547. *The Synthesis of Thyroxine and Related Substances. Part VII. The Preparation of Diphenyl Ethers from* 2 : 6-*Di-iodophenols.*

By J. H. Barnes, E. T. Borrows, J. Elks, B. A. Hems, and A. G. Long.

p-Halogenonitrobenzenes and *p*-nitrophenylpyridinium salts do not react with 2 : 6-di-iodophenols but the corresponding 2 : 4-dinitro-compounds give 2 : 6-di-iodo-2 : 4-dinitro-diphenyl ethers. Attempts to reduce one or both of the nitro-groups of 3 : 5-di-iodo-4-(2 : 4-di-nitrophenoxy)-*N*-acetyl-L-phenylalanine ethyl ester failed to yield a pure product. When 2 : 6-dinitrophenylpyridinium salts were treated with 2 : 6-di-iodophenols in hot pyridine, one iodine atom was lost and 2-iodo-2′ : 6′-dinitrodiphenyl ethers were produced. A 2 : 6-di-iodo-2′ : 6′-dinitrodiphenyl ether resulted from the reaction of methyl 4-chloro-3 : 5-di-nitro-benzoate and 3 : 5-di-iodo-*p*-cresol under mild conditions, but this method could not be applied to less highly activated halogeno-compounds.

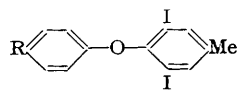
Attempts to prepare 2 : 6-di-iododiphenyl ethers *via* di-iodoso- or di-iodoxy-phenols were unsuccessful. 4-Acetoxy*cyclo*hex-2-enyl ethers of 2 : 6-di-iodophenols were prepared but could not be dehydrogenated to 2 : 6-di-iodo-diphenyl ethers. 3 : 5-Di-iodo-4-(3-keto*cyclo*hex-1-enyloxy)toluene was readily converted into 2 : 6-di-iodo-3′-hydroxy-4-methyldiphenyl ether by successive bromination, dehydrobromination, and rearrangement, but attempts to prepare the 4′-hydroxy-compound by similar means were unsuccessful.

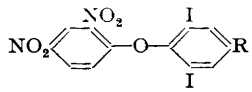
The difficulties associated with the synthesis of thyroxine have been largely caused by the lack of convenient methods for the preparation of 2 : 6-di-iododiphenyl ethers. Harington and Barger (*Biochem. J.*, 1927, **21**, 169) in their original synthesis of the hormone built up this system by reaction of 3 : 4 : 5-tri-iodonitrobenzene with *p*-methoxyphenol, but were then faced

with the elaboration of an α-alanine side-chain from an aromatic nitro-group. An attempt to simplify this process (Part I of this series; Borrows, Clayton, and Hems, *J.*, 1949, S 185) failed because neither 4-chloro-3 : 5-di-iodobenzoic acid nor its methyl ester could be made to react with quinol or its monomethyl ether. The syntheses of DL- and L-thyroxine reported in previous papers of this series (*J.*, 1949, 3424, S 185, S 190, S 199) have depended on the preparation of 2 : 6-dinitrodiphenyl ethers from halogeno-2 : 6-dinitrobenzenes or 2 : 6-dinitrophenols and the replacement of the nitro-groups by iodine atoms *via* the diamines. These methods have allowed the use as starting materials of tyrosine or its derivatives in which the required side chain is already present and convenient syntheses of thyroxine have been devised, but one of our aims throughout this work has been to find a more direct method, proceeding *via* 3 : 5-di-iodotyrosine which is very readily available.

The only method so far described for the preparation of diphenyl ethers from 2 : 6-di-iodophenols is the oxidation, under mild conditions, of 3 : 5-di-iodotyrosine or its derivatives to the corresponding derivative of thyroxine (see Harington, *J.*, 1944, 193, for earlier references; Harington and Pitt Rivers, *Biochem. J.*, 1945, **39**, 157; Pitt Rivers, *ibid.*, 1948, **43**, 223; Turner and Reineke, U.S.P. 2,435,947; Every, B.P. 598,691). By selection of a suitable derivative of 3 : 5-di-iodotyrosine this method can be made to give thyroxine in fair yield (Pitt Rivers, *loc. cit.*), but it is very inflexible; apart from simple derivatives of 3 : 5-di-iodotyrosine, the only compound that has been used successfully is the related β-(3 : 5-di-iodo-4-hydroxyphenyl)lactic acid (Saul and Trikojus, *Biochem. J.*, 1948, **42**, 80).

Attempts to prepare ethers by treatment of 2 : 6-di-iodophenols with aryl halides have been described by Harington and Barger (*loc. cit.*), by Canzanelli, Harington, and Randall (*ibid.*, 1934, **28**, 68), and by Borrows, Clayton, and Hems (*J.*, 1949, S 185), but even as reactive a halide as *p*-iodonitrobenzene failed to react. *p*-Fluoronitrobenzene was shown by Rarick, Brewster, and Dains (*J. Amer. Chem. Soc.*, 1933, **55**, 1289) to be particularly reactive towards rather inert phenols but we have been unable to prepare 2 : 6-di-iodo-4′-nitro-4-methyldiphenyl ether (I; R = NO_2) from this fluoro-compound and 3 : 5-di-iodo-*p*-cresol.

(I.) 

 (II.)

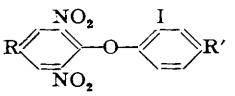
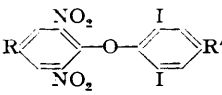
Since one nitro-group appeared to cause insufficient activation, the reactions of 1-chloro-2 : 4-dinitrobenzene and of 1-(2 : 4-dinitrophenyl)pyridinium chloride were next investigated. This chloride with 3 : 5-di-iodo-*p*-cresol in boiling pyridine gave 2 : 6-di-iodo-2′ : 4′-dinitro-4-methyldiphenyl ether (II; R = Me) in 62% yield, and the same compound resulted from the reaction between 1-chloro-2 : 4-dinitrobenzene and 3 : 5-di-iodo-*p*-cresol, either in alcoholic sodium ethoxide or in methyl ethyl ketone in the presence of potassium carbonate. By one or other of these methods the diphenyl ethers, (II; R = CHO, CO_2Me, and $CH_2{\cdot}CH_2{\cdot}CO_2Et$), were also prepared.

Attention was next turned to the preparation of diphenyl ethers from 3 : 5-di-iodotyrosine. Previous experience suggested that both the amino- and the carboxy-group should be protected and the derivative chosen was 3 : 5-di-iodo-*N*-acetyltyrosine ethyl ester, the preparation of which from 3 : 5-di-iodo-L-tyrosine has been improved (see Experimental section). Both the L- and the DL-ester lost iodine on crystallisation, but this could be prevented by the presence of a little mineral acid. An attempt to prepare the L-acetamido-ester directly from 3 : 5-di-iodo-*ON*-diacetyl-L-tyrosine was unsuccessful; esterification of this compound in chloroform solution left the acetoxy-group intact and the resulting 3 : 5-di-iodo-*ON*-diacetyl-L-tyrosine ethyl ester was stable to boiling alcoholic hydrogen chloride.

