S 42. *The Synthesis of Thyroxine and Related Substances. Part I. The Preparation of Tyrosine and Some of its Derivatives, and a New Route to Thyroxine.*

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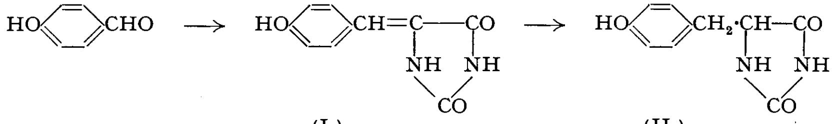
A new synthesis of tyrosine has been devised. The iodination of this amino-acid and the attempted iodination of thyronine and related diphenyl ethers are described and discussed. Contrary to a previous report, it has been found possible to tetrazotise 2 : 6-diaminodiphenyl ethers and to replace the diazo-groups by iodine atoms. This reaction is used to develop an alternative synthesis of thyroxine.

Methods for the isolation and synthesis of thyroxine, the active principle of the thyroid gland, are already available (Kendall, *J. Biol. Chem.*, 1919, **39**, 125; Harington, *Biochem. J.*, 1926, **20**, 293, 300; Harington and Barger, *ibid.*, 1927, **21**, 169; Savitzkii, *Med. Exptl., Ukraine*, 1934, No. 1, 39), but use of the substance has never become widespread although it is known to be highly active physiologically. This is partly because of the difficulties attached to its synthesis and partly because its relative insolubility, even in the form of its alkali-metal salts, was held to cause erratic absorption, with consequent unreliability of action. Although several derivatives of thyroxine have been prepared, and some shown to be capable of exerting full activity (Gaddum, *J. Physiol.*, 1927, **64**, 246; 1930, **68**, 383), they are no more soluble.

The work reported in the papers of this series was initiated to devise improved methods for preparing thyroxine and in an attempt to obtain water-soluble derivatives that would have reliable clinical activity. It was also hoped, if suitable methods were found, to synthesise analogues of thyroxine, some of which might show antithyroid activity. Several analogues have already been synthesised (Schuegraf, *Helv. Chim. Acta*, 1929, **12**, 405; Ungnade, *J. Amer. Chem. Soc.*, 1941, **63**, 2091; Niemann *et al.*, *ibid.*, 1941, **63**, 1549, 2204, 2685; 1944, **66**, 1870; Block and Powell, *ibid.*, 1942, **64**, 1070), but these have been tested only for thyroxine activity.

For our investigations the preparation of tyrosine and several of its derivatives was of importance and a considerable amount of work has been carried out on existing methods and their modifications. In addition to its isolation from natural sources tyrosine has previously been prepared by several different procedures, principally the condensation of hippuric acid or hydantoin with anisaldehyde or *p*-hydroxybenzaldehyde. The use of the latter has the advantage of making subsequent demethylation unnecessary but it gives poor yields in the azlactone synthesis (Erlenmeyer and Halsey, *Ber.*, 1897, **30**, 2981; *Annalen*, 1899, **307**, 138; Fischer, *Ber.*, 1899, **32**, 3638) and better results are obtained by condensation with hydantoin in the presence of basic catalysts followed by reduction of the *p*-hydroxybenzylidenehydantoin (I) so formed. Boyd and Robson (*Biochem. J.*, 1935, **29**, 542, 546) used diethylamine or piperidine as catalysts in the preparation of (I), followed by reduction of (I) to (II) with ammonium sulphide solution. It has now been found that morpholine is a very convenient catalyst for the condensation, enabling the reaction to be carried out at normal pressures at 160° with a good yield. In the absence of solvent, the reaction mixture becomes a hard cake. The use of excess of other bases as diluents results in a reduction in yield, but glycerol is found to give satisfactory results. Although both (I) and (II) are sparingly soluble in alcohol, (I) is reduced almost quantitatively in this solvent in the presence of Raney nickel catalyst at 130° under 60 atmospheres of hydrogen, the insoluble product being separated from the catalyst by dissolution in aqueous sodium hydroxide. The hydrolysis of (II) proceeds normally to give tyrosine in an overall yield of 55%.


(I.) (II.)

