544. *The Synthesis of Thyroxine and Related Substances. Part VIII.* The Preparation of Some Halogeno- and Nitro-diphenyl Ethers.*

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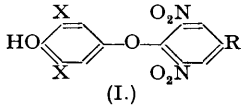
A number of dinitrodiphenyl ethers and their halogen derivatives have been prepared by methods described in the earlier papers of the series. The preparation of 3 : 5 : 3′ : 5′-tetranitro-L- and -DL-thyronine is described.

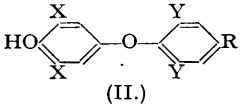
In Part I of this series (Borrows, Clayton, and Hems *J.*, 1949, S 185) we stated that we hoped to prepare analogues of thyroxine, which might show antithyroid activity. At present the drugs employed in the treatment of hyperthyroidism are sulphur-containing compounds; they bear no structural relation to thyroxine and act by preventing the formation of the hormone, whereas chemical analogues might be expected to inhibit its peripheral effects.

Some analogues of thyroxine have already been prepared by other workers. Thus, Harington (*Biochem. J.*, 1948, **43**, 434) prepared the sulphide analogue; Woolley (*J. Biol. Chem.*, 1946, **164**, 11) prepared a few aliphatic ethers of *N*-acetyl-3 : 5-di-iodotyrosine; Frieden and Winzler (*ibid.*, 1949, **179**, 423) prepared 4-benzyloxy-3 : 5-di-iodobenzoic acid and several similar compounds. Many of these were found to have antithyroid activity when tested on tadpoles, but recent work (Maclagan and Sheahan, *J. Endocrinol.*, 1950, **6**, 456) has shown them to be much less effective in mice. Tetrahalogenated thyronines prepared by Shuegraf (*Helv. Chim. Acta*, 1929, **12**, 405), in which chlorine or bromine replaced the iodine of thyroxine, had weak thyroxine activity.

The present communication describes the preparation of diphenyl ethers of types (I) and (II), which possess the same general nuclear structure as thyroxine.



(I.)



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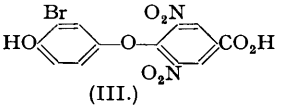


(III.)

The new compounds (I; R = CO_2H or CHO, X = H) were prepared by condensing the appropriately substituted dinitrobenzene with quinol; preparation of (I; R = Me, X = H) has already been described (Borrows, Clayton, Hems, and Long, *J.*, 1949, S 190). Attempts

* Part VII, *J.*, 1950, 2824.

to prepare these compounds by demethylation of their methyl ethers (Borrows *et al.*, *loc. cit.*, p. 190) with hydriodic acid in acetic acid were unsuccessful; demethylation of the methyl ether of (I; R = CO_2H, X = H) by hydrobromic acid in acetic acid took place, but the product contained bromine in the phenolic nucleus, owing to oxidation of the hydrobromic acid by the nitro-groups. The same compound 4-(3-bromo-4-hydroxyphenoxy)-3 : 5-dinitrobenzoic acid (III) was obtained by condensing monobromoquinol with 4-chloro-3 : 5-dinitrobenzoic acid in the usual manner. While it is recognised that this condensation leads to a product of ambiguous constitution, it is thought that, taken in conjunction with the original method of preparation as outlined above, it offers adequate proof of structure. Tars were formed from the methyl ether of (I; R = Me, X = H) by hydriodic or hydrobromic acid in acetic acid or by aluminium chloride in benzene but it was demethylated giving (I; R = Me, X = H) in 53% yield by pyridine hydrochloride at a high temperature.

The substituted propionic acid (I; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$, X = H) was prepared by condensation of ethyl β-(4-hydroxy-3 : 5-dinitrophenyl)propionate with quinol by the general method described in Part II of this series (Borrows *et al.*, *loc. cit.*, p. 190), followed by acid hydrolysis of the ester, but the preparation of the corresponding unsaturated acid, 4-*p*-hydroxyphenoxy-3 : 5-dinitrocinnamic acid (I; R = $CH{:}CH{\cdot}CO_2H$, X = H) was much more troublesome. Reaction of the aldehyde (I; R = CHO, X = H) and malonic acid in the presence of bases was anomalous; no pure compound was obtained by use of mixtures of pyridine and piperidine, and replacement of the latter by aniline led only to the formation of 4-anilino-3 : 5-dinitrobenzylidenemalonic acid. The required reaction was, however, successfully accomplished in the presence of pyridine alone or dimethylaniline, thereby avoiding fission of the labile ether linkage.

The dinitrophenyl ethers were then halogenated in the 3′- and the 5′-position by a variety of methods. Bromination proceeded readily with bromine in acetic acid, to give the compounds (I; R = Me, CHO, CO_2H, $CH_2{\cdot}CH_2{\cdot}CO_2H$, $CH{:}CH{\cdot}CO_2H$; X = Br). 4-(3 : 5-Dibromo-4-hydroxyphenoxy)-3 : 5-dinitrocinnamic acid (I; R = $CH{:}CH{\cdot}CO_2H$, X = Br) was also obtained by direct condensation of (I; R = CHO, X = Br) with malonic acid in the presence of pyridine : again no pure product could be isolated if piperidine was also present.

The corresponding chloro-compounds, 4-(3 : 5-dichloro-4-hydroxyphenoxy)-3 : 5-dinitrobenzoic acid and -benzaldehyde (I; R = CO_2H or CHO, X = Cl) were prepared by direct chlorination in acetic acid, but this method failed to give crystalline products from the compounds (I; R = Me, $CH_2{\cdot}CH_2{\cdot}CO_2H$, $CH{:}CH{\cdot}CO_2H$, X = H). The failure was attributed to chlorination of the side chain in the presence of excess of halogen, but the two chloro-compounds (I; R = Me or $CH_2{\cdot}CH_2{\cdot}CO_2H$, X = Cl) were prepared successfully by use of the theoretical amount of chlorine in carbon tetrachloride. The toluene derivative was also obtained by Brown's method (*Ind. Eng. Chem.*, 1944, **36**, 785) using sulphuryl chloride in the presence of aluminium chloride and sulphur chloride. All attempts to prepare the cinnamic acid derivative (I; R = $CH{:}CH{\cdot}CO_2H$, X = Cl) failed.

