. The *tri-iodo-acid* separated and was recrystallized from aqueous ethanol, giving 4·4 g. (35%) of material, m. p. 259—261·5° (Found: C, 25·5; H, 1·2; I, 62·7. $C_{13}H_6I_3O_4$ requires C, 25·7; H, 1·0; I, 62·8%).

3,5-*Dibromo*-4-p-*methoxyphenoxyphenylacetic Acid*.—3,5-Dinitro-4-*p*-methoxyphenoxyphenylacetic acid (9·8 g.) was reduced and the diamine tetrazotized as described by Meltzer *et al.*[15] The tetrazonium solution was added in a thin stream to a stirred solution of cuprous bromide (20 g.) in aqueous 50% w/v hydrobromic acid (300 ml.) containing chloroform (200 ml.). Stirring was continued for 45 min., water (300 ml.) added, the chloroform separated, and the aqueous layer again extracted with chloroform. The combined chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue (11 g.) was dissolved in cold benzene, and light petroleum was added; the solution was poured off from a dark oil, and this process repeated until a pale yellow solution was obtained. The solution was evaporated to dryness and the residue crystallized from aqueous acetic acid. The *dibromo-acid* (7·8 g., 78%) separated as off-white crystals, m. p. 142—143·5° (Found: Br, 37·6. $C_{15}H_{12}Br_2O_4$ requires Br, 38·4%).

3,5-*Dibromo*-4-(p-*hydroxyphenoxy*)*phenylacetic Acid*.—The preceding compound (9·1 g.) was refluxed in acetic acid saturated with hydrogen bromide (250 ml.) for 1¾ hr. The solvent was removed under reduced pressure and the residue boiled in ethanol (150 ml.) with charcoal. The filtered solution was evaporated, leaving an almost colourless solid, which recrystallized from benzene containing a little acetone. The *dibromo-acid* (6·2 g.) had m. p. 215—217° (Found: Br, 39·0. $C_{14}H_{10}Br_2O_4$ requires Br, 39·7%).

3,5-*Dichloro*-4-(3-*chloro*-4-*hydroxyphenoxy*)*phenylacetic Acid*.—3,5-Dichloro-4-*p*-hydroxyphenoxyphenylacetic acid (0·962 g.) in acetic acid (50 ml.) was treated dropwise with a 0·0905M-solution of chlorine in carbon tetrachloride (7·00 ml., 1·03 equiv.) with stirring at room temperature. After 2 hr. the solvent was removed under reduced pressure and the residual oil crystallized from benzene–light petroleum, giving the trichloro-acid (1·00 g., 93%), m. p. 146—148° (Found: C, 48·5; H, 2·7; Cl, 30·5. Calc. for $C_{14}H_9Cl_3O_4$: C, 48·4; H, 2·6; Cl, 30·6%). This material contained not more than 6% and 3% respectively of the di- and tetra-chloro-compounds.

3,5-*Dichloro*-4-(3,5-*dichloro*-4-*hydroxyphenoxy*)*phenylacetic Acid*.—Treatment of the dichloro-acid with 2·5 equiv. of chlorine as in the preceding preparation gave a solid, which was recrystallized twice from benzene–light petroleum. The *tetrachloro-acid* separated as prisms, m. p. 180—185° (23% yield) (Found: C, 44·3; H, 2·3; Cl, 37·4. $C_{14}H_8Cl_4O_4$ requires C, 44·0; H, 2·1; Cl, 37·2%).

3,5-*Dibromo*-4-(3-*bromo*-4-*hydroxyphenoxy*)*phenylacetic Acid*.—Treatment of the dibromo-acid with 0·99 equiv. of bromine in acetic acid as in the preceding preparation gave the *tribromo-acid*, m. p. 166—168° (from benzene–light petroleum) (83%) (Found: C, 35·0; H, 2·0; Br, 50·1. $C_{14}H_9Br_3O_4$ requires C, 35·0; H, 1·9; Br, 50·0%). This material contained <1% and <2% respectively of the dibromo- and tetrabromo-acid.