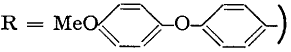
For several approaches to thyroxine, one of the most important derivatives of tyrosine is the di-iodo-compound. A number of methods are available for its preparation, all involving iodination in aqueous alkaline solutions (Wheeler and Jamieson, *Amer. Chem. J.*, 1905, **33**, 365; Bauer and Strauss, *Ber.*, 1935, **68**, 1108; Savitzkii, *J. Gen. Chem. Russia*, 1939, **9**, 1342). We have examined all these procedures in some detail but none was found to give a satisfactory yield of clean product, and we obtained much the best results by iodinating tyrosine in hot dilute hydrochloric acid with a solution of iodine monochloride in concentrated hydrochloric acid. This method has given di-iodotyrosine consistently in 86% yield and of excellent quality. [The use of iodine monochloride in acetic acid (Block and Powell, *J. Amer. Chem. Soc.*, 1943, **65**, 1430) only came to our notice after our own work had been completed.]

The methods of preparation of thyroxine may be conveniently divided into two categories : (*a*) oxidation or incubation of di-iodotyrosine, its derivatives, or proteins containing di-iodotyrosine (Harington, Pedler Lecture, *J.*, 1944, 193), and (*b*) chemical synthesis, of which there is still no alternative to the classical method devised by Harington and Barger (*loc. cit.*). Both have received attention, and for the present we are mainly reporting progress on section (*b*).

An additional approach involving the direct iodination of thyronine (deiodothyroxine) and other *p*-hydroxydiphenyl ethers was examined by Harington and Barger (*loc. cit.*), who found that these compounds would take up only two atoms of iodine, yielding products which were very difficult to purify. 3′ : 5′- and 2′ : 6′-Di-iodothyronine have been shown to be resistant to further iodination (Block and Powell, *J. Amer. Chem. Soc.*, 1942, **64**, 1070; Niemann and McCasland, *ibid.*, 1944, **66**, 1870), and it is of interest that the former, which could arise from the iodination of thyronine, tends to lose iodine on warming in the solid state or in neutral solution. During a thorough re-examination of this problem we have been unable to isolate any products containing iodine from thyronine, though of the intermediates used in its synthesis some containing a methoxyl rather than a free hydroxyl group underwent iodination to a limited extent.

Thyronine, prepared by the method of Harington and Pitt Rivers (*J.*, 1940, 1101), was caused to react with iodine in dilute sodium hydroxide solutions, with iodide and iodate mixtures in dilute sulphuric acid solutions, and with iodine in 15% oleum at 120°. The products obtained from these reactions were invariably amorphous solids or gums and no pure materials could be isolated. It was thought that one possible explanation might be the oxidative nature of the reagents employed, and a number of experiments were carried out with iodine monochloride in aqueous hydrochloric and acetic acid solutions under various temperatures and conditions; again only intractable solids were obtained and from them no pure materials could be isolated. Since it is known that benzoylhistidine, histidine anhydride, and tyrosine amide can be iodinated under conditions that leave the parent amino-acids unaffected (Bauer and Strauss, *Ber.*, 1935, **68**, 1108), similar experiments were carried out on thyronine methyl ester and its *N*-toluene-*p*-sulphonyl derivative. The former underwent extensive decomposition on treatment with iodine or iodine monochloride in acid solution, and in alkaline solution yielded a high-melting unidentified material containing neither iodine nor nitrogen, showing that oxidative destruction of the side chain had taken place. The *N*-toluene-*p*-sulphonyl ester was more stable and was recovered unchanged after experiments at room temperature, but it also yielded intractable material at higher temperatures. Finally, a number of experiments were carried out, with iodine monochloride in acetic acid, on intermediates (III—VI) obtained during the preparation of thyronine.

$R{\cdot}CO_2Et$	$R{\cdot}CO{\cdot}NH{\cdot}NH_2$	$R{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}SO_2{\cdot}C_6H_4Me(p)$	$R{\cdot}CHO$
(III.)	(IV.)	(V.)	(VI.)