The acetamido-esters were converted into the corresponding 3 : 5-di-iodo-4-(2′ : 4′-dinitrophenoxy)-*N*-acetylphenylalanine ethyl esters [II; R = $CH_2{\cdot}CH(NHAc){\cdot}CO_2Et$] by the usual method. A number of attempts were made to reduce, selectively, the 2-nitro-group of [II; R = L-$CH_2{\cdot}CH(NHAc){\cdot}CO_2Et$] both with stannous chloride and with alkali sulphides under various conditions, but no crystalline product could be isolated. Attempts to reduce the dinitro-compound to the diamine with stannous chloride or titanous chloride also gave impure material.

It seemed probable that halogeno-2 : 6-dinitrobenzenes and 1-(2 : 6-dinitrophenyl)pyridinium salts would behave in much the same way as their 2 : 4-dinitro-analogues and some model experiments were carried out. When 1-(2 : 6-dinitro-4-methylphenyl)pyridinium toluene-*p*-sulphonate was treated with 3 : 5-di-iodo-4-hydroxybenzaldehyde in boiling pyridine, the only

solid product, which was isolated in small yield, was 3-iodo-4-(2 : 6-dinitro-4-methylphenoxy)-benzaldehyde (III; R = Me, R′ = CHO). Treatment of the material with morpholine at 100° gave 3-iodo-4-hydroxybenzaldehyde and 3 : 5-dinitro-4-morpholinotoluene, the latter being also prepared from morpholine and 4-chloro-3 : 5-dinitrotoluene. For comparison the 3-iodo-4-hydroxybenzaldehyde was prepared very conveniently by addition of iodine to *p*-hydroxy-benzaldehyde in dimethylamine solution. Treatment of the monoiodo-aldehyde in pyridine solution with 1-(2 : 6-dinitro-4-methylphenyl)pyridinium toluene-*p*-sulphonate gave (III; R = Me, R′ = CHO) identical with the material obtained as described above.

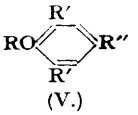
(III.)   (IV.)

This rather remarkable loss of an iodine atom has been observed in reactions between 1-(2 : 6-dinitro-4-methylphenyl)pyridinium toluene-*p*-sulphonate and 3 : 5-di-iodo-*p*-cresol, between 1-(2 : 6-dinitro-4-carbomethoxyphenyl)pyridinium chloride and methyl 3 : 5-di-iodo-4-hydroxybenzoate, and between 1-(2 : 6-dinitro-4-methoxyphenyl)pyridinium toluene-*p*-sulphonate and 3 : 5-di-iodo-*p*-cresol, pyridine at 100° being used as solvent. From each only one compound could be obtained pure and this in very poor yield. Analysis indicated an iodine : nitrogen ratio of 1 : 2 and, by analogy, the products of these three reactions are regarded as having the structures (III; R = R′ = Me), (III; R = R′ = CO_2Me), and (III; R = OMe, R′ = Me), respectively.

Although this loss of iodine might appear to be related to the difficulty in accommodating four bulky groups in the positions *ortho* to the oxygen atom, it has nevertheless been possible to prepare a 2 : 6-di-iodo-2′ : 6′-dinitrodiphenyl ether by employing less vigorous conditions; thus, methyl 4-chloro-3 : 5-dinitrobenzoate with 3 : 5-di-iodo-*p*-cresol in the presence of potassium carbonate in methyl ethyl ketone gave a fair yield of a compound giving the correct analysis for methyl 3 : 5-dinitro-4-(2 : 6-di-iodo-4-methylphenoxy)benzoate (IV; R = CO_2Me, R′ = Me). On prolonged heating with morpholine this gave 3 : 5-di-iodo-*p*-cresol, showing that there had been no migration of the iodine atoms.

Attempts to prepare (IV; R = R′ = Me) by reaction of 4-chloro-3 : 5-dinitrotoluene with 3 : 5-di-iodo-*p*-cresol under similar conditions were unsuccessful, and it seems probable that the ability of methyl 4-chloro-3 : 5-dinitrobenzoate to undergo the reaction depends on the extra activation of the chlorine atom by the *p*-carbomethoxy-group.

There are some indications in the literature (Vorländer, *Ber.*, 1925, **58**, 1893; Masson, Race and Pounder, *J.*, 1935, 1669) that iodoxy-groups, like nitro-groups, are electrophilic, and the possibility arose of obtaining diphenyl ethers from 2 : 6-di-iodoso- (V; R = H, R′ = IO) or 2 : 6-di-iodoxyphenols (V; R = H, R′ = IO_2) *via* their toluene-*p*-sulphonic esters and the quaternary salts (VI; R′ = IO or IO_2). Reduction of the product would then give a 2 : 6-di-iododiphenyl ether.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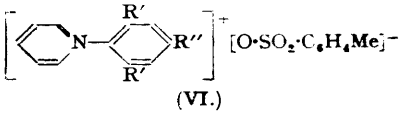
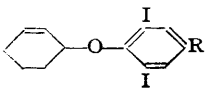

(VI.)

Attempts to prepare di-iodoxy-compounds by direct oxidation of either 3 : 5-di-iodo-*p*-cresol or 3 : 5-di-iodo-*p*-cresyl toluene-*p*-sulphonate with Caro's acid (Bamberger and Hill, *Ber.*, 1900, **33**, 533) were unsuccessful, the iodo-compounds being recovered unchanged.

Treatment of the esters (V; R = *p*-$C_6H_4Me{\cdot}SO_2$, R′ = I, R″ = Me or CO_2Me) with chlorine in aqueous pyridine [Ortoleva, *Gazzetta*, 1900, **30**, (ii), 1] or in chloroform (King and McCombie, *J.*, 1913, 220) led to chlorinated products, from which no pure compounds could be obtained; the products reverted to the parent di-iodo-compounds on treatment with sodium hypochlorite or with alkali.

Another approach arose from the knowledge that 2 : 6-di-iodophenols, although they do not form ethers with simple aromatic halides, form aliphatic ethers readily. An appropriately substituted *cyclo*hexenyl ether (*e.g.*, VIII) could subsequently be converted into a diaryl ether (IX) by dehydrogenation. Consequently, the preparation of unsaturated ethers of 3 : 5-di-iodophenols was studied with allyl bromide and 3-bromo*cyclo*hexene. Neither of these compounds yielded ethers (*e.g.*, VII) on treatment with 3 : 5-di-iodo-*N*-acetyl-DL-tyrosine in

aqueous alkaline solution, but they did so in alcoholic sodium ethoxide or in methyl ethyl ketone containing potassium carbonate. Similarly were prepared the ethers (VII; R = CO_2Me, Me, and CHO), which were required for the study of methods of dehydrogenation.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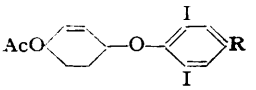
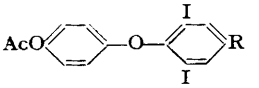

(VIII.)

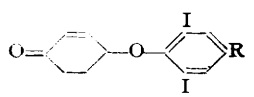

(IX.)