3,5-*Dibromo*-4-(3,5-*dibromo*-4-*hydroxyphenoxy*)*phenylacetic Acid*.—The dibromo-acid (0·50 g.) in acetic acid (50 ml.) was treated with bromine in acetic acid (4·4 ml.; 10% w/v solution; 2·2 equiv.) at room temperature, with stirring, and left overnight. More bromine in acetic acid (2·0 ml.; 10% solution) was added, and the mixture left at 50—60° for 8 hr., then at room temperature overnight. The solvent was removed and the residue recrystallized from acetone and benzene, giving almost colourless needles (300 mg., 52%), m. p. 200—203°, of the *product* (Found: C, 29·95; H, 1·4; Br, 56·9. $C_{14}H_8Br_4O_4$ requires C, 30·0; H, 1·4; Br, 57·2%).

[16] Clayton, Green, and Hems, *J.*, 1951, 2467.

Ethyl Ester of N-*Acetyl*-3,5-*dinitro*-4-*phenoxy*-D-*phenylalanine*.—This *compound*, prepared by methods similar to those used for the L-compound,[17] had m. p. 139·5—141°, $[\alpha]_D^{21}$ −45·3° (Found: N, 10·1. $C_{19}H_{19}N_3O_8$ requires N, 10·1%). For the L-compound, Barnes *et al.*[17] report m. p. 136—137°, $[\alpha]_D^{22}$ +44·9°.

3,5-*Di-iodo*-4-*phenoxy*-D-*phenylalanine*.—The preceding compound was reduced, and the diamine (not isolated) converted by known methods [17] into the *di-iodo-compound*, m. p. 249—250° (decomp.), $[\alpha]_D^{22}$ −29·7° (Found: C, 35·1; H, 2·6; N, 2·6; I, 49·3. $C_{15}H_{13}I_2NO_4$ requires C, 35·4; H, 2·6; N, 2·8; I, 49·9%). For the DL-compound, Barnes *et al.*[17] report m. p. 237—238°.

Ethyl Ester of N-*Acetyl*-3,5-*dibromo*-4-p-*methoxyphenoxy*-D- *and* -L-*phenylalanine*.—*N*-Acetyl-3,5-diamino-4-*p*-methoxyphenoxy-L-phenylalanine ethyl ester (19·3 g.) was tetrazotized as described by Chalmers *et al.*[4] The tetrazonium solution was added in a slow stream to a stirred solution of cuprous bromide (24 g.) in aqueous 50% w/v hydrobromic acid (320 ml.) containing chloroform (200 ml.). The mixture was worked up as above, and the residual brown gum (26·1 g.) recrystallized from isopropyl alcohol (18 ml.), giving the *dibromo-ester* (21·1 g., 82%), m. p. 113—115° (Found: Br, 30·65; N, 3·05. $C_{20}H_{21}Br_2NO_5$ requires Br, 31·0; N, 2·7%). The D-*compound*, prepared similarly, had m. p. 112·5—115° (Found: Br, 30·9%).

3,5-*Dibromo*-D- *and* -L-*thyronine*.—The preceding D-compound (1·0 g.) was demethylated with hydriodic acid, giving colourless 3,5-*dibromo*-D-*thyronine* (0·63 g., 75%), m. p. 262—265° (decomp.), $[\alpha]_D^{22}$ −30·5° (Found: N, 3·2. $C_{15}H_{13}Br_2NO_4$ requires N, 3·25%). The L-*amino-acid*, prepared similarly, had m. p. 262—265° (decomp.), $[\alpha]_D^{20}$ +29·9° (Found: C, 41·7; H, 3·2. $C_{15}H_{13}Br_2NO_4$ requires C, 41·7; H, 3·0%).

3,5,3′-*Tribromo*-D- *and* -L-*thyronine*.—3,5-Dibromo-D-thyronine (8·0 g.) in glacial acetic acid (370 ml.) and 2N-hydrochloric acid (185 ml.) was stirred and treated at room temperature with bromine (2·85 g.) in acetic acid (28 ml.). After 30 min. the acids were removed and the residue crystallized twice from 2N-hydrochloric acid. The hydrochloride in hot 70% ethanol was neutralized with sodium acetate solution. 3,5,3′-*Tribromo*-D-*thyronine* separated (4·27 g., 45%), having m. p. 239—245°, $[\alpha]_D^{20}$ −28° (Found: C, 35·1; H, 2·6; Br, 47·0. $C_{15}H_{12}Br_3NO_4$ requires C, 35·3; H, 2·3; Br, 47·0%). 3,5,3′-*Tribromo*-L-*thyronine*, prepared similarly, had m. p. 233—234°, $[\alpha]_D^{20}$ +28° (Found: Br, 47·1%).