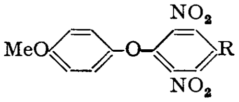
Products obtained from (IV) and (V) had usually suffered degradation and contained neither halogen nor nitrogen, and only the parent carboxylic acid was identified among the reaction products. Both (III) and (VI), however, yielded crystalline products containing iodine, and giving satisfactory analyses for derivatives containing one iodine atom. The product from (VI) was isolated and analysed as a *dinitrophenylhydrazone*. The introduction of one iodine atom represented the most that could be achieved, and more vigorous reaction conditions led to no greater degree of substitution.

All attempts to di-iodinate diphenyl ethers having failed, attention was directed to the alternative of synthesising diphenyl ethers in which the 2 : 6-positions were already occupied by iodine or by other groups that could be converted subsequently into iodine. It had been already recognised that dinitrophenols in general (Raiford and Colbert, *J. Amer. Chem. Soc.*, 1926, **48**, 2652) do not react with aryl halides. Similarly, 2 : 6-di-iodophenols such as 3 : 5-di-iodo-4-hydroxybenzoic acid (Harington and Barger, *loc. cit.*) and 3 : 5-di-iodotyrosine (Canzanelli, Harington, and Randall, *Biochem. J.*, 1934, **28**, 68) will not form diphenyl ethers, an observation we have confirmed for the reaction of 3 : 5-di-iodo-4-hydroxybenzaldehyde with *p*-iodonitrobenzene or *p*-bromoanisole. However, the preparation of diphenyl ethers from

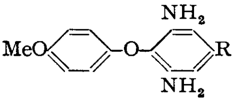
3 : 4 : 5-tri-iodonitrobenzene and quinol monomethyl ether or *N*-benzoyltyrosine ethyl ester (Harington and Barger, *loc. cit.*; Canzanelli, Harington, and Randall, *loc. cit.*) proceed normally. An attempt to simplify the present thyroxine synthesis by condensing 4-chloro-3 : 5-di-iodobenzoic acid or its *methyl* ester with quinol or quinol monomethyl ether failed under a large variety of conditions. This indicated that an activating group such as nitro- at the *p*-position is essential for successful reaction of a tri-iodo-component.

It is well known that aromatic halogen compounds in which the halogen is activated by nitro-groups in the *o*- and *p*-positions will readily undergo ether formation with either alcohols or phenols. The application of this principle to a thyroxine synthesis was questionable because of the reported failure (Harington and Barger, *loc. cit.*) to convert the 3 : 5-diaminodiphenyl ether (VIII; R = Me), prepared by reduction of the corresponding dinitro-compound, into the 2 : 6-di-iododiphenyl ether (IX; R = Me) by tetrazotisation and treatment with iodide solutions. Although these compounds were obtained, their preparation and properties were not recorded, and this has now been done in the experimental section of this paper. We have re-examined this issue, employing anhydrous conditions for the tetrazotisation.

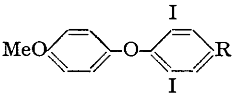
Condensation of 4-bromo-3 : 5-dinitrotoluene with quinol monomethyl ether gave the *dinitrodiphenyl ether* (VII; R = Me), which could be reduced catalytically to an unstable diamine (VIII; R = Me), characterisable as a stable *dihydrochloride.* When a solution of this diamine (VIII; R = Me) in glacial acetic acid was run into a cold, stirred solution of nitrosylsulphuric acid in concentrated sulphuric acid (cf. Hodgson and Walker, *J.*, 1935, 530), a solution of the tetrazonium salt was obtained: this on decomposition by aqueous potassium iodide solution yielded the required di-iodo-compound, 2 : 6-*di-iodo*-4′-*methoxy*-4-*methyldiphenyl ether* [3 : 5-*di-iodo*-4-(4′-*methoxyphenoxy*)*toluene*] (IX; R = Me).



(VII.)



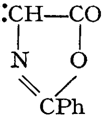
(VIII.)



(IX.)