Iodination of diphenyl ethers of type (I; X = H) was difficult and no single method was found successful when applied to all the compounds. The use of iodine and aqueous solutions of ammonia or organic primary or secondary bases at room temperature (Clayton and Hems, *J.*, 1950, 840) led to fission of the dinitrodiphenyl ethers. Thus the attempted iodination of (I; R = CO_2H, X = H) in strong aqueous ammonia or in aqueous 20% methylamine solutions led only to 4-amino- or 4-methylamino-3 : 5-dinitrobenzoic acid. The required di-iodo-compounds (I; R = CO_2H and $CH{:}CH{\cdot}CO_2H$, X = I) were, however, obtained when cold dilute aqueous solutions of ammonia were used. Owing to the insolubility of the compound (I; R = Me, X = H) in dilute aqueous solutions and its cleavage in strong solutions of bases, iodination was achieved in good yield only by adding iodine to the starting material in a mixture of aqueous ammonia with enough added dioxan to secure solution. In this way 4′-hydroxy-3′ : 5′-di-iodo-4-methyl-2 : 6-dinitrodiphenyl ether (I; R = Me, X = I) was obtained without cleavage. The corresponding aldehyde (I; R = CHO, X = I) could not be prepared by this method and was obtained by the action of iodine chloride on 4-*p*-hydroxyphenoxy-3 : 5-dinitrobenzaldehyde (I; R = CHO, X = H) in acetic acid.

Iodo-derivatives of the acidic compounds of this group (I; R = CO_2H and $CH{:}CH{\cdot}CO_2H$, X = I) were also obtained by the addition of iodine to a solution of the starting material in a saturated solution of sodium hydrogen carbonate.

The preparation of tetrahalogenated diphenyl ethers of type (II; R = various, X = Y = halogen) was carried out by first converting the methyl ethers of compounds of type (I) (Borrows *et al.*, *loc. cit.*, p. 190) into the corresponding halogeno-compounds (II; X = H;

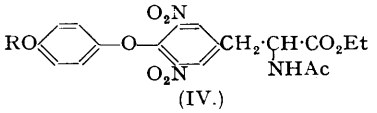
Y = halogen) by catalytic hydrogenation to the diamino-compounds followed by the Sandmeyer reaction. The products after demethylation were then halogenated to give the required compounds (II; X = Y = halogen). In one case (I; R = $CH_2 \cdot CH_2 \cdot CO_2H$, X = H) the reactions were carried out with the free phenol.

A method of tetrazotising 2 : 6-diaminodiphenyl ethers was described in Part I (*loc. cit.*), but treating the solutions of tetrazonium salts with iodides under the conditions of the Sandmeyer reaction led to poor yields. Further investigation of this reaction with the improvements already discussed in Part V (*J.*, 1949, 3424) gave increased yields and 2 : 6-di-iodo-4'-methoxy-4-methyldiphenyl ether and the corresponding methyl benzoate have now been thus prepared. Demethylation and, for the ester, hydrolysis were carried out with hydriodic acid and acetic acid to give the hydroxy-derivatives (II; R = Me or CO_2H, X = H, Y = I). The last compound has already been prepared by a different method (Harington and Barger, *Biochem. J.*, 1927, **21**, 169). Similarly, ethyl β-(4-*p*-hydroxyphenoxy-3 : 5-dinitrophenyl)propionate (I; R = $CH_2 \cdot CH_2 \cdot CO_2Et$, X = H) was converted into the diamino-compound, thence into ethyl β-(4-*p*-hydroxyphenoxy-3 : 5-di-iodophenyl)propionate, and thus by hydrolysis into (II; R = $CH_2 \cdot CH_2 \cdot CO_2H$, Y = I). In the last example tetrazotisation and the Sandmeyer reaction were carried out on the free phenol, and not on the methyl ether, a procedure we have previously found satisfactory (cf. Part V, *loc. cit.*). The three di-iodo-compounds were readily iodinated in aqueous ammonia or ethylamine, to give the tetraiodo-compounds; the benzoic acid derivative has been described by Harington and Barger (*loc. cit.*).

The substituted acrylic acids (II; R = $CH{:}CH \cdot CO_2H$, Y = I, X = I or H) have been prepared from thyroxine and 3 : 5-di-iodothyronine by exhaustive methylation : the method will be described later (cf. Wawzonek, Wang, and Lyons, *J. Org. Chem.*, 1950, **15**, 593).

By methods similar to those described above 3 : 5-dichloro-4'-hydroxy-4-methyldiphenyl ether and the corresponding benzoic acid (II; R = Me or CO_2H, X = H, Y = Cl) were prepared. The latter was successfully chlorinated to give (II; R = CO_2H, X = Y = Cl) but all attempts to chlorinate the toluene derivative failed.

The preparation of analogous derivatives of thyronine was then undertaken. Although the methyl ether of *N*-acetyl-3 : 5-dinitro-L-thyronine ethyl ester (IV; R = Me) was readily



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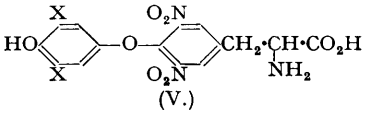

(V.)

available (Part V, *loc. cit.*), it did not seem to be suitable for the preparation of 3 : 5-dinitrothyronine itself, in view of the failure to demethylate the methyl ether of (I; R = CO_2H, X = H). However, condensation of *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester or the L-compound with *p*-benzoyloxyphenol instead of *p*-methoxyphenol (cf. Part V, *loc. cit.*) gave the L- and DL-isomers of *N*-acetyl-4-*p*-benzoyloxyphenoxy-3 : 5-dinitrophenylalanine ethyl ester (IV; R = Bz). Acid hydrolysis readily yielded the 3 : 5-dinitro-L- and -DL-thyronine (V; X = H) which were nitrated to give 3 : 5 : 3' : 5'-tetranitro-L- and -DL-thyronine (V; X = NO_2) respectively. The free amino-acids did not crystallise well and were characterised as their *N*-acetyl derivatives. 3 : 5-Dinitro-DL-thyronine with iodine in sodium hydrogen carbonate gave a product that appeared from its analysis to consist essentially of the di-iodo-compound (V; X = I), but it could not be obtained pure, and in this instance acetylation did not lead to a more tractable substance.