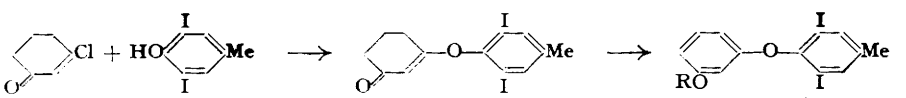
The action of selenium dioxide on some of the above-mentioned ethers was investigated with the object of introducing a hydroxyl or ketonic group at the 4′-position. Treatment of (VII; R = CO_2Me) with selenium dioxide in 95% acetic acid, aqueous alcohol, or aqueous dioxan caused loss of iodine and gave an unidentified selenium-containing compound that could not readily be purified. Guillemonat (*Ann. Chim.*, 1939, **11**, 143; *Compt. rend.*, 1937, **205**, 67) converted *cyclo*hexene into 3-acetoxy*cyclo*hexene by treatment with selenium dioxide in a mixture of acetic acid and acetic anhydride; however, (VII; R = Me or CO_2Me) with acetic anhydride, with or without selenium dioxide, gave only the acetate of the parent di-iodo-phenol. This interesting reaction appears to be related to the presence of the iodine atoms, since 3-phenoxy*cyclo*hexene is unaffected by acetic anhydride. The reaction apparently does not proceed through the di-iodophenols, as these compounds are not acetylated under the conditions of the reaction.

Since the *cyclo*hex-2-enyl ethers were such unpromising intermediates, attention was turned to the 4′-acetoxy-compounds (VIII); these were prepared from 3-bromo-6-acetoxy*cyclo*hexene, which with methyl 3 : 5-di-iodo-4-hydroxybenzoate or 3 : 5-di-iodo-*p*-cresol in methyl ethyl ketone in the presence of potassium carbonate gave the ethers (VIII; R = CO_2Me or Me), respectively.

The 4′-acetoxy*cyclo*hex-2′-enyl ethers (VIII; R = CO_2Me or Me) are fairly stable to heat, being recovered almost quantitatively after several hours' heating in boiling xylene, although the *cyclo*hex-2-enyl ethers were rather rapidly decomposed by this treatment. An attempt to dehydrogenate (VIII; R = Me) by chloranil in boiling xylene was unsuccessful, only traces of phenolic material being produced after hydrolysis of the crude product. This failure was not merely due to the presence of iodine in the molecule, for even the simple analogue, 3-phenoxy-*cyclo*hexene, gave no appreciable quantity of diphenyl ether on such treatment. An attempt to convert (VIII; R = Me) into the diphenyl ether (IX; R = Me) by bromination-dehydrobromination was equally unsuccessful; treatment with two equivalents of *N*-bromosuccinimide in the presence of potassium acetate (cf. Barnes, *J. Amer. Chem. Soc.*, 1948, **70**, 145) gave a small quantity of halogen-free material as the only pure product.

We next turned our attention to the 4-keto*cyclo*hex-2-enyl ethers (X) of di-iodophenols, which require the removal of only two hydrogen atoms to give 2 : 6-di-iodo-4′-hydroxydiphenyl ethers. The preparation of compounds of type (X) promised to be difficult, and preliminary experiments were therefore carried out with the more readily accessible 3-keto*cyclo*hex-1-enyl ethers.

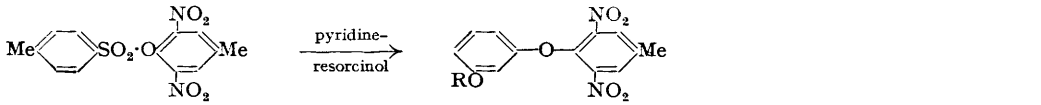
(X.) 


(XI.) (XII.)

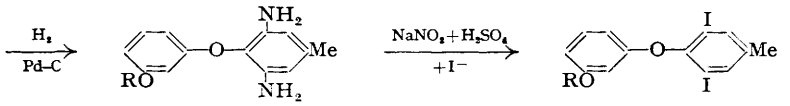
3-Chloro*cyclo*hex-2-enone (Crossley and Haas, *J.*, 1903, 494) was treated with 3 : 5-di-iodo-*p*-cresol in methyl ethyl ketone in the presence of potassium carbonate, yielding 3 : 5-di-iodo-4-(3-keto*cyclo*hex-1-enyloxy)toluene (XI); this was fairly stable, being recovered in good yield after 2 hours in boiling xylene or after 24 hours in acetic anhydride at 100°. It was unaffected by palladised charcoal in boiling xylene or by selenium dioxide in boiling alcohol or aqueous alcohol. However, it reacted with selenium dioxide in acetic acid, either pure or aqueous, as shown by the quantitative liberation of selenium. Because the required phenol (XII; R = H), which had been prepared by a different route (see below), was known to be unstable to selenium dioxide, the oxidation of (XI) was then attempted with selenium dioxide in a mixture of acetic acid and acetic anhydride in order that any phenolic material formed

should be protected from further oxidation by acetylation. However, although selenium was formed there was no evidence of the presence among the reaction products of the expected diphenyl ether (XII; R = Ac). Dehydrogenation of (XI) was finally achieved by successive bromination and dehydrobromination (*N*-bromosuccinimide, then 2 : 4 : 6-collidine), subsequent acetylation affording (XII; R = Ac) in 77% yield [based on (XI)].

In an alternative synthesis of (XII; R = Ac) the methods used were similar to those described in earlier papers in this series :



(XIII.)



(XIV.) (XII.)

Treatment of 3 : 5-dinitro-*p*-tolyl toluene-*p*-sulphonate with resorcinol in pyridine gave some *m*-di-(2′ : 6′-dinitro-4′-methylphenoxy)benzene as an alkali-insoluble fraction and, as the main product, 2 : 6-dinitro-3′-hydroxy-4-methyldiphenyl ether (XIII; R = H) as an oil, best purified by way of its solid acetate. Hydrogenation of the acetate (XIII; R = Ac) in the presence of palladised charcoal gave the diamine (XIV; R = Ac), which (crude) was tetrazotised, etc., yielding the di-iodo-compound (XII; R = Ac) in rather poor yield.

Attempts to apply this method to the preparation of 2 : 6-di-iodo-4′-hydroxydiphenyl ethers failed. Treatment of *cyclo*hex-2-enone with *N*-bromosuccinimide gave an extremely unstable product which with 3 : 5-di-iodo-*p*-cresol afforded a small quantity of an oily ketone. This appeared, from the composition of the 2 : 4-dinitrophenylhydrazone, to be (X) or an isomer but could not be dehydrogenated to the corresponding diphenyl ether by any of the usual methods.

The failure of so many attempts to prepare thyroxine from di-iodophenols, together with the development of the rather convenient preparation of L-thyroxine described in Part V (*J.*, 1949, 3424), has now led us to abandon this line of research.

Experimental.

2 : 6-*Di-iodo*-2′ : 4′-*dinitro*-4-*methyldiphenyl Ether*.—(*a*) 1-Chloro-2 : 4-dinitrobenzene (2·02 g.) and pyridine (20 ml.) were heated together on the water-bath till separation of solid was complete. 3 : 5-Di-iodo-*p*-cresol (10 g.) was added and the mixture boiled under reflux for 90 minutes. The solution was poured into an excess of dilute hydrochloric acid, and the aqueous layer decanted from the lower oily layer. The oil solidified on treatment with 2N-sodium hydroxide and was filtered off, washed with water, and crystallised from aqueous acetic acid. In order to remove dark impurities a solution of the material in acetone was passed through a short column of alumina, acetone being used for elution. After removal of the solvent the *diphenyl ether* (3·3 g., 62%) crystallised from glacial acetic acid in pale yellow prisms, m. p. 200—202° (Found : N, 5·4; I, 48·5. $C_{13}H_8O_5N_2I_2$ requires N, 5·3; I, 48·25%).