3,5,3′,5′-*Tetrabromo*-D- *and* -L-*thyronine*.—3,5,-Dibromo-D-thyronine (5·7 g.) in acetic acid (120 ml.) was treated with bromine (4·2 g.) in acetic acid (40 ml.). Removal of solvent left a residue shown by chromatography to contain some tribromothyronine. The residue was dissolved in glacial acetic acid (100 ml.), and bromine (1·6 g.) in acetic acid (16 ml.) added, at 100°, to the stirred solution. The solution was allowed to cool overnight, the solvent removed, and the residue dissolved in 70% ethanol. Addition of sodium acetate solution at the b. p. gave 3,5,3′,5′-*tetrabromo*-D-*thyronine* (3·4 g., 35%), m. p. 207—211°, $[\alpha]_D^{20}$ −11·5° (*c* 1 in dioxan containing 10% of 2N-hydrochloric acid) (Found: N, 2·2; Br, 54·5. $C_{15}H_{11}Br_4NO_4$ requires N, 2·4; Br, 54·4%). 3,5,3′,5′-*Tetrabromo*-L-*thyronine*, prepared similarly, was obtained as the hydrate, m. p. 233—236°, $[\alpha]_D^{20}$ +10° (Found: Br, 52·3. $C_{15}H_{11}Br_4NO_4,H_2O$ requires Br, 52·7%).

3,5,3′-*Trichloro*-D- *and* -L-*thyronine*.—3,5-Dichloro-D-thyronine (11·2 g.) was dissolved in glacial acetic acid (1 l.) by passing in a little hydrogen chloride, and a freshly prepared solution of chlorine (2·33 g.) in acetic acid (70 ml.) was added, with shaking, during 2 min. After 30 min. at room temperature (negative starch–iodide reaction) the acids were removed and the residue boiled in 2N-hydrochloric acid (390 ml.) with charcoal and filtered. The filtrate, on cooling, deposited the hydrochloride. This was dissolved in 2N-hydrochloric acid (196 ml.), and the solution brought at the b. p. to pH 5 with sodium acetate. 3,5,3′-*Trichloro*-D-*thyronine* (10·0 g., 81%) separated as colourless needles, m. p. 238—241°, $[\alpha]_D^{20}$ −36° (Found: C, 47·5; H, 3·6; Cl, 27·7; N, 3·8. $C_{15}H_{12}Cl_3NO_4$ requires C, 47·8; H, 3·2; Cl, 28·4; N, 3·7%). This material contained <2% each of dichloro- and tetrachloro-thyronine. 3,5,3′-*Trichloro*-L-*thyronine*, prepared similarly, had m. p. 244—247°, $[\alpha]_D^{20}$ +33° (Found: Cl, 28·4%).

3,5,3′,5′-*Tetrachloro*-D-*thyronine*.—3,5-Dichloro-D-thyronine (1·3 g.) was dissolved in glacial acetic acid (50 ml.) by passing in a little hydrogen chloride, and a freshly prepared solution of chlorine (0·27 g.) in acetic acid (16 ml.) added, with shaking, during 2 min. The solution was left for 1½ hr., then cooled to 8°. Chlorine was passed in slowly, with stirring, for ½ hr., the hydrochloride separating. The solution was then set aside for ½ hr., next air was bubbled through it, and the cooling-bath removed. When no more chlorine was present the precipitate was collected and dissolved in 0·5N-hydrochloric acid; sodium acetate was added to the boiling

[17] Barnes, Elks, Stephens, and Waller, *J.*, 1953, 764.

solution until the pH was 5. 3,5,3′,5′-*Tetrachloro*-D-*thyronine* (0·89 g., 57%) separated as colourless crystals, m. p. 240° (decomp.), $[\alpha]_D^{20}$ −32·2° (Found: C, 43·6; H, 3·1; Cl, 34·1; N, 3·4. $C_{15}H_{11}Cl_4NO_4$ requires C, 43·8; H, 2·7; Cl, 34·5; N, 3·4%). 3,5,3′,5′-*Tetrachloro*-L-*thyronine*, obtained similarly, had m. p. 233—234·5°, $[\alpha]_D^{20}$ +31° (Found: Cl, 34·3%).