Experimental.

4-p-*Hydroxyphenoxy*-3 : 5-*dinitrobenzaldehyde*.—A mixture of quinol (2·7 g.), sodium carbonate (0·26 g.), 4-chloro-3 : 5-dinitrobenzaldehyde (1·15 g.), sodium dithionite (hydrosulphite) (0·05 g.), and water (10 ml.) was heated under reflux for 1 hour. The reaction mixture was diluted with water (250 ml.), then filtered, and the solid was extracted with hot acetic acid. After filtration a little water was added, whereupon the *aldehyde* separated as yellow needles, m. p. 157° (0·5 g.) (Found : C, 51·5; H, 2·1; N, 9·5. $C_{13}H_8O_7N_2$ requires C, 51·3; H, 2·6; N, 9·2%).

4-p-*Hydroxyphenoxy*-3 : 5-*dinitrobenzoic Acid*.—Quinol (2·25 g.), potassium carbonate (0·56 g.), 4-chloro-3 : 5-dinitrobenzoic acid (1 g.), and water (5 ml.) were heated under reflux for an hour. The mixture was poured into water and acidified with 2N-hydrochloric acid, yellow crystals being deposited. The *acid* recrystallised from aqueous ethanol as bright yellow prisms, m. p. 224° (decomp.) (0·9 g., 69%) (Found : C, 48·2; H, 2·7; N, 8·9. $C_{13}H_8O_8N_2$ requires C, 48·7; H, 2·5; N, 8·7%).

4'-*Hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenyl Ether*.—A solution of 4'-methoxy-2 : 6-dinitro-4-methyldiphenyl ether (1 g.) in benzene (50 ml.) and pyridine (1 ml.) was saturated with dry hydrogen chloride and then heated to 220—225° for 1 hour, the solvent being allowed to evaporate. The solid was cooled

and extracted thoroughly with hot benzene, and the extracts were washed with dilute hydrochloric acid, sodium carbonate solution, and water and evaporated. The residual gum crystallised from aqueous acetic acid as yellow needles, m. p. 160—161° (0·5 g., 53%) alone or mixed with an authentic specimen (Borrows *et al.*, *J.*, 1949, S 190).

4-(3-*Bromo*-4-*hydroxyphenoxy*)-3 : 5-*dinitrobenzoic Acid.*—(*a*) 4-*p*-Methoxyphenoxy-3 : 5-dinitrobenzoic acid (*loc. cit.*) (2 g.) in acetic acid (14 ml.) and hydrobromic acid (*d* 1·5; 10 ml.) was heated under reflux for 15 hours. The brown solid which separated on pouring of the mixture into water was recrystallised from aqueous ethanol; the *acid* separated as brown crystals, m. p. 227—230° (decomp.) (Found: C, 39·6; H, 1·9; N, 7·0; Br, 19·6. $C_{13}H_7O_8N_2Br$ requires C, 39·1; H, 1·8; N, 7·0; Br, 20·0%).

(*b*) A mixture of potassium carbonate (0·28 g.), bromoquinol (1 g.), 4-chloro-3 : 5-dinitrobenzoic acid (0·5 g.), and water (5 ml.) was heated under reflux for 1 hour, then poured into water, and acidified with 2N-hydrochloric acid, whereupon a sticky solid was deposited. Crystallisation from aqueous ethanol gave a yellow solid (0·1 g.) which had m. p. 228° (decomp.), not depressed on admixture with a sample of the acid prepared by demethylation.

Ethyl β-(4-p-*Hydroxyphenoxy*-3 : 5-*dinitrophenyl*)*propionate.*—Ethyl β-(4-hydroxy-3 : 5-dinitrophenyl)-propionate (5 g.) and toluene-*p*-sulphonyl chloride (3·35 g.) were heated on the steam-bath with pyridine (100 ml.) for 10 minutes. Quinol (8 g.) was added and the solution heated under reflux for 1 hour; the pyridine was then removed under reduced pressure and ethanol (80 ml.) added to the residual gum. The solution was filtered, water added, and the mixture extracted with chloroform. The extracts were washed with water and evaporated to small bulk; addition of light petroleum caused the separation of yellow prisms of the product. The *ester*, recrystallised from aqueous acetic acid, had m. p. 79—82° (4·35 g., 65%) (Found: C, 52·3; H, 4·6; N, 6·4. $C_{17}H_{16}O_8N_2,CH_3{\cdot}CO_2H$ requires C, 52·3; H, 4·6; N, 6·4%). The *acid* was obtained by heating the ester (10 g.) under reflux with acetic acid (50 ml.) and hydrochloric acid (50 ml.) for 30 minutes. The product separated from aqueous ethanol as yellow prisms, m. p. 184—186° (7·6 g., 82%) (Found: C, 52·0; H, 3·4; N, 8·1. $C_{15}H_{12}O_8N_2$ requires C, 51·7; H, 3·5; N, 8·0%).

4-*Anilino*-3 : 5-*dinitrobenzylidenemalonic Acid.*—4-*p*-Hydroxyphenoxy-3 : 5-dinitrobenzaldehyde (1 g.), malonic acid (2 g.), and aniline (0·3 ml.) in pyridine (25 ml.) were warmed on a steam-bath for 30 minutes and heated under reflux for 15 minutes. The mixture was poured into excess of dilute hydrochloric acid; the orange crystals which separated recrystallised from aqueous ethanol and then had m. p. 256—258° (Found: C, 51·6; H, 3·1; N, 11·2. $C_{16}H_{11}O_8N_3$ requires C, 51·5; H, 3·0; N, 11·3%).