(*b*) Sodium (0·23 g.) was dissolved in absolute ethanol (15 ml.), 1-chloro-2 : 4-dinitrobenzene (2·03 g.) and 3 : 5-di-iodo-*p*-cresol (3·6 g.) were added, and the solution was boiled under reflux for 90 minutes. The solution was poured into water, and the solid was filtered off and purified as above, to give 2·5 g. (47%) of the diphenyl ether, m. p. 200°.

(*c*) A mixture of 1-chloro-2 : 4-dinitrobenzene (1·0 g.), 3 : 5-di-iodo-*p*-cresol (1·8 g.), potassium carbonate (1·38 g.), and methyl ethyl ketone (20 ml.) was boiled under reflux for 1 hour. After cooling, the mixture was filtered and the filtrate evaporated. The residual crystalline solid crystallised from glacial acetic acid as prisms (1·3 g., 50%) melting at 200—202°.

3 : 5-*Di-iodo*-4-(2′ : 4′-*dinitrophenoxy*)*benzaldehyde*.—This compound was prepared from 1-chloro-2 : 4-dinitrobenzene (1·10 g.), 3 : 5-di-iodo-4-hydroxybenzaldehyde (2·8 g.), and pyridine (10 ml.) as in method (*a*) above. The *aldehyde* separated from glacial acetic acid as almost colourless prisms (1·3 g., 48%), m. p. 258—259° (decomp.) (Found : N, 5·0. $C_{13}H_6O_6N_2I_2$ requires N, 5·2%).

Methyl 3 : 5-*Di-iodo*-4-(2′ : 4′-*dinitrophenoxy*)*benzoate*.—A mixture of 1-fluoro-2 : 4-dinitrobenzene (1·86 g.), methyl 3 : 5-di-iodo-4-hydroxybenzoate (4·04 g.), potassium carbonate (2·76 g.), and methyl ethyl ketone (25 ml.) was boiled under reflux for 1 hour. After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The residual solid was washed with 2N-sodium hydroxide and was then crystallised from aqueous ethanol. The *diphenyl ether* separated as yellow prisms (3·2 g., 56%) melting at 181—182° (Found : N, 5·1; I, 44·5. $C_{14}H_8O_7N_2I_2$ requires N, 4·9; I, 44·5%).

β-(3 : 5-*Di-iodo*-4-*hydroxyphenyl*)*propionic Acid*.—A solution of iodine (50 g.) and potassium iodide (48 g.) in water (150 ml.) was added gradually to a stirred solution of β-*p*-hydroxyphenylpropionic acid

(16·2 g.) in aqueous methylamine (20%; 200 ml.). When the addition was complete the mixture was stirred for a further 10 minutes and was then acidified to Congo-red by the gradual addition of 2N-hydrochloric acid. The white solid was filtered off, washed with water, and dried. Recrystallisation from ethanol yielded the di-iodo-compound as colourless needles (38 g., 90%), m. p. 166—168° (decomp.) (Found: C, 26·2; H, 2·2; I, 60·9. Calc. for $C_9H_8O_3I_2$: C, 25·9; H, 1·9; I, 60·7%). Bougault (*Compt. rend.*, 1900, **131**, 43) gives m. p. 162°.

The *ethyl* ester was prepared in 84% yield by esterification of the acid in chloroform solution with toluene-*p*-sulphonic acid as catalyst, water being removed azeotropically. It crystallised from ethanol as white prisms, m. p. 86—88° (Found: C, 29·8; H, 2·9; I, 57·0. $C_{11}H_{12}O_3I_2$ requires C, 29·6; H, 2·7; I, 56·9%).

Ethyl β-[3 : 5-Di-iodo-4-(2′ : 4′-dinitrophenoxy)phenyl]propionate.—Ethyl β-(3 : 5-di-iodo-4-hydroxyphenyl)propionate (4·46 g.) was added to 1-(2 : 4-dinitrophenyl)pyridinium bromide, prepared by heating 1-bromo-2 : 4-dinitrobenzene (1·24 g.) with pyridine (20 ml.) at 100° for 30 minutes. The mixture was heated on the water-bath for 2 hours and the product isolated in the usual way. The *diphenyl ether* crystallised from acetic acid as yellowish prisms (1·2 g., 39%), m. p. 128—130° (Found: N, 4·5; I, 40·9. $C_{17}H_{14}O_7N_2I_2$ requires N, 4·6; I, 41·5%).

3 : 5-*Di-iodo-*L*-tyrosine.*—A solution of iodine (320 g.) and sodium iodide (400 g.) in water (1·3 l.) was added dropwise to a stirred solution of L-tyrosine (100 g.) in 20% aqueous ethylamine (1 l.). When the addition was complete the mixture was stirred for a further 30 minutes. Excess of iodine was removed by treatment with sodium pyrosulphite, and the amino-acid was precipitated by adjustment of the pH to 5—6 with acetic acid. The solid was filtered off, washed with water, and purified by dissolution in N-hydrochloric acid and re-precipitation with ammonia. The yield was 200 g. (75%).

3 : 5-*Di-iodo-*N*-acetyl-*L*-tyrosine.*—A solution of 3 : 5-di-iodo-L-tyrosine (167 g.) in 2N-sodium hydroxide (1670 ml.) was kept between 5° and 10° and stirred while acetic anhydride (184 ml.) was added during 1 hour. After being kept overnight the solution was treated with sodium hydroxide (80 g.) in water (200 ml.) and left at room temperature for 3 hours. After addition of alcohol (1 l.) the solution was stirred and acidified to pH 2 by means of concentrated hydrochloric acid. The solid was filtered off and washed with water; a small second crop was obtained by dilution of the filtrate. The acetamido-acid (159 g., 87%) melted at 112—118°, and was used without further purification.

3 : 5-*Di-iodo-*N*-acetyl-*L*-tyrosine Ethyl Ester.*—3 : 5-Di-iodo-*N*-acetyl-L-tyrosine (158 g.), toluene-*p*-sulphonic acid (10 g.), ethanol (100 ml.), and chloroform (1 l.) were boiled together under reflux for 8 hours, water being separated automatically from the azeotrope. After cooling, the solution was washed with sodium hydrogen carbonate solution, then with water, and was evaporated to dryness. The residual solid was crystallised from aqueous ethanol containing a few drops of hydrochloric acid. The *ethyl* ester was obtained as colourless needles (147·5 g., 88%), m. p. 154—155°, $[\alpha]_D^{23}$ +15·4° (*c*, 2·0 in ethanol) (Found: C, 31·3; H, 3·2; N, 2·5; I, 52·0. $C_{13}H_{15}O_4NI_2$ requires C, 31·0; H, 3·0; N, 2·8; I, 50·5%).