Similarly, methyl 4-chloro-3 : 5-dinitrobenzoate, on condensation with quinol monomethyl ether in the presence of potassium hydroxide at 150°, yielded methyl 3 : 5-dinitro-4-(4′-methoxyphenoxy)benzoate (VII; R = CO_2Me) in good yield, though the use of excess alkali in the condensation led to the formation of 3 : 5-dinitro-4-hydroxybenzoic acid as the main product of the reaction, presumably by fission of the diphenyl ether first formed; the same material was obtained by the aqueous alkaline hydrolysis of (VII; R = CO_2Me). Acid hydrolysis, however, gave the free *acid* (VII; R = CO_2H) without disruption of the ether bond. The ester (VII; R = CO_2Me) could be reduced to (VIII; R = CO_2Me) by tin and hydrochloric acid, active iron, or preferably catalytic hydrogenation with the aid of palladised charcoal, and the *diamine* (VIII; R = CO_2Me) was further characterised by the preparation of *diacetyl* and *dibenzoyl* derivatives. Tetrazotisation of this diamine by the above technique yielded the new *di-iododiphenyl ether* (IX; R = CO_2Me). It was established therefore that two 2 : 6-dinitrodiphenyl ethers substituted in the 4-position by different groups, namely, methyl and carbomethoxy-, could be converted into the corresponding di-iodo-compounds by reduction and tetrazotisation, provided the latter reaction was carried out under substantially anhydrous conditions. It may be mentioned that the use of the more usual aqueous conditions of diazotisation failed to give the iodo-compounds after treatment with iodides.

Conversion of (IX; R = CO_2Me) into (IX; R = CHO) was attempted by three procedures. Rosenmund reductions of (VII; R = COCl) and (IX; R = COCl) in refluxing toluene in presence of palladised charcoal or platinum oxide with a stream of hydrogen, and thiourea as inhibitor (Weygand and Meusel, *Ber.*, 1943, **76**, 503), proved slow and failed to go to completion. Aldehyde derivatives could not be obtained from the mixtures of products obtained, nor could any pure reaction product be isolated. Although no tractable material resulted when (VII; R = CO_2H) or 4-chloro-3 : 5-dinitrobenzoic acid was treated with formic acid and titanium oxide at 250° according to the method developed by Davies and Hodgson (*J.*, 1943, 84), (IX; R = CO_2H) was recovered largely unchanged. The aldehyde (IX; R = CHO) was, however, obtained as its *dinitrophenylhydrazone* from the *toluene*-p-*sulphonyl* derivative of 3 : 5-*di-iodo*-4-(4′-*methoxyphenoxy*)*benzhydrazide* [IX; R = $CO{\cdot}NH{\cdot}NH{\cdot}SO_2{\cdot}C_6H_4Me(p)$] by reaction with sodium carbonate in ethylene glycol (cf. McFadyen and Stevens, *J.*, 1936, 584). The toluenesulphonhydrazide was prepared by the usual methods from (IX; R = CO_2Me), but its decomposition to the aldehyde was difficult, as the conditions of the reaction were critical and any increase in the time of heating over 30 seconds resulted in a fall in yield. At best, the aldehyde was obtained in 35% yield in the form of its dinitrophenylhydrazone, but the free aldehyde was not isolated. By treating the crude reaction mixture with hippuric acid, acetic anhydride, and sodium acetate in the usual way, a substance was obtained identical in melting point and other properties with the oxazalone (IX; R = •CH:CH—CO) obtained by Harington and Barger in their synthesis of thyroxine.



$$\cdot CH{:}\underset{N \searrow\!\!\swarrow O}{C}H{-}CO \quad (N{=}CPh{-}O)$$

Thus a new synthesis of thyroxine involving a 2 : 6-dinitrodiphenyl ether as an intermediate has been achieved and could be employed instead of the existing method.

EXPERIMENTAL.

5-(4′-*Hydroxybenzylidene*)*hydantoin* (I).—To an intimate mixture of hydantoin (500 g.) and *p*-hydroxybenzaldehyde (750 g.) in a 5-litre round-bottom flask, glycerol (1 l.) and morpholine (180 ml.) were added. The flask was fitted with an air condenser and heated for 3½ hours at 160°. The reaction mixture formed a deep red solution as the temperature rose, and a small quantity of liquid refluxed. After 15 mins.' refluxing solid began to separate. On completion of the heating period the flask was cooled and ethyl alcohol (1 l.) was added. The solid was removed by filtration, washed with alcohol, and dried at 100°; yield 820 g. (80%); m. p. 308° (lit. 315°).