4-p-*Hydroxyphenoxy*-3 : 5-*dinitrocinnamic Acid.*—4-*p*-Hydroxyphenoxy-3 : 5-dinitrobenzaldehyde (2 g.), malonic acid (3 g.), and dry pyridine (25 ml.) were heated on a steam-bath for 1 hour and then under reflux for 30 minutes. The solution was poured into excess of dilute hydrochloric acid and the *acid* was recrystallised from aqueous acetic acid. It formed yellow prisms, m. p. 225° (decomp.) (1·8 g., 80%) (Found: C, 51·6; H, 3·0; N, 7·8. $C_{15}H_{10}O_8N_2$ requires C, 52·0; H, 2·9; N, 8·1%).

3′ : 5′-*Dibromo*-4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenyl Ether.*—Bromine in acetic acid (10% w/v; 42 ml.) was added dropwise to a stirred solution of 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenyl ether (2 g.) in acetic acid (50 ml.) during 15 minutes. After 1 hour, water was added and the yellow crystalline *ether* which was deposited was recrystallised from ethanol as glistening plates, m. p. 194—195° (2·1 g., 69%) (Found: C, 35·0; H, 2·0; N, 6·0; Br, 35·4. $C_{13}H_8O_6N_2Br_2$ requires C, 34·8; H, 1·8; N, 6·2; Br, 35·7%).

By similar methods the following compounds were prepared.

4-(3 : 5-*Dibromo*-4-*hydroxyphenoxy*)-3 : 5-*dinitrobenzoic acid*, yellow prisms (from aqueous ethanol), m. p. 259° (decomp.) (Found: N, 5·7; Br, 32·8. $C_{13}H_6O_8N_2Br_2$ requires N, 5·9; Br, 33·5%).

4-(3 : 5-*Dibromo*-4-*hydroxyphenoxy*)-3 : 5-*dinitrobenzaldehyde*, yellow prisms (from aqueous acetic acid), m. p. 186—187° (decomp.) (Found: C, 33·2; H, 1·2; N, 6·1; Br, 34·0. $C_{13}H_6O_7N_2Br_2$ requires C, 33·8; H, 1·3; N, 6·1; Br, 34·6%).

β-[4-(3 : 5-*Dibromo*-4-*hydroxyphenoxy*)-3 : 5-*dinitrophenyl*]*propionic acid*, yellow prisms (from aqueous ethanol), m. p. 173—175° (Found: C, 36·1; H, 2·3; N, 5·5; Br, 30·5. $C_{15}H_{10}O_8N_2Br_2$ requires C, 35·6; H, 2·0; N, 5·5; Br, 31·6%).

4-(3 : 5-*Dibromo*-4-*hydroxyphenoxy*)-3 : 5-*dinitrocinnamic acid*, yellow prisms (from aqueous acetic acid), m. p. 260° (decomp.) (Found: C, 36·3; H, 1·5; N, 5·7; Br, 31·2. $C_{15}H_8O_8N_2Br_2$ requires C, 35·7; H, 1·6; N, 5·6; Br, 31·7%).

4-(3 : 5-*Dibromo*-4-*hydroxyphenoxy*)-3 : 5-*dinitrocinnamic Acid.*—4-(3 : 5-Dibromo-4-hydroxyphenoxy)-3 : 5-dinitrobenzaldehyde (2 g.) and malonic acid (5 g.) in dry pyridine (40 ml.) were heated on a steam-bath for 1 hour and then under reflux for 10 minutes. The pyridine was removed under reduced pressure and the residue triturated with a little acetic acid, whereupon a yellow solid separated having m. p. and mixed m. p. 260° (decomp.).

3′ : 5′-*Dichloro*-4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenyl Ether.*—(*a*) 4′-Hydroxy-4-methyl-2 : 6-dinitrodiphenyl ether (1 g.) was dissolved in acetic acid (50 ml.); sulphuryl chloride (2 ml.), aluminium chloride (2 g.), and sulphur chloride (0·05 ml.) were added and the mixture was stirred for 15 hours. Addition of water caused the precipitation of a yellow solid *ether* which separated from aqueous acetic acid as yellow prisms, m. p. 151° (decomp.) (Found: N, 7·8; Cl, 19·7. $C_{13}H_8O_6N_2Cl_2$ requires N, 7·8; Cl, 19·8%).

(*b*) To 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenyl ether (1 g.) in acetic acid (50 ml.) the calculated amount of chlorine solution in carbon tetrachloride (13·3% w/v; 3·65 ml.) was added. After the reactants had been kept in the dark for 1 hour, water was added, precipitating a solid which separated from aqueous acetic acid as yellow prisms (0·66 g., 53%), m. p. 149—152° (decomp.), alone or mixed with a sample prepared as in (*a*) above.

4-(3 : 5-*Dichloro*-4-*hydroxyphenoxy*)-3 : 5-*dinitrobenzaldehyde*.—Dry chlorine was passed into a solution of 4-*p*-hydroxyphenoxy-3 : 5-dinitrobenzaldehyde (1 g.) in acetic acid (50 ml.) for 1½ hours. Addition of water precipitated the *aldehyde* which recrystallised from benzene as yellow prisms, m. p. 207—208° (Found : C, 41·5; H, 1·6; N, 7·8; Cl, 18·6. $C_{13}H_6O_7N_2Cl_2$ requires C, 41·8; H, 1·6; N, 7·5; Cl, 19·0%).

4-(3 : 5-*Dichloro*-4-*hydroxyphenoxy*)-3 : 5-*dinitrobenzoic Acid*.—Dry chlorine was passed into a solution of 4-*p*-hydroxyphenoxy-3 : 5-dinitrobenzoic acid (1 g.) in acetic acid (50 ml.) for 1½ hours. The solution was concentrated to small bulk and when this was kept a solid *acid* separated which recrystallised from aqueous acetic acid as glistening yellow plates, m. p. 250° (decomp.) (0·61 g., 50%) (Found : C, 40·4; H, 1·6; N, 7·4; Cl, 17·8. $C_{13}H_6O_8N_2Cl_2$ requires C, 40·2; H, 1·5; N, 7·2; Cl, 18·2%).