3,5,3′-*Trichloro*-5′-*iodo*-D-*thyronine*.—3,5,3′-Trichloro-D-thyronine (4·0 g.) in aqueous 33% w/v ethylamine (100 ml.) was stirred and treated at 25—30° with a 1·05N-solution of iodine in potassium iodide (30 ml.) during 1 hr. After 1 hr. more the pH was adjusted to 5 with 10N-hydrochloric acid. The hydrochloride recrystallized from a little 2N-hydrochloric acid (charcoal), and the product was dissolved in 0·5N-hydrochloric acid and neutralized at the b. p. with aqueous sodium acetate. 3,5,3′-Trichloro-5′-iodo-D-thyronine separated (2·1 g., 39%), having m. p. 206—208° (Found: C, 36·4; H, 2·7; I, 24·4. Calc. for $C_{15}H_{11}Cl_3INO_4$: C, 35·8; H, 2·2; I, 25·3%).

3′-*Bromo*-3,5-*dichloro*-D-*thyronine*.—3,5-Dichloro-D-thyronine (1·0 g.), dissolved in acetic acid (50 ml.) containing a little dry hydrogen chloride, was treated at room temperature with bromine (0·47 g.) in acetic acid (7·4 ml.). After 16 hr. the solvent was removed, the residue dissolved in boiling aqueous ethanol, and sodium acetate solution added. The *bromo-compound* separated (1·14 g., 92%), having m. p. 242—244°, $[\alpha]_D^{20}$ −32·2° (Found: C, 42·95; H, 3·1. Hal, 34·7; N, 3·6. $C_{15}H_{12}BrCl_2NO_4$ requires C, 42·8; H, 2·9; Hal, 35·8; N, 3·3%). This material contained <1% of dichloro- and <2% of dibromodichloro-thyronine.

3′,5′-*Dibromo*-3,5-*dichloro*-D-*thyronine*.—3,5-Dichloro-D-thyronine (1 g.), treated as in the last preparation with bromine (1·4 g.) at room temperature for 70 hr., gave 3′,5′-*dibromo*-3,5-*dichloro*-D-*thyronine* (1·28 g., 87%), m. p. 235° (decomp.), $[\alpha]_D^{20}$ −27·5° (Found: C, 35·8; H, 2·4; Hal, 46·5; N, 2·5. $C_{15}H_{11}Br_2Cl_2NO_4$ requires C, 36·0; H, 2·2; Hal, 46·15; N, 2·8%).

3,5-*Dichloro*-3′-*iodo*-D-*thyronine*.—Treatment of 3,5-dichloro-D-thyronine (5·0 g.) in aqueous 33% ethylamine (40 ml.) with a 1·05N-solution of iodine in potassium iodide (30 ml.) during 1 hr. at 25—30°, then neutralization to pH 5 with hydrochloric acid, recrystallization from 2N-hydrochloric acid, and neutralization with sodium acetate, gave 3,5-*dichloro*-3′-*iodo*-D-*thyronine* (2·8 g., 41%), m. p. 197—200°, $[\alpha]_D^{20}$ −27° (Found: C, 38·9; H, 4·0; I, 27·8. $C_{15}H_{12}Cl_2INO_4$ requires C, 38·4; H, 3·8; I, 27·1%). This material contained 1% of dichlorothyronine and 2% of dichlorodi-iodothyronine.

3,5-*Dichloro*-3′,5′-*di-iodo*-D-*thyronine*.—Treatment of 3,5-dichloro-D-thyronine (5·0 g.) with a 1·05N-solution of iodine in potassium iodide (75·8 ml.) as above gave 3,5-*dichloro*-3′,5′-*di-iodo*-D-*thyronine* (3·03 g., 38%), m. p. 205—210° (decomp.) (Found: C, 30·2; H, 2·1; I, 42·5. $C_{15}H_{11}Cl_2I_2NO_4$ requires C, 30·3; H, 1·8; I, 42·7%).

3-*Chloro*-5,3′,5′-*tri-iodo*-D- *and* -L-*thyronine*.—3-Chloro-5-iodo-D-thyronine [18] (2·0 g.) in 33% aqueous ethylamine (40 ml.) was treated with a N-solution of iodine in potassium iodide (28·0 ml.) at room temperature. After 3 hr. the pH was adjusted to 5 with hydrochloric acid and the solid dissolved in hot ethanol containing a little 2N-sodium hydroxide. Neutralization with N-hydrochloric acid gave 3-chloro-5,3′,5′-tri-iodo-D-thyronine (2·62 g., 83%), m. p. 211—213° (decomp.), $[\alpha]_D^{20}$ −13·2° (Found: C, 27·0; H, 1·9; I, 52·5. Calc. for $C_{15}H_{11}ClI_3NO_4,\frac{1}{2}EtOH$: C, 27·1; H, 2·0; I, 53·7; N, 2·0%). 3-*Chloro*-5,3′,5′-*tri-iodo*-L-*thyronine*, prepared similarly, had m. p. 212—213° (Found: C, 27·4; H, 2·0; N, 1·9%).