5-(4′-*Hydroxybenzyl*)*hydantoin* (II).—The above hydantoin (100 g.) was suspended in alcohol (350 ml.) with Raney nickel catalyst (9 g.). The mixture was then hydrogenated at 50 atm. pressure of hydrogen until absorption ceased. This took about 5 hours at 130°. After cooling, the product and catalyst were filtered off. The filtrate was evaporated to dryness in a vacuum and the two solid fractions were combined and extracted with 2N-sodium hydroxide solution (700 ml.). The solution was filtered through kieselguhr to remove suspended solid, and the filtrate after dilution with water (400 ml.) was neutralised with concentrated hydrochloric acid, with cooling. The precipitate was filtered off, washed with water, and dried at 80°; yield 95 g. (94%), m. p. 259° (lit. 258—260°).

DL-*Tyrosine*.—The reduced hydantoin (258 g.) was hydrolysed with 2N-sodium hydroxide solution (2·6 l.) by refluxing for 24 hours. The hot solution was filtered from a small quantity of insoluble material, diluted with water (500 ml.), and neutralised with concentrated hydrochloric acid (about 250 ml.) and acetic acid (100 ml.). The pH of the solution should be about 7·4. After standing for some time in the refrigerator the tyrosine was filtered off, washed with cold water and alcohol, and dried at 60°; yield 192 g. (84%), m. p. 320—322° (lit. 316°).

DL-3 : 5-*Di-iodotyrosine*.—DL-Tyrosine (62 g.) was stirred with 2N-hydrochloric acid (186 ml.) and water (510 ml.) at 90°. A solution of iodine monochloride (112 g.) in concentrated hydrochloric acid (155 ml.) was run in during 30 minutes with stirring. Water (200 ml.) was added and the mixture was stirred for another 90 minutes after the addition of the iodine monochloride solution. A 10% solution of sodium metabisulphite was added to the hot solution until decolorisation was almost complete, followed by sodium hydroxide solution (40%) till solid began to separate out. At this point the solution should be slightly acid to Congo-red paper. After cooling, the precipitated solid was filtered off, washed with water and alcohol, and dried in a desiccator; yield 128 g. (86%), m. p. 197—198° (Found : N, 3·15; I, 58·3. Calc. for $C_9H_9O_3NI_2$: N, 3·2; I, 58·5%).

Iodination of Ethyl 4-(4′-*Methoxyphenoxy*)*benzoate*.—This benzoate (1 g.) was dissolved in glacial acetic acid (10 ml.) and a solution of iodine monochloride (2·4 g.; 4 equivs.) in glacial acetic acid (5 ml. was run in slowly with shaking. The mixture was heated on a steam-bath for 30 minutes and water (50 ml.) was added, whereupon a dark oil separated. The oil was extracted with ether, and the extracts were washed with sodium metabisulphite solution, calcium hydroxide suspension, and water. The ethereal solution was dried (Na_2SO_4) and evaporated, leaving an oil which crystallised on standing. The solid was filtered off and crystallised from methyl alcohol (charcoal); yield 1·1 g., m. p. 79—80°. A solution of the material in benzene was run through a short column of alumina. The column was washed with benzene, the eluate evaporated to dryness, and the *iodo*-ester crystallised from methanol; yield 0·4 g., m. p. 83° (Found : C, 48·05; H, 3·9; I, 31·2; OCH_3, 8·0; *M*, 376. $C_{16}H_{15}O_4I$ requires C, 48·3; H, 3·8; I, 31·9; OCH_3, 7·8%; *M*, 398).

Iodination of 4-(4′-*Methoxyphenoxy*)*benzaldehyde*.—The aldehyde (1·14 g.) was dissolved in hot glacial acetic acid (20 ml.) and iodinated with a solution of iodine monochloride (0·75 ml.) in acetic acid. Addition of water to the cooled reaction mixture precipitated an oil which, on dissolving in acetic acid and treatment with a solution of 2 : 4-dinitrophenylhydrazine, gave a *dinitrophenylhydrazone*, m. p. 194° (Found : N, 10·6; I, 23·8. $C_{20}H_{15}O_6N_4I$ requires N, 10·5; I, 23·8%).