β-[4-(3 : 5-*Dichloro*-4-*hydroxyphenoxy*)3 : 5-*dinitrophenyl*]*propionic Acid*.—Chlorine in carbon tetrachloride (8·2% w/v; 25 ml.) was added to a solution of β-4-(*p*-hydroxyphenoxy)-3 : 5-dinitrophenylpropionic acid (5 g.) in acetic acid (250 ml.), and the solution kept in the dark for 1 hour. Addition of water precipitated the *acid* which recrystallised from aqueous ethanol as yellow prisms, m. p. 177—179° (3·2 g., 53%) (Found : C, 43·2; H, 2·5; N, 6·8; Cl, 16·4. $C_{15}H_{10}O_8N_2Cl_2$ requires C, 43·2; H, 2·4; N, 6·7; Cl, 17·0%).

4-*Amino*-3 : 5-*dinitrobenzoic Acid*.—4-*p*-Hydroxyphenoxy-3 : 5-dinitrobenzoic acid (1 g.) was dissolved in ammonia solution (*d* 0·88; 20 ml.) and the solution set aside for 10 minutes. Acidification with 2N-hydrochloric acid caused the separation of a brown solid which recrystallised from ethyl acetate–light petroleum as yellow crystals, m. p. 269—271° (Found : N, 18·4. Calc. for $C_7H_5O_6N_3$: N, 18·5%).

4-*Methylamino*-3 : 5-*dinitrobenzoic acid*.—4-*p*-Hydroxyphenoxy-3 : 5-dinitrobenzoic acid (1 g.) was dissolved in methylamine solution (20% w/v; 20 ml.), set aside for 10 minutes, and then acidified with 2N-hydrochloric acid. The precipitated amino-acid crystallised from aqueous acetone as yellow prisms, m. p. 223—224° (Found : C, 40·2; H, 2·9; N, 17·6. Calc. for $C_8H_7O_6N_3$: C, 39·9; H, 2·9; N, 17·4%).

4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*dinitrobenzoic Acid*.—(*a*) Iodine solution (1·9N.) in an excess of sodium iodide (13·2 ml.) was added dropwise to a stirred solution of 4-*p*-hydroxyphenoxy-3 : 5-dinitrobenzoic acid (2 g.) in a saturated solution of sodium hydrogen carbonate (100 ml.). After 30 minutes the mixture was acidified with dilute hydrochloric acid; the resultant yellow precipitate of *iodo-acid* separated from aqueous ethanol as bright yellow crystals, m. p. 241° (decomp.) (Found : C, 27·5; H, 1·3; N, 5·1; I, 44·3. $C_{13}H_6O_8N_2I_2$ requires C, 27·3; H, 1·1; N, 4·9; I, 44·4%).

(*b*) 4-*p*-Hydroxyphenoxy-3 : 5-dinitrobenzoic acid (1 g.) was dissolved in ammonia solution [50 ml.; 25% (v/v) of ammonia (*d* 0·88) in water] at −5°. A solution of iodine (1·9N.) in an excess of sodium iodide solution (6·6 ml.) was added dropwise, the temperature being kept between −5° and 0°. The solution was poured into a large excess of water and acidified with 2N-hydrochloric acid, whereupon a sticky yellow solid separated. Recrystallisation from aqueous ethanol yielded yellow prisms, m. p. 246° (decomp.) (1·0 g., 55%).

4′-*Hydroxy*-3′ : 5′-*di-iodo*-4-*methyl*-2 : 6-*dinitrodiphenyl Ether*.—To a stirred solution of 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenyl ether (9·3 g.) in dioxan (110 ml.) and ammonia (*d* 0·88; 93 ml.), iodine solution in excess of sodium iodide solution (2N.; 59 ml.) was added. The mixture was poured into dilute hydrochloric acid, and the precipitated *ether* was recrystallised from acetone, forming yellow prisms, m. p. 206—207° (decomp.) (11 g., 69%) (Found : C, 29·5; H, 1·4; N, 5·3; I, 45·6. $C_{13}H_8O_6N_2I_2$ requires C, 28·8; H, 1·5; N, 5·2; I, 46·8%).

4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*dinitrobenzaldehyde*.—Iodine monochloride in acetic acid (15% w/v; 7·2 ml.) was added to a solution of 4-*p*-hydroxyphenoxy-3 : 5-dinitrobenzaldehyde (1 g.) in acetic acid (50 ml.), and the mixture stirred for 15 hours. Addition of excess of water precipitated a brown solid *aldehyde* which recrystallised from aqueous acetic acid as fine yellow needles, m. p. 180° (decomp.) (0·6 g., 30%) (Found : N, 5·1; I, 45·3. $C_{13}H_6O_7N_2I_2$ requires N, 5·0; I, 45·7%).

4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*dinitrocinnamic Acid*.—Iodine in excess of sodium iodide solution (1·9N.; 32 ml.) was added dropwise to a stirred solution of 4-*p*-hydroxyphenoxy-3 : 5-dinitrocinnamic acid (7·8 g.) in saturated sodium hydrogen carbonate solution (100 ml.). After 30 minutes the mixture was acidified with dilute hydrochloric acid and the resultant *acid* crystallised from aqueous methyl cyanide as yellow needles, m. p. 226° (decomp.) (6·0 g., 45%) (Found : C, 30·2; H, 1·5; N, 4·9; I, 43·0. $C_{15}H_8O_8N_2I_2$ requires C, 30·1; H, 1·4; N, 4·7; I, 42·4%).

β-[4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*dinitrophenyl*]*propionic Acid*.—Iodine in excess of sodium iodide solution (1·9N.; 12·1 ml.) was added rapidly to a stirred solution of β-(4-*p*-hydroxyphenoxy-3 : 5-dinitrophenyl)propionic acid (2 g.) in aqueous ammonia (*d* 0·88; 20 ml.) at 0°. After 5 minutes the solution was acidified with hydrochloric acid and the resultant precipitate was recrystallised from benzene, forming yellow needles, m. p. 189—191° (0·7 g., 20%) (Found : C, 33·8; H, 2·2; N, 4·2; I, 40·0. $C_{15}H_{10}O_8N_2I_2$,0·5C_6H_6 requires C, 33·8; H, 2·0; N, 4·4; I, 39·7%).