3 : 5-*Di-iodo-*N*-acetyl-*DL*-tyrosine Ethyl Ester.*—This compound was prepared from 3 : 5-di-iodo-*N*-acetyl-DL-tyrosine by the method described above for the L-compound. The *ester* was obtained as small white needles (89%), m. p. 145—146° (Found: N, 2·9; I, 50·9. $C_{13}H_{15}O_4NI_2$ requires N, 2·8; I, 50·5%).

3 : 5-*Di-iodo-*O,N*-diacetyl-*L*-tyrosine Ethyl Ester.*—3 : 5-Di-iodo-*ON*-diacetyl-L-tyrosine (Myers, *J. Amer. Chem. Soc.*, 1932, **54**, 3718) (5·2 g.) was esterified in the usual way by treatment with ethanol (3 ml.) in chloroform (120 ml.) with toluene-*p*-sulphonic acid (2 g.) as catalyst. The *ethyl* ester crystallised from benzene–light petroleum in colourless prisms, m. p. 109—112°, $[\alpha]_D^{23}$ +27° (*c*, 1·4 in ethanol) (Found: C, 32·8; H, 3·0. $C_{15}H_{17}O_5NI_2$ requires C, 33·0; H, 3·0%).

3 : 5-*Di-iodo-*4*-(2′ : 4′-dinitrophenoxy)-*N*-acetyl-*L*-phenylalanine Ethyl Ester.*—3 : 5-Di-iodo-*N*-acetyl-L-tyrosine ethyl ester (50 g.), 1-chloro-2 : 4-dinitrobenzene (20 g.), potassium carbonate (28 g.), and methyl ethyl ketone (400 ml.) were boiled together under reflux for 1 hour. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in benzene and the solution was washed with sodium hydroxide solution and with water. The gum left on evaporation of the solvent was dissolved in a very little methanol and treated with warm ether. On cooling, the *diphenyl ether* (57 g., 82%) separated as a solvate, m. p. 102—104°. The material lost its solvent at 110°/10 mm. and then had the correct analysis (Found: C, 34·3; H, 2·7. $C_{19}H_{17}O_8N_3I_2$ requires C, 34·1; H, 2·5%). $[\alpha]_D^{22}$ was +5·9° (*c*, 2·0 in alcohol). The solvent-free material could not be recrystallised from any of the usual solvents.

3 : 5-*Di-iodo-*4*-(2′ : 4′-dinitrophenoxy)-*N*-acetyl-*L*-phenylalanine.*—A solution of the above ester (10 g.) in alcohol (50 ml.) was treated with a solution of potassium hydroxide (5·6 g.) in alcohol (50 ml.). After 10 minutes the solution was poured into water (500 ml.), and the solution was acidified with hydrochloric acid. Crystallisation of the solid from aqueous alcohol gave the *acetamido-acid* (8 g., 84%) melting at 210—212°, $[\alpha]_D^{22}$ +12° (*c*, 1·0 in 90% ethanol) (Found: C, 31·9; H, 2·2; N, 6·7. $C_{17}H_{13}O_8N_3I_2$ requires C, 31·8; H, 2·0; N, 6·55%).

3 : 5-*Di-iodo-*4*-(2′ : 4′-dinitrophenoxy)-*L*-phenylalanine Hydrochloride.*—A solution of the acetamido-ester (5 g.) in a mixture of glacial acetic acid (20 ml.) and concentrated hydrochloric acid (20 ml.) was refluxed for 6 hours. Yellow needles separated on cooling, which changed to a colourless powder when washed with water. This powder dissolved readily in hot acetic acid and the *amino-acid hydrochloride* separated rapidly as pale yellow needles, m. p. 212—216°, $[\alpha]_D^{26}$ +5·6° (*c*, 0·63 in ethanol) (Found: C, 28·2; H, 2·1. $C_{15}H_{12}O_7N_3ClI_2$ requires C, 28·2; H, 1·9%).

3 : 5-*Di-iodo-*4*-(2′ : 4′-dinitrophenoxy)-*N*-acetyl-*DL*-phenylalanine Ethyl Ester.*—(*a*) 3 : 5-Di-iodo-*N*-acetyl-DL-tyrosine ethyl ester (2·5 g.) and pyridine (5 ml.) were added to 1-(2 : 4-dinitrophenyl)pyridinium chloride prepared from 1-chloro-2 : 4-dinitrobenzene (0·5 g.) and pyridine (5 ml.); the mixture was heated on the steam-bath for 2 hours and the product isolated in the usual way. The *diphenyl ether*

crystallised from aqueous acetic acid as a white powder (1·0 g., 60%) melting at 204—206° (Found: C, 34·4; H, 2·6; N, 6·1; I, 38·7. $C_{19}H_{17}O_8N_3I_2$ requires C, 34·1; H, 2·5; N, 6·3; I, 38·0%).

(*b*) 1-Chloro-2 : 4-dinitrobenzene (2·03 g.), 3 : 5-di-iodo-*N*-acetyl-DL-tyrosine ethyl ester (5·03 g.), potassium carbonate (2·76 g.), and methyl ethyl ketone (40 ml.) were boiled together under reflux for 1 hour. The hot solution was filtered and the filtrate, on cooling, deposited a white powder melting at 202—204°. A further quantity was obtained by concentration of the mother-liquors. Crystallisation from aqueous acetic acid and finally from a mixture of acetone and light petroleum (b. p. 60—80°) gave material (5·5 g., 82%), m. p. 204—206°.

Reaction of 1-(2 : 6-*Dinitro*-4-*methylphenyl*)*pyridinium Toluene*-p-*sulphonate with* 3 : 5-*Di-iodo*-4-*hydroxybenzaldehyde*.—A solution of the quaternary salt (Borrows, Clayton, Hems, and Long, *J.*, 1949, S 190) (8·6 g.) and 3 : 5-di-iodo-4-hydroxybenzaldehyde (15 g.) in pyridine (50 ml.) was boiled under reflux for 1 hour and the solution was then cooled and poured on a mixture of 2N-hydrochloric acid and ice. The deposited oil was taken up in chloroform, and the solution was washed successively with 2N-hydrochloric acid, 2N-sodium hydroxide, and water, and was then evaporated to small bulk. The chloroform solution was poured on an alumina column which was washed with more chloroform. On evaporation of the eluate a brown syrup was obtained which crystallised on storage and, on recrystallisation from aqueous acetic acid, gave 3-*iodo*-4-(2′ : 6′-*dinitro*-4′-*methylphenoxy*)*benzaldehyde* as greenish prisms (3·1 g., 36%), m. p. 159—160° (Found: N, 6·4; I, 29·5. $C_{14}H_9O_6N_2I$ requires N, 6·5; I, 29·7%).

The compound (2·5 g.) was heated with morpholine (10 ml.) on the water-bath for 2 hours and the solution was poured on excess of 2N-hydrochloric acid and ice. The deposited oil was taken up in chloroform and the chloroform solution was extracted repeatedly with sodium hydrogen carbonate solution. The carbonate extract, on acidification, gave 3-iodo-4-hydroxybenzaldehyde, m. p. 113—115°, undepressed on admixture with an authentic specimen. Evaporation of the chloroform solution gave an oil which crystallised from ethanol as orange needles, m. p. 127—129°, undepressed on admixture with a specimen of 3 : 5-dinitro-4-morpholinotoluene prepared as described below.