4-*Chloro*-3 : 5-*di-iodobenzoic Acid* (cf. Fr.P. 835,727).—*p*-Chlorobenzoic acid (4 g.), 10% oleum (18 ml.), and iodine (10 g.) were heated to 160° till all the iodine had reacted. A further quantity of iodine (4 g.) was added, and heating continued until this also had disappeared. The cooled mixture was poured into water, and the solid filtered off and dried. The crude *acid* was partly purified by boiling with chloroform and the insoluble material was crystallised from ethyl alcohol, forming white needles (7·6 g., 73%), m. p. 303—304° (Found : C, 20·6; H, 0·7; Halogen, 74·0. $C_7H_3O_2ClI_2$ requires C, 20·6; H, 0·85; Halogen, 70·9%).

Methyl 4-*Chloro*-3 : 5-*di-iodobenzoate*.—4-Chloro-3 : 5-di-iodobenzoic acid (5 g.) was dissolved in dry methyl alcohol (200 ml.), and the boiling solution saturated with hydrogen chloride. On cooling, the required *methyl* ester crystallised, and was filtered off and recrystallised from methyl alcohol; yield 5 g. (95%), m. p. 151° (Found : Halogen, 67·5. $C_8H_5O_2ClI_2$ requires Halogen, 68·5%).

2 : 6-*Dinitro*-4′-*methoxy*-4-*methyldiphenyl Ether* [3 : 5-*Dinitro*-4-(4′-*methoxyphenoxy*)*toluene*] (VII; R = Me).—4-Bromo-3 : 5-dinitrotoluene (10 g.), potassium hydroxide (3 g.), quinol monomethyl ether

(6·25 g.), and water (15 ml.) were heated under reflux for 5 hours at 150°. The cooled mixture was diluted with alkali, and the insoluble material, filtered off and crystallised from ethyl alcohol, formed bright yellow prisms (6 g., 50%), m. p. 144—145° (Found: C, 55·7; H, 4·0; N, 9·9. $C_{14}H_{12}O_6N_2$ requires C, 55·4; H, 3·95; N, 9·2%).

2 : 6-*Diamino*-4′-*methoxy*-4-*methyldiphenyl Ether Dihydrochloride* (as VIII; R = Me).—The above dinitro-compound (1 g.) was suspended in glacial acetic acid and shaken in an atmosphere of hydrogen with palladised charcoal (10%; 1 g.) until the theoretical amount of hydrogen was absorbed. The filtered liquid was evaporated to dryness, and the residual solid taken up in a little ethyl alcohol. Dry hydrogen chloride was passed in for a few minutes, and ethyl acetate was added until precipitation was complete. The *dihydrochloride* was filtered off and crystallised from alcohol–ethyl acetate; yield 0·9 g. (90%), m. p. 224° (decomp.) (Found: C, 53·7; H, 5·9; N, 8·75; Cl, 21·0. $C_{14}H_{18}O_2N_2Cl_2$ requires C, 53·0; H, 5·7; N, 8·8; Cl, 22·4%).

2 : 6-*Di-iodo*-4′-*methoxy*-4-*methyldiphenyl Ether* (IX; R = Me).—The above diamine dihydrochloride (0·9 g.) in glacial acetic acid (20 ml.) was added slowly and with stirring to a cooled solution of sodium nitrite (0·6 g.) in concentrated sulphuric acid (6 ml.). After 30 mins.' stirring, the deep red solution was poured into potassium iodide (7 g.) in water (20 ml.). After standing for some hours, the dark oily product was separated and shaken with benzene and a 0·5% solution of sodium thiosulphate. The pale red benzene solution was separated, filtered, and the product adsorbed on a short column of alumina. Elution of the alumina with 5% methyl alcohol in benzene caused a deep red band to pass down the column. The product was obtained by evaporating the eluate collected before this band reached the bottom of the column, and the resulting solid was crystallised from aqueous acetone, forming buff-coloured plates (0·2 g., 15%), m. p. 112—113° (Found: C, 36·15; H, 2·5; I, 53·5. $C_{14}H_{12}O_2I_2$ requires C, 36·0; H, 2·6; I, 54·5%).