2 : 6-*Di-iodo*-4′-*methoxy*-4-*methyldiphenyl Ether* (cf. Part I, *loc. cit.*).—2 : 6-Diamino-4′-methoxy-4-methyldiphenyl ether dihydrochloride (5 g.) was dissolved in acetic acid (100 ml.), and the solution added with cooling to sulphuric acid (130 ml.). This solution was added during 30 minutes to a stirred solution of sodium nitrite (2·5 g.) in sulphuric acid (50 ml.) and acetic acid (50 ml.), the temperature being kept at −5°; stirring was continued for 1½ hours at −2°. The tetrazonium salt solution was added dropwise to sodium iodide (20 g.) and iodine (20 g.) in water (700 ml.) and chloroform (100 ml.) with vigorous stirring. After being kept overnight the organic phase was separated, washed with sodium hydrogen sulphite solution and water, and then evaporated. The residue was taken up in benzene, and the solution chromatographed on a column of alumina. Evaporation of the eluate left a gum which crystallised from ethanol as prisms (3·89 g., 52%), m. p. 110—112°, undepressed on admixture with an authentic specimen.

4′-Hydroxy-2 : 6-*di-iodo*-4-*methyldiphenyl Ether*.—2 : 6-Di-iodo-4′-methoxy-4-methyldiphenyl ether (1 g.) in acetic acid (12 ml.) and hydriodic acid (*d* 1·7; 5 ml.) was heated under reflux for 1 hour. Addition of water precipitated a solid *phenol* which separated from aqueous acetic acid as prisms, m. p. 150—151° (0·8 g., 83%) (Found: C, 34·5; H, 2·4; I, 56·2. $C_{13}H_{10}O_2I_2$ requires C, 34·5; H, 2·2; I, 56·1%).

4-p-*Hydroxyphenoxy*-3 : 5-*di-iodobenzoic Acid*.—Methyl 3 : 5-di-iodo-4-*p*-methoxyphenoxybenzoate (10 g.) in acetic acid (70 ml.) and hydriodic acid (*d* 1·7; 40 ml.) was heated under reflux for 1 hour. On cooling, the product separated as minute crystals, m. p. 260° (6·34 g., 67%) (Found: I, 52·8. Calc. for $C_{13}H_8O_4I_2$: I, 52·7%) (Harington and Barger, *loc. cit.*, give m. p. 250—254°).

Ethyl β-(4-p-*Hydroxyphenoxy*-3 : 5-*di-iodophenyl*)*propionate*.—Ethyl β-(4-*p*-hydroxyphenoxy-3 : 5-dinitrophenyl)propionate (7·9 g.) in acetic acid (200 ml.) was hydrogenated at room temperature and pressure over palladised charcoal (10%; 2 g.). The diamine solution was filtered and added dropwise during 30 minutes to a stirred solution of sodium nitrite (6·8 g.) in acetic acid (100 ml.) and sulphuric acid (100 ml.) at 0°. After a further hour's stirring the tetrazonium salt solution was added dropwise to a solution of iodine (20 g.) and sodium iodide (30 g.) in water (400 ml.) with vigorous stirring, while the temperature was kept below 40°. Next morning the mixture was extracted with chloroform, and the extract shaken with sodium metabisulphite solution and evaporated to dryness. The residue was dissolved in benzene (100 ml.) and chromatographed on a column of alumina. Elution was achieved by using a solution of methanol (10% w/v) in benzene, and the eluate was concentrated to 20 ml. Addition of light petroleum caused the separation of the desired *ester* as pale brown prisms, m. p. 153—156° (5·6 g., 50%) (Found: C, 38·3; H, 3·1; I, 46·9. $C_{17}H_{10}O_4I_2$ requires C, 37·9; H, 3·0; I, 47·2%).

β-(4-p-*Hydroxyphenoxy*-3 : 5-*di-iodophenyl*)*propionic Acid*.—The foregoing ester (4·6 g.), dissolved in acetic acid (50 ml.) and hydrochloric acid (40 ml.), was heated under reflux for 1 hour. On cooling, the phenolic *acid* separated as buff-coloured crystals, m. p. 250° (4·1 g., 94%) (Found: I, 50·2. $C_{15}H_{12}O_4I_2$ requires I, 49·8%).

4′-Hydroxy-2 : 6 : 3′ : 5′-*tetraiodo*-4-*methyldiphenyl Ether*.—Iodine in excess of sodium iodide solution (1·9N.; 4·5 ml.) was added dropwise to a stirred suspension of 4′-hydroxy-2 : 6-di-iodo-4-methyldiphenyl ether (1 g.) in aqueous ethylamine (33%; 10 ml.). After 2 hours the mixture was acidified with hydrochloric acid, and a little sodium metabisulphite added to remove free iodine. Recrystallisation of the resultant solid from aqueous ethanol yielded the *ether* as prisms m. p. 198—200° (0·3 g., 20%) (Found: I, 72·1. $C_{13}H_8O_2I_4$ requires I, 72·1%).

4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*di-iodobenzoic Acid*.—Iodine in excess of sodium iodide solution (1·9N.; 41 ml.) was added dropwise to a stirred solution of 4-*p*-hydroxyphenoxy-3 : 5-di-iodobenzoic acid (10 g.) in ammonia (*d* 0·88; 500 ml.) during 30 minutes. After 1 hour the solution was acidified with hydrochloric acid, and the precipitate recrystallised from aqueous acetone (charcoal) from which it separated as white crystals, m. p. 267—269° (decomp.) (12·8 g., 84%) (Found: I, 69·8. Calc. for $C_{13}H_6O_4I_4$: I, 69·2%) (Harington and Barger, *loc. cit.*, give m. p. 255°).