3 : 5-*Dinitro*-4-*morpholinotoluene*.—A mixture of 4-chloro-3 : 5-dinitrotoluene (0·19 g.) and morpholine (1 ml.) was heated on the steam-bath for 90 minutes, cooled, and poured into excess of 2N-hydrochloric acid and ice. The precipitate crystallised from ethanol as long orange needles (0·21 g., 90%), m. p. 127—129° (Found: C, 49·4; H, 5·0; N, 15·4. $C_{11}H_{13}O_5N_3$ requires C, 49·4; H, 4·9; N, 15·7%).

3-*Iodo*-4-*hydroxybenzaldehyde*.—A solution of iodine (25·4 g.) and potassium iodide (22 g.) in water (300 ml.) was added to *p*-hydroxybenzaldehyde (12·2 g.) in aqueous dimethylamine (100 ml., 30%), with stirring, during 90 minutes. The dark precipitate was filtered off and the filtrate acidified by the addition of 2N-hydrochloric acid. Crystallisation of the precipitated solid from hot water gave colourless leaflets, m. p. 113—115° (Found: C, 34·1; H, 2·1; I, 51·5. Calc. for $C_7H_5O_2I$: C, 33·9; H, 2·0; I, 51·2%). Paal (*Ber.*, 1895, **28**, 2407) gives m. p. 108°.

The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid as an orange-red powder, m. p. 269—271° (decomp.) (Found: N, 12·8; I, 30·65. $C_{13}H_9O_5N_4I$ requires N, 13·1; I, 29·6%).

Unambiguous Synthesis of 3-*Iodo*-4-(2′ : 6′-*dinitro*-4′-*methylphenoxy*)*benzaldehyde*.—A solution of 1-(2 : 6-dinitro-4-methylphenyl)pyridinium toluene-*p*-sulphonate (2·15 g.) and 3-iodo-4-hydroxybenzaldehyde (1·24 g.) in pyridine (20 ml.) was boiled under reflux for 1 hour. After cooling, the mixture was poured into 2N-hydrochloric acid containing ice, and the deposited syrup was taken up in chloroform and washed successively with 2N-hydrochloric acid, 2N-sodium hydroxide, and water. The chloroform solution was evaporated to small bulk and poured on an alumina column. The material was eluted with chloroform and, after removal of the solvent, was crystallised from aqueous acetic acid. The compound (0·65 g., 30%) melted at 159—160° and did not depress the m. p. of the material prepared from 3 : 5-di-iodo-4-hydroxybenzaldehyde.

2′-*Iodo*-2 : 6-*dinitro*-4 : 4′-*dimethyldiphenyl Ether*.—This was prepared from 1-(2 : 6-dinitro-4-methylphenyl)pyridinium toluene-*p*-sulphonate (4·31 g.) and 3 : 5-di-iodo-*p*-cresol (7·2 g.) in pyridine (20 ml.) by the method described above for the benzaldehyde analogue. The *diphenyl ether* (1·4 g., 34%) separated from aqueous acetic acid as pale yellow prisms, m. p. 140—141° (Found: N, 6·8; I, 31·3. $C_{14}H_{11}O_5N_2I$ requires N, 6·8; I, 30·7%).

Methyl 3-*Iodo*-4-(2′ : 6′-*dinitro*-4′-*carbomethoxyphenoxy*)*benzoate*.—Methyl 4-chloro-3 : 5-dinitrobenzoate (1·30 g.) and pyridine (6·5 ml.) were heated together on the steam-bath for 20 minutes. Methyl 3 : 5-di-iodo-4-hydroxybenzoate (4·04 g.) was added and the solution was heated on the steam-bath for a further 2 hours. The *diphenyl ether* (1·1 g., 44%), purified by passage of its acetone solution through an alumina column, crystallised from aqueous acetic acid in prisms, m. p. 159—160° (Found: N, 5·6; I, 25·4. $C_{16}H_{11}O_9N_2I$ requires N, 5·6; I, 25·3%).

2 : 6-*Dinitro*-4-*methoxyphenyl Toluene*-p-*sulphonate*.—A mixture of 2 : 6-dinitro-4-methoxyphenol (Weselsky and Benedikt, *Monatsh.*, 1881, **2**, 369) (1·07 g.), toluene-*p*-sulphonyl chloride (1·0 g.), and water (10 ml.) was heated on the steam-bath with stirring while sodium carbonate (1·06 g.) was added in small portions. Since the deep-red colour persisted, further quantities of toluene-*p*-sulphonyl chloride and sodium carbonate were added until the alkaline solution was only faintly red. The solid was filtered off, and washed well with warm sodium carbonate solution and then with water. The *toluene*-p-*sulphonate* (1·75 g., 96%) melted at 140—141° after crystallisation from ethanol (Found: N, 7·9; S, 9·1. $C_{14}H_{12}O_8N_2S$ requires N, 7·65; S, 8·75%).

1-(2 : 6-*Dinitro*-4-*methoxyphenyl*)*pyridinium Toluene*-p-*sulphonate*.—The foregoing ester (1 g.) in pyridine (5 ml.) was kept overnight at room temperature and ether was added to precipitate the quaternary *salt* (0·9 g., 74%) which crystallised as needles from ethanol–ether and melted at 199—201° (Found: C, 51·0; H, 3·8; S, 7·3. $C_{19}H_{17}O_8N_3S$ requires C, 51·0; H, 3·8; S, 7·2%).

2-Iodo-2' : *6'-dinitro-4'-methoxy-4-methyldiphenyl Ether.*—The foregoing quaternary salt (4 g.) in pyridine (25 ml.) was treated with 3 : 5-di-iodo-*p*-cresol (8 g.), and the solution was heated on the steam-bath for 2 hours. The *diphenyl ether*, isolated in the usual way, was a light yellow solid (0·4 g.) which melted at 161—163° after crystallisation from aqueous acetic acid (Found : N, 6·2; I, 30·0. $C_{14}H_{11}O_6N_2I$ requires N, 6·5; I, 29·5%).

Methyl 3 : 5-*Dinitro*-4-(3 : 5-*di-iodo*-4-*methylphenoxy*)*benzoate.*—Methyl 4-chloro-3 : 5-dinitrobenzoate (2·6 g.), 3 : 5-di-iodo-*p*-cresol (3·6 g.), potassium carbonate (2·8 g.), and methyl ethyl ketone (10 ml.) were boiled together under reflux for 1 hour. The solution was filtered and the filtrate evaporated leaving a dark red oil which was dissolved in chloroform. The solution was washed with N-sodium hydroxide and then with water, dried ($MgSO_4$), and evaporated. The residual yellow solid was washed with a little ether and crystallised from aqueous acetic acid, the *diphenyl ether* (3·0 g., 51%) being obtained as pale yellow plates, m. p. 170—172° (Found : N, 4·8; I, 43·9. $C_{15}H_{10}O_7N_2I_2$ requires N, 4·8; I, 43·5%).

After heating this compound (2·5 g.) with morpholine (10 ml.) on the steam-bath for 2 hours it was possible to isolate, from the alkali-soluble fraction, a small quantity of 3 : 5-di-iodo-*p*-cresol, m. p. and mixed m. p. 60—62°.