Methyl 3 : 5-*Dinitro*-4-(4′-*methoxyphenoxy*)*benzoate* (VII; R = CO_2Me).—Methyl 4-chloro-3 : 5-dinitrobenzoate (10 g.), potassium hydroxide (2·3 g.), quinol monomethyl ether (5 g.), and water (10 ml.) were heated at 150° for 3 hours under reflux. The cooled mixture was stirred with 2N-sodium hydroxide, and the insoluble *ester* was filtered off and crystallised from ethyl alcohol, forming bright yellow lances (9·5 g., 71%), m. p. 129° (Found: C, 52·0; H, 3·4; N, 7·9. $C_{15}H_{12}O_8N_2$ requires C, 51·5; H, 3·4; N, 8·05%).

3 : 5-*Dinitro*-4-(4′-*methoxyphenoxy*)*benzoic Acid* (VII; R = CO_2H).—The above ester (0·5 g.) was boiled for 30 minutes with glacial acetic acid (15 ml.), concentrated hydrochloric acid (5 ml.), and water (5 ml.). The solution was evaporated to dryness, and the residual *acid* was crystallised from benzene; m. p. 205—206° (Found: C, 50·25; H, 2·9. $C_{14}H_{10}O_8N_2$ requires C, 50·25; H, 3·0%).

The acid (5 g.) was converted into the *acid chloride* by treatment with excess of thionyl chloride (15 ml.) on a steam-bath till the reaction ceased. Excess of thionyl chloride was evaporated in a vacuum and the residual oil was triturated with carbon tetrachloride until it solidified. The solid was crystallised from chloroform–carbon tetrachloride and formed yellow needles, m. p. 128—129° (decomp.) (Found: N, 7·9; Cl, 10·0; OCH_3, 9·1. $C_{14}H_9O_7N_2Cl$ requires N, 7·9; Cl, 10·1; OCH_3, 8·8%).

Methyl 3 : 5-*Diamino*-4-(4′-*methoxyphenoxy*)*benzoate* (VIII; R = CO_2Me).—Methyl 3 : 5-dinitro-4-(4′-methoxyphenoxy)benzoate (5 g.), suspended in glacial acetic acid (40 ml.), was shaken in an atmosphere of hydrogen with palladised charcoal (10%; 1 g.) until the uptake of hydrogen ceased (about ½ hour). The filtered solution was evaporated to dryness, and the residual *diamino*-ester crystallised from aqueous acetone to give white prisms (3·7 g., 90%), m. p. 166° (Found: C, 62·4; H, 5·6; N, 9·75. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·55; N, 9·7%). The *dibenzoyl* derivative, prepared by benzoylation in pyridine with benzoyl chloride and precipitation with water, crystallised from ethyl alcohol in the form of white prisms, m. p. 208° (decomp.) (Found: N, 5·6. $C_{29}H_{24}O_6N_2$ requires N, 5·6%). The *diacetyl* derivative was prepared by treatment of the base with acetic anhydride at room temperature for 30 mins. After decomposition of the excess of anhydride with water, the solid was collected, and crystallised from alcohol in the form of white needles, m. p. 198—199° (Found: N, 7·15. $C_{19}H_{20}O_6N_2$ requires N, 7·5%).

Methyl 3 : 5-*Di-iodo*-4-(4′-*methoxyphenoxy*)*benzoate* (IX; R = CO_2Me).—Methyl 3 : 5-diamino-4-(4′-methoxyphenoxy)benzoate (2 g.), dissolved in glacial acetic (20 ml.), was added slowly to a cooled solution of sodium nitrite (1·2 g.) in concentrated sulphuric acid (12 ml.) with stirring and cooling in ice. The deep red solution was stirred for a further 30 minutes and poured into a solution of potassium iodide (10 g.) in water. After standing for 1 hour, the mixture was heated to 80° on the water-bath and cooled, and the insoluble sticky crude product was filtered off, dried in a vacuum, and dissolved in acetone. The acetone solution was filtered through a pad of alumina to remove coloured impurities, and the filtrate was evaporated to dryness, triturated with ethyl alcohol, and the insoluble residue crystallised from aqueous acetone to give buff-coloured plates (1·9 g., 40%), m. p. 153—154° (Found: C, 35·7; H, 2·4; I, 49·1. $C_{15}H_{12}O_4I_2$ requires C, 35·3; H, 2·35; I, 49·7%).