3,5-*Dibromo*-3′-*chloro*-D-*thyronine*.—3,5-Dibromo-D-thyronine hydrochloride (4·0 g.) in glacial acetic acid (220 ml.) was treated at room temperature with chlorine (0·61 g.) in acetic acid (22 ml.). After 2 hr. the acetic acid was removed and the residue crystallized from 2N-hydrochloric acid, then redissolved in hydrochloric acid and neutralized at the b. p. with sodium acetate solution. 3,5-*Dibromo*-3′-*chloro*-D-*thyronine* separated as colourless crystals (2·8 g., 65%), m. p. 238—241° (Found: C, 38·8; H, 2·6; Hal, 41·9. $C_{15}H_{12}Br_2ClNO_4$ requires C, 38·4; H, 2·6; Hal, 41·9%). This material contained <2% each of dibromo- and dibromodichloro-thyronine.

3,5,3′-*Tribromo*-5′-*iodo*-D-*thyronine*.—3,5,3′-Tribromo-D-thyronine (4·0 g.) in aqueous 33% ethylamine (75 ml.) was treated at room temperature with a N-solution of iodine in potassium iodide (20 ml.) during 45 min. Most of the ethylamine solution was distilled off under reduced pressure and the remaining solution neutralized at 0° with 10N-hydrochloric acid. The hydrochloride separated and recrystallized (charcoal) from 2N-hydrochloric acid containing a little ethanol; it was then dissolved in 0·2N-hydrochloric acid and ethanol and neutralized with sodium acetate solution. 3,5,3′-*Tribromo*-5′-*iodo*-D-*thyronine* separated as colourless crystals

[18] Dibbo, Stephenson, Walker, and Warburton, *J.*, 1961, 2645.

(2·2 g., 44%), m. p. 198—201° (Found: C, 28·8; H, 1·7; I, 19·5. $C_{15}H_{11}Br_3INO_4$ requires C, 28·3; H, 1·7; I, 20·0%).

3,5-*Dibromo*-3′-*iodo*-D-*thyronine*.—3,5-Dibromo-D-thyronine hydrochloride (1·27 g.) in aqueous 33% ethylamine (50 ml.) was treated with a N-solution of iodine in potassium iodide (5·4 ml.). After 3 hr. the pH was adjusted to 5 with 10N-hydrochloric acid below 25° and the precipitated hydrochloride redissolved in hot 0·5N-hydrochloric acid containing a little ethanol, then neutralized with sodium acetate. The impure amino-acid (1·34 g., 88%) was crystallized from N-hydrochloric acid containing a little ethanol, and the resulting hydrochloride neutralized with sodium acetate as before, giving 3,5-dibromo-3′-iodo-D-thyronine (0·97 g., 63%), m. p. 223—225° (decomp.), $[\alpha]_D^{22}$ −22·5° (Found: C, 32·0; H, 2·3; Hal, 52·0; I, 23·4; N, 2·2. Calc. for $C_{15}H_{12}Br_2INO_4$: C, 32·35; H, 2·15; Hal, 51·5; I, 22·8; N, 2·5%). This material contained 1% of dibromo- and 6% of dibromodi-iodo-thyronine.

3,5-*Dibromo*-3′,5′-*di-iodo*-D-*thyronine*.—3,5-Dibromo-D-thyronine hydrochloride (1·50 g.) in aqueous 33% ethylamine (100 ml.) was treated with a 1·06N-solution of iodine in potassium iodide (19 ml.) at room temperature. Next day the pH was adjusted to 5 at 10° by adding 5N-hydrochloric acid. The pale yellow precipitate was dried and washed with hot ethanol (3 × 20 ml.), leaving 3,5-dibromo-3′,5′-di-iodo-D-thyronine as a cream powder (1·70 g., 77%), m. p. 195—198° (decomp.), $[\alpha]_D^{20}$ −22·5° (Found: C, 26·8; H, 2·1; Hal, 58·6; I, 35·8. Calc. for $C_{15}H_{11}Br_2I_2NO_4$: C, 26·4; H, 1·6; Hal, 60·6; I, 37·2%).