3 : 5-*Di-iodo*-4-*allyloxy*-N-*acetyl*-DL-*phenylalanine.*—3 : 5-Di-iodo-*N*-acetyl-DL-tyrosine (4·49 g.), dissolved in absolute ethanol (80 ml.) containing sodium (0·49 g., 2 equivs.), was boiled under reflux with allyl chloride (6 ml.) for 5 hours and then treated with a further 6 ml. of allyl chloride for 2 hours. After 48 hours at room temperature the reaction mixture was concentrated under reduced pressure, diluted with water, acidified, and extracted with ether. The ethereal extract was washed with water and dried. Evaporation of the ether left the *allyl ether* (4 g.) which crystallised from aqueous alcohol as needles, m. p. 176·5° (Found : C, 32·9; H, 3·1; N, 2·6; I, 49·0. $C_{14}H_{15}O_4NI_2$ requires C, 32·6; H, 2·9; N, 2·7; I, 49·3%).

3 : 5-*Di-iodo*-4-(cyclo*hex*-2-*enyloxy*)-N-*acetyl*-DL-*phenylalanine.*—3 : 5-Di-iodo-*N*-acetyl-DL-tyrosine (4·75 g.), 3-bromo*cyclo*hexene (2 g.), potassium carbonate (4 g.), and methyl ethyl ketone (25 ml.) were boiled together under reflux for 16 hours. The solution was filtered and evaporated to dryness under reduced pressure. The residue was treated with water and a little 2N-sodium hydroxide to effect complete dissolution of the black gum. The aqueous solution was washed with ether, covered with fresh ether, and acidified with 2N-hydrochloric acid. Evaporation of the dried ethereal solution yielded a gum (3·7 g.), which was dissolved in acetone (*ca.* 20 ml.). The acetone solution was filtered from a little insoluble product, treated with charcoal, and then diluted with light petroleum (b. p. 60—80°). Slow evaporation of this solution at room temperature yielded the desired *ether*, which crystallised from aqueous acetone as a colourless powder, m. p. 147° (decomp.) (Found : C, 36·4; H, 3·4; N, 2·5; I, 46·6. $C_{17}H_{19}O_4NI_2$ requires C, 36·8; H, 3·4; N, 2·5; I, 45·8%).

Methyl 3 : 5-*Di-iodo*-4-(cyclo*hex*-2-*enyloxy*)*benzoate.*—Methyl 3 : 5-di-iodo-4-hydroxybenzoate (3·0 g.), 3-bromo*cyclo*hexene (1·7 g.), potassium carbonate (4·0 g.), and methyl ethyl ketone (20 ml.) were boiled together under reflux for 20 hours. After concentration the resulting gum was washed with water and extracted with ether. The extract was washed with 2N-sodium hydroxide and then with water, dried ($MgSO_4$), and concentrated to yield an oil (3·1 g., 86%) which slowly crystallised. This *ether* crystallised from ethanol or light petroleum (b. p. 60—80°) as clusters of colourless needles, m. p. 91°. It could be sublimed rapidly at 150°/0·0005 mm. (Found : C, 34·8; H, 3·2; I, 53·75. $C_{14}H_{14}O_3I_2$ requires C, 34·7; H, 2·9; I, 52·5%).

Although the ether seemed stable at temperatures just above its melting point, slow gas evolution occurred at *ca.* 190°, becoming more rapid at *ca.* 220°. After 2 hours in boiling xylene 70% of the ether was split to methyl 3 : 5-di-iodo-4-hydroxybenzoate, and 50% of the ether was destroyed by similar treatment lasting only 30 minutes.

The ester grouping of the ether was hydrolysed by heating the compound with 2N-sodium hydroxide on the steam-bath for 90 minutes. This yielded 3 : 5-*di-iodo*-4-(cyclo*hex*-2-*enyloxy*)*benzoic acid* which crystallised from benzene as rosettes or soft white needles. The melting point varied according to the rate of heating but when placed in a bath at 150°, the compound appeared to lose solvent at 160—165° and melted sharply at 238° (decomp.) with evolution of iodine (Found : C, 33·9; H, 2·6. $C_{13}H_{12}O_3I_2$ requires C, 33·2; H, 2·55%).

3 : 5-*Di-iodo*-4-(cyclo*hex*-2-*enyloxy*)*benzaldehyde.*—This ether was prepared in 76% yield by treatment of 3 : 5-di-iodo-4-hydroxybenzaldehyde (19·5 g.) with 3-bromo*cyclo*hexene (11·0 g.) in the presence of potassium carbonate (19·0 g.) in methyl ethyl ketone (120 ml.) in the usual way. Several attempts to purify it by distillation at pressures down to 0·0005 mm. resulted in rapid decomposition with loss of iodine. The ether, an alkali-insoluble syrup, was characterised as its orange-coloured 2 : 4-*dinitrophenylhydrazone*, m. p. 258—260° (decomp.) (Found : N, 8·2. $C_{19}H_{16}O_5N_4I_2$ requires N, 8·8%).

The stability of the ether in boiling xylene was of the same order as that of the corresponding benzoate.

3 : 5-*Di-iodo*-4-(cyclo*hex*-2-*enyloxy*)*toluene.*—3 : 5-Di-iodo-*p*-cresol (5 g.) in methyl ethyl ketone (30 ml.) was boiled under reflux with 3-bromo*cyclo*hexene (2·9 g.) and potassium carbonate (5 g.) for 20 hours. The reaction mixture was worked up in the usual manner to yield the *ether* as a crude oil (6·0 g.) which could be distilled rapidly at 140°/0·00005 mm. as a very pale yellow oil (Found : C, 35·3; H, 3·3; I, 59·4. $C_{13}H_{14}OI_2$ requires C, 35·45; H, 3·2; I, 57·7%).

This ether was markedly more stable to heat than the related aldehyde and ester. Thus, in boiling xylene, iodine was liberated much more slowly and even after 3½ hours 25% of the material was recovered as an alkali-insoluble, non-volatile oil.

Reaction of Methyl 3 : 5-*Di-iodo*-4-(cyclo*hex*-2-*enyloxy*)*benzoate with Selenium Dioxide.*—The ether (2·0 g.), selenium dioxide (1·1 g.), acetic acid (10 ml.), and water (0·5 ml.) were heated together on the steam-bath for 15 hours. During this period much iodine was liberated and an insoluble solid separated.

This solid (0·85 g.) was very insoluble in the usual organic solvents, but dissolved in aqueous sodium hydrogen carbonate, from which solution it was precipitated unchanged by acidification. Before analysis, it was washed successively with aqueous sodium pyrosulphite, aqueous potassium cyanide, acetone, and ethanol. It melted at 290° (decomp.) and contained selenium (Found: C, 36·3; H, 2·7; I, 27·9%). The same compound resulted when aqueous ethanol or aqueous dioxan was used as solvent for the oxidation.