β-[4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*di-iodophenyl*]*propionic Acid*.—To a stirred solution of β-(4-*p*-hydroxyphenoxy-3 : 5-di-iodophenyl)propionic acid (5 g.) in aqueous ethanol (33%; 100 ml.), a solution of iodine in excess of aqueous sodium iodide (1·9N.; 21 ml.) was added dropwise during 30 minutes. After 1 hour hydrochloric acid was added; the precipitated solid *acid* recrystallised from aqueous acetone as minute white crystals, m. p. 218—222° (7 g., 94%) (Found: C, 24·1; H, 1·6; I, 67·3. $C_{15}H_{10}O_4I_4$ requires C, 23·7; H, 1·3; I, 66·6%).

2 : 6-*Dichloro*-4′-*hydroxy*-4-*methyldiphenyl Ether*.—2 : 6-Diamino-4′-methoxy-4-methyldiphenyl ether dihydrochloride (10 g.) in acetic acid (100 ml.) was added dropwise during 30 minutes to a stirred solution of sodium nitrite (4·1 g.) in sulphuric acid (72 ml.) at 0°. After 2 hours' stirring the solution was added at 0° to a solution of cuprous chloride, prepared by heating under reflux cupric sulphate (10·8 g.), sodium chloride (5·5 g.), copper powder (6 g.), and concentrated hydrochloric acid (150 ml.). Next morning the product was extracted with benzene, and the benzene extracts after drying were passed down a column of alumina, the colourless eluate being collected. Evaporation yielded a gum and on treatment with ethanol crystals of 2 : 6-dichloro-4′-methoxy-4-methyldiphenyl ether, m. p. 76—78°, separated. A satisfactory microanalysis was not obtained and the ether was demethylated by heating it under reflux for 1 hour with acetic acid (60 ml.) and hydriodic acid (*d* 1·7; 25 ml.), to give 2 : 6-*dichloro*-4′-*hydroxy*-4-*methyldiphenyl ether*, m. p. 110—111° (4·5 g.) (Found: Cl, 26·6. $C_{13}H_{10}O_2Cl_2$ requires Cl, 26·4%).

3 : 5-*Dichloro*-4-p-*hydroxyphenoxybenzoic Acid*.—This compound was prepared from methyl 3 : 5-diamino-4-*p*-methoxyphenoxybenzoate by the procedure described above for the toluene derivative. The *acid* formed prisms, m. p. 223—225°, from acetic acid (Found: C, 52·3; H, 2·9; Cl, 23·1. $C_{13}H_8O_4Cl_2$ requires C, 52·2; H, 2·7; Cl, 23·7%).

3 : 5-*Dichloro*-4-(3 : 5-*dichloro*-4-*hydroxyphenoxy*)*benzoic Acid*.—3 : 5-Dichloro-4-*p*-hydroxyphenoxybenzoic acid (1 g.) was dissolved in acetic acid (10 ml.) and chlorine passed in for 3 hours. The acetic acid was evaporated under reduced pressure and the residual yellow oily *tetrachloro-acid* was induced to crystallize from aqueous methyl cyanide. It formed buff-coloured prisms, m. p. 216—218° (0·2 g., 16%) (Found: Cl, 38·6. $C_{13}H_6O_4Cl_4$ requires Cl, 38·5%).

3 : 5-*Dinitro*-DL-*tyrosine*.—DL-Tyrosine (50 g.) was added to sulphuric acid (200 ml.) with stirring, the temperature being kept below 10°. Nitric acid (*d* 1·42; 45 ml.) was added dropwise during 45 minutes, the temperature being kept below 15°. After a further 30 minutes the mixture was poured on ice (1 kg.), and sodium hydroxide solution (40%; 750 ml.) was added until the pH was 4—5. The red *monosodium* salt was filtered off hot (69 g., 75%) (Found: N, 13·0; Na, 7·0. $C_9H_8O_7N_3Na,2H_2O$ requires N, 12·8; Na, 7·0%). The sodium salt was suspended in methanol (500 ml.), and methanolic hydrogen chloride added until the hydrochloride dissolved on warming. The solution was evaporated to dryness after clarification (charcoal), and taken up in water, whereupon the free *amino-acid* separated (Found: C, 37·2; H, 4·1; N, 14·2. $C_9H_9O_7N_3,H_2O$ requires C, 37·4; H, 3·9; N, 14·5%).

N-*Acetyl*-3 : 5-*dinitro*-DL-*tyrosine*.—3 : 5-Dinitro-DL-tyrosine (10 g.) was dissolved in 2N-sodium hydroxide (80 ml.) and stirred whilst acetic anhydride (6 ml.) was added dropwise during 30 minutes, the temperature being below 20°. After 1 hour's stirring the solution was warmed to 40° to decompose excess of anhydride, and acidified, bright yellow prisms, m. p. 209° (8·7 g., 76%), being precipitated (Found : C, 42·3; H, 3·5; N, 13·4. $C_{11}H_{11}O_8N_3$ requires C, 42·2; H, 3·6; N, 13·4%).

N-*Acetyl*-3 : 5-*dinitro*-DL-*tyrosine Ethyl Ester*.—(*a*) The acid (25 g.) was dissolved in chloroform (500 ml.)–ethyl alcohol (60 ml.), and toluene-*p*-sulphonic acid (2 g.) added. The solution was heated under reflux for 8 hours under an azeotropic water-removal head, 30 ml. more ethanol being added after 3 hours. The cooled solution was extracted twice with 2N-sodium carbonate, and the extract acidified with hydrochloric acid. The thick brown oil which was precipitated, solidified upon scratching. The resultant *ester* separated from ethanol as yellow crystals, m. p. 129—130° (Found : C, 45·9; H, 4·6; N, 11·6. $C_{13}H_{15}O_8N_3,\frac{1}{2}EtOH$ requires C, 46·2; H, 5·0; N, 11·5%).