3′-*Chloro*-3,5-*di-iodo*-D-*thyronine*.—3,5-Di-iodo-D-thyronine (5·25 g.) was dissolved in glacial acetic acid (500 ml.) by passing in a little hydrogen chloride. Chlorine (0·71 g.) in acetic acid (70 ml.) was added in one portion, at room temperature, with shaking. After 30 min. (negative starch–iodide reaction) the acetic acid was removed under reduced pressure and the residue recrystallized twice from 2N-hydrochloric acid (80 ml.) and ethanol (15 ml.) (charcoal). The resulting hydrochloride (4·4 g.) was dissolved in hydrochloric acid and ethanol and neutralized with sodium acetate solution. 3′-*Chloro*-3,5-*di-iodo*-D-*thyronine* separated as colourless needles (3·53 g., 63%), m. p. 256° (decomp.), $[\alpha]_D^{20}$ −23·0° (Found: C, 32·0; H, 2·2; Cl, 6·3; I, 45·4. $C_{15}H_{12}Cl_2INO_4$ requires C, 32·2; H, 2·2; Cl, 6·3; I, 45·4%). This compound contained <2% each of di-iodo- and dichlorodi-iodo-thyronine.

3′,5′-*Dichloro*-3,5-*di-iodo*-D-*thyronine*.—3,5-Di-iodo-D-thyronine (5·25 g.) in glacial acetic acid (500 ml.) containing a little hydrogen chloride was treated with chlorine (0·8 g.) in acetic acid (70 ml.). After 30 min. the mixture was cooled to 10° and chlorine passed slowly through the supercooled solution for 1 hr. The excess of chlorine was removed by bubbling air through the solution, then the solvent was removed under reduced pressure. The residue was boiled with 0·5N-hydrochloric acid (500 ml.), ethanol (75 ml.), and sodium hydrogen sulphite, and the solution decanted from some tar and again treated with charcoal and sodium hydrogen sulphite. The cooled solution deposited the hydrochloride as a grey solid (2·8 g.) which recrystallized from 0·5N-hydrochloric acid (charcoal); it was neutralized with sodium acetate. 3′,5′-Dichloro-3,5-di-iodo-D-thyronine was obtained in 30% overall yield as colourless needles, m. p. 261—262° (decomp.), $[\alpha]_D^{20}$ −23·6° (Found: C, 29·7; H, 2·3; Hal, 55·8; N, 2·1. Calc. for $C_{15}H_{11}Cl_2I_2NO_4,H_2O$: C, 29·4; H, 2·1; Hal, 54·8; N, 2·3%).

3′-*Bromo*-3,5-*di-iodo*-D-*thyronine*.—3,5-Di-iodo-D-thyronine (3·0 g.) in glacial acetic acid (150 ml.) containing a little hydrogen chloride was treated at room temperature with bromine (0·91 g.) in acetic acid (9·5 ml.) and left for 20 hr. The solvent was removed under reduced pressure and the residue dissolved in hot aqueous ethanol (2 l.) containing a little hydrochloric acid. Neutralization with sodium acetate gave 3′-*bromo*-3,5-*di-iodo*-D-*thyronine* (3·23 g., 94%), m. p. 247—249° (decomp.), $[\alpha]_D^{20}$ −25·6° (Found: C, 29·8; H, 2·0; Hal, 55·25; N, 2·3. $C_{15}H_{12}BrI_2NO_4$ requires C, 30·1; H, 2·1; Hal, 54·6; N, 1·9%). This material contained <2% each of di-iodo- and dibromodi-iodo-thyronine.

3′,5′-*Dibromo*-3,5-*di-iodo*-D-*thyronine*.—3,5-Di-iodo-D-thyronine, treated as in the last experiment with bromine (2·73 g.) for 80 hr., gave 3′,5′-*dibromo*-3,5-*di-iodo*-D-*thyronine* (3·66 g., 94%), m. p. 246° (decomp.), $[\alpha]_D^{20}$ −21·0° (Found: C, 27·0; H, 1·8; Hal, 60·0; N, 2·2. $C_{15}H_{11}Br_2I_2NO_4$ requires C, 26·4; H, 1·6; Hal, 60·6; N, 2·05%). This material contained 3% of 3′-bromo-3,5-di-iodo-D-thyronine.

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