Methyl 3 : 5-*Di-iodo*-4-(4-*acetoxy*cyclo*hex*-2-*enyloxy*)*benzoate*.—A mixture of methyl 3 : 5-di-iodo-4-hydroxybenzoate (5 g.), 3-bromo-6-acetoxy*cyclo*hexene (Ziegler *et al.*, *Annalen*, 1942, **551**, 80) (3·75 g.), potassium carbonate (5 g.), and methyl ethyl ketone (25 ml.) was boiled under reflux for 21 hours. The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was treated with ether and water, and some insoluble material was filtered off. The ethereal layer from the filtrate was washed with alkali and water in the usual way to yield a crude oil after evaporation. Distillation of the crude ether at 130—140°/0·00005 mm. yielded a solid by-product which crystallised from aqueous methyl alcohol as buff-coloured needles, m. p. 254° (decomp.), which were soluble in 2N-sodium hydroxide and saturated aqueous sodium hydrogen carbonate; the material was not examined further.

The required *ether* distilled at 220°/0·00005 mm. as a yellow glass (Found: C, 35·5; H, 3·0; I, 47·6. $C_{16}H_{16}O_5I_2$ requires C, 35·4; H, 2·95; I, 46·9%).

The acetoxy*cyclo*hexenyl ether (1·1 g.) was hydrolysed by heating it for 1 hour on the steam-bath with a mixture of 2N-sodium hydroxide (10 ml.) and ethanol (15 ml.). The resulting solution was treated with charcoal, filtered, washed with ether, and then acidified, to yield a white precipitate which crystallised from aqueous methanol as feathery needles, m. p. 257° (decomp.), not depressed on admixture with an authentic specimen of 3 : 5-di-iodo-4-hydroxybenzoic acid.

The acetoxy*cyclo*hexenyl ether proved to be much more stable than the corresponding *cyclo*hexenyl ether, 80% being recovered after 1 hour's heating in xylene.

3 : 5-*Di-iodo*-4-(4-*acetoxy*cyclo*hex*-2-*enyloxy*)*toluene*.—A mixture of 3 : 5-di-iodo-*p*-cresol (4·9 g.), 3-bromo-6-acetoxy*cyclo*hexene (3·7 g.), potassium carbonate (5 g.), and methyl ethyl ketone (25 ml.) was boiled under reflux for 21 hours. Worked up in the usual manner, the required *ether* was obtained as a crude oil (5·35 g., 79%) which could be distilled as a pale yellow syrup at 140°/0·001 mm. (Found: C, 36·3; H, 3·0; I, 51·1. $C_{15}H_{16}O_3I_2$ requires C, 36·15; H, 3·2; I, 51·0%).

After boiling of a xylene solution of the ether for 2 hours, 93% of the ether was recovered unchanged.

Dihydroresorcinol.—The method of Birch (*J.*, 1947, 102) was used, but in the last stage the liquor from which the first crop of dihydroresorcinol had separated was evaporated to a gum and subjected again to the treatment with hydrochloric acid to complete the decomposition of the dimethyl compound. In this way an overall yield of 40% was achieved. The compound, in ethanol solution, had $E^{1\%}_{1\,cm.} = 2530$ at $\lambda_{max.}$ 282 mμ.; in the presence of sodium ethoxide (1 equiv.) this became $E^{1\%}_{1\,cm.} = 1680$ at $\lambda_{max.}$ 255 mμ.

3 : 5-*Di-iodo*-4-(3-*keto*cyclo*hex*-1-*enyloxy*)*toluene*.—Crude 3-chloro*cyclo*hex-2-enone (Crossley and Haas, *J.*, 1903, 494) (4·72 g.) was dissolved in methyl ethyl ketone (50 ml.) containing 3 : 5-di-iodo-*p*-cresol (13·1 g.) and anhydrous potassium carbonate (18 g.). The solution was boiled under reflux for 24 hours, and the solid was filtered off. The filtrate was evaporated to small bulk and extracted with ether. The extract was washed successively with 2N-sodium hydroxide (to remove unchanged 3 : 5-di-iodo-*p*-cresol), acid, and water, dried ($MgSO_4$), and evaporated to an oil (9·66 g.). This was extracted with a little cold ethanol, giving (*a*) a soluble unidentified fraction (6·38 g.) most of which boiled at 90°/3 × 10^{-5} mm. and (*b*) an insoluble crystalline solid (3·28 g.), separating from ethanol as large white prisms, which melted at 152—153° and evolved iodine at 280°. This was 3 : 5-*di-iodo*-4-(3-*keto*cyclo*hex*-1-*enyloxy*)*toluene* (Found: C, 34·6; H, 2·6; I, 55·9%; *M*, 429. $C_{13}H_{12}O_2I_2$ requires C, 34·4; H, 2·6; I, 55·9%; *M*, 454). It gave no colour with ferric chloride in aqueous ethanol. In warm ethanol it yielded a 2 : 4-*dinitrophenylhydrazone*, as very small red crystals, m. p. 193°, giving no colour with ferric chloride or acid potassium chromate solution (Found: C, 36·3; H, 2·5; N, 8·8; I, 40·1. $C_{19}H_{16}O_5N_4I_2$ requires C, 36·0; H, 2·5; N, 8·8; I, 40·1%). It was recovered unchanged after being heated for 24 hours on the steam-bath with acetic anhydride, or after 2 hours in boiling xylene, with or without a palladised charcoal catalyst.

Bromination and Dehydrobromination of 3 : 5-*Di-iodo*-4-(3-*keto*cyclo*hex*-1-*enyloxy*)*toluene*.—A solution of the ether (2·27 g.) and *N*-bromosuccinimide (0·89 g.) in carbon tetrachloride (25 ml.) was boiled under reflux for 8 hours. The resulting succinimide (0·41 g.) was filtered off, and the filtrate was concentrated to an oil, setting to a semicrystalline mass. The bromo-ketone yielded a 2 : 4-*dinitrophenylhydrazone*, which crystallised from ethanol as very small red crystals, m. p. 140—145° (Found: N, 8·4. $C_{19}H_{15}O_5N_4BrI_2$ requires N, 7·9%).

A solution of the crude bromo-compound in 2 : 4 : 6-collidine (10 ml.) was boiled under reflux for 70 minutes. The cooled solution was treated with ether, the insoluble part being a water-soluble, brown solid, presumably collidine hydrobromide. The solution was washed with acid (slight excess) and water, dried ($MgSO_4$), and concentrated to a brown oil, which could be crystallised from ether or alcohol as a white solid, m. p. 148—149° (1·9 g.), insoluble in alkali. This had the composition of a 3 : 5-*di-iodo*-4-(3-*keto*cyclo*hexadienyloxy*)*toluene* (Found: I, 55·9. $C_{13}H_{10}O_2I_2$ requires I, 56·3%). It yielded a 2 : 4-*dinitrophenylhydrazone* which separated from ethanol–ethyl acetate as red needles, m. p. 173—175° (Found: N, 8·7; I, 39·3. $C_{19}H_{14}O_5N_4I_2$ requires N, 8·9; I, 40·2%).

The crude dehydrobromination product was left at room temperature for 5 hours in acetic anhydride (30 ml.) containing sulphuric acid (5 drops). The solution was poured into ice–water, whereupon 2 : 6-*di-iodo*-3′-*acetoxy*-4-*methyldiphenyl ether* (1·9 g., 77%) separated as a solid which crystallised from

aqueous ethanol as a feathery mass, m