(*b*) This compound was also prepared by racemisation of the corresponding L-compound. *N*-Acetyl-3 : 5-dinitro-L-tyrosine ethyl ester (6·82 g.) was added to a solution of sodium (1 g.) in ethanol (100 ml.). After 4 hours' mechanical shaking chloroform (120 ml.) was added and to the vigorously stirred mixture N-hydrochloric acid (44 ml.) was added with cooling. The chloroform layer was separated, washed, and evaporated, to leave a gum which separated from ethanol as yellow needles, m. p. 129° (5·6 g., 81%). The material was optically inactive.

N-*Acetyl*-4-p-*benzoyloxyphenoxy*-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester*.—The acetyl ester (20 g.), toluene-*p*-sulphonyl chlorde (12·4 g.), and pyridine (100 ml.) were heated on the steam-bath for 30 minutes. *p*-Benzoyloxyphenol (25 g.) was added and the solution heated under reflux for 1 hour. To the cold mixture chloroform (150 ml.) was added and the mixture washed with 2N-hydrochloric acid and 2N-sodium carbonate. After evaporation of the chloroform layer the resultant solid *ester* was crystallised from ethanol, forming buff-coloured prisms, m. p. 173—175° (23 g., 72%) (Found : C, 58·2; H, 4·2; N, 7·8. $C_{26}H_{23}O_{10}N_3$ requires C, 58·1; H, 4·3; N, 7·8%).

The corresponding L-*compound* was prepared in the same way. It formed feathery pale yellow crystals, m. p. 159—160° (Found : C, 58·0; H, 4·35; N, 7·6. $C_{26}H_{23}O_{10}N_3$ requires C, 58·1; H, 4·3; N, 7·8%), and had $[\alpha]_D^{22}$ −12° (*c*, 1·2% in dioxan).

3 : 5-*Dinitro*-DL-*thyronine*.—*N*-Acetyl-4-*p*-benzoyloxyphenoxy-3 : 5-dinitro-DL-phenylalanine ethyl ester (5 g.) was heated in acetic acid (20 ml.) and hydrobromic acid (20 ml.; *d* 1·49) under reflux for 1 hour. After evaporation under reduced pressure the *hydroxy*-compound was crystallised from water from which it separated as yellow prisms, m. p. 230° (decomp.) (2·9 g., 85%) (Found : C, 47·6; H, 4·4; N, 11·3. $C_{15}H_{13}O_8N_3,H_2O$ requires C, 47·3; H, 4·0; N, 11·0%).

3 : 5-*Dinitro*-L-*thyronine*, prepared similarly, formed yellow-brown prisms, m. p. 215° (decomp.) (Found : C, 49·3; H, 3·6; N, 11·6. $C_{15}H_{13}O_8N_3$ requires C, 49·6; H, 3·6; N, 11·6%), and had $[\alpha]_D^{22}$ +20° (*c*, 0·7% in N-hydrochloric acid).

3 : 5 : 3′ : 5′-*Tetranitro*-DL-*thyronine*.—3 : 5-Dinitro-DL-thyronine (1 g.) was added in portions to sulphuric acid (60 ml.), stirred at 10°. The solution was cooled to 0° and nitric acid (0·37 ml.; *d* 1·4) was added portionwise. After 30 minutes' stirring at 0°, the solution was poured on ice and the resultant yellow solid filtered off and dissolved in boiling water (20 ml.); on cooling, orange-yellow needles separated, having m. p. 222° (decomp.). Recrystallisation proved troublesome and a satisfactory analysis was not obtained (Found : C, 35·6; H, 2·3; N, 13·6. $C_{15}H_{11}O_{12}N_5,3H_2O$ requires C, 35·5; H, 3·4; N, 13·8%).

N-*Acetyl*-3 : 5 : 3′ : 5′-*tetranitro*-DL-*thyronine*.—The free amino-acid (2 g.) was suspended in a saturated solution of sodium hydrogen carbonate (50 ml.), and the mixture stirred during the addition of acetic anhydride (2·5 ml.). The solid gradually dissolved and the solution was acidified with 2N-hydrochloric acid. The *acetyl* derivative which was precipitated crystallised from ethanol as yellow prisms, m. p. 230—231° (Found : C, 41·0; H, 2·8; N, 13·8. $C_{17}H_{13}O_{13}N_5$ requires C, 41·2; H, 2·6; N, 14·15%).

3 : 5 : 3′ : 5′-*Tetranitro*-L-*thyronine*.—This *compound* was prepared by the method described above for the corresponding DL-compound. It formed yellow orange prisms, m. p. 225° (decomp.) (Found : C, 39·7; H, 3·0; N, 14·8. $C_{15}H_{11}O_{12}N_5$ requires C, 39·7; H, 2·5; N, 15·45%). No rotation measurement was carried out as the material was insufficiently soluble in hydrochloric acid and formed a dark red solution in alkali.

N-*Acetyl*-3 : 5 : 3′ : 5′-*tetranitro*-L-*thyronine*.—Acetylation was carried out as described above. The *product* formed yellow prisms, m. p. 237° (decomp.), $[\alpha]_D^{22}$ −22° (*c*, 0·2% in dioxan) (Found : C, 41·3; H, 2·9; N, 13·7%).

3′ : 5′-*Di-iodo*-3 : 5-*dinitro*-DL-*thyronine*.—To 3 : 5-dinitro-DL-thyronine (1 g.) in a saturated solution of sodium hydrogen carbonate (100 ml.) a solution of iodine in excess of sodium iodide solution (1·9N.; 58 ml.) was added. After 20 minutes the solution was brought to pH 5 by addition of hydrochloric acid; a yellow precipitate slowly formed. The material was recrystallised by dissolving it in ethanol–hydrochloric acid, removing the ethanol by evaporation, and adjusting the pH to 5 by sodium acetate solution. The solid *iodo*-compound obtained after a number of such crystallisations had m. p. 206—207° (decomp.), but did not give a satisfactory analysis (Found : C, 28·3; H, 2·2; N, 5·6; I, 40·6. $C_{15}H_{11}O_8N_3I_2$ requires C, 29·3; H, 1·8; N, 6·8; I, 41·3%).

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