The *acid* was obtained from the above *ester* by refluxing with 2N-sodium hydroxide solution for 2 hours. The solution was cooled, filtered, and acidified, and the precipitated acid was filtered off and crystallised from aqueous alcohol; m. p. 233° (Found: C, 34·1; H, 2·2. $C_{14}H_{10}O_4I_2$ requires C, 34·0; H, 2·0%).

3 : 5-*Di-iodo*-4-(4′-*methoxyphenoxy*)*benzoyl Chloride* (IX; R = COCl).—This was obtained when the above acid (1 g.) was heated on the steam-bath with thionyl chloride (5 ml.) until reaction was complete. Excess of thionyl chloride was removed in a vacuum, and the crystalline residue recrystallised from petrol (b. p. 80—100°) as pale yellow prisms (80%), m. p. 138—139° (Found: Halogen, 57·5. $C_{14}H_9O_3ClI_2$ requires Halogen, 56·8%).

3 : 5-*Di-iodo*-4-(4′-*methoxyphenoxy*)*benzhydrazide* (IX; R = CO·NH·NH_2).—Methyl 3 : 5-di-iodo-4-(4′-methoxyphenoxy)benzoate (6·6 g.) was suspended in dry methyl alcohol (30 g.) in a pressure bottle, hydrazine hydrate (90%; 3·3 ml.) was added, and the mixture heated for 8 hours in a boiling water-bath. Crystals of the *hydrazide* separated out on cooling the reaction mixture, and were filtered off and crystallised from methyl alcohol, giving fine white needles (5·9 g., 90%), m. p. 239—240° (Found: N, 5·6; I, 50·3. $C_{14}H_{12}O_3N_2I_2$ requires N, 5·5; I, 49·7%). The hydrazide could also be prepared by

refluxing a solution of the ester with hydrazine hydrate in *n*-butyl alcohol for 5 hours. Its *toluene-*p-*sulphonyl* derivative was prepared by dissolving the hydrazide (1·4 g.) in dry pyridine (50 ml.) and adding toluene-*p*-sulphonyl chloride (0·56 g.). The mixture was kept for 30 mins. and poured into 5N-hydrochloric acid (200 ml.). The precipitated yellow solid was filtered off and crystallised from ethyl alcohol as pale yellow prisms (60%), m. p. 196—197° (Found: N, 4·5; S, 4·8. $C_{21}H_{18}O_5N_2I_2S$ requires N, 4·2; S, 4·8%).

3 : 5-*Di-iodo*-4-(4′-*methoxyphenoxy*)*benzaldehyde* 2 : 4-*Dinitrophenylhydrazone*.—The above mixed hydrazide (2 g.) was suspended in ethylene glycol (10 ml.), and the suspension heated to 160° in an oil-bath. Anhydrous sodium carbonate (0·5 g.) was added, and the mixture heated for 30 seconds longer and poured into water. The oily material was extracted with ether, and the extract dried and evaporated. The residue was dissolved in ethyl alcohol, and the solution filtered and added to an acid alcoholic solution of 2 : 4-dinitrophenylhydrazine. The crude *dinitrophenylhydrazone* separated as a deep red solid which was crystallised from aqueous acetic acid, giving red prisms (0·5 g., 35%), m. p. 212° (decomp.) (Found: N, 8·5. $C_{20}H_{14}O_6N_4I_2$ requires N, 8·5%).

2-Phenyl-4-[3′ : 5′-di-iodo-4′-(4″-methoxyphenoxy)benzylidene]oxazol-5-one was prepared from the ethereal extract after evaporation and condensation with hippuric acid in the usual fashion (Harington and Barger, *loc. cit.*); m. p. 211°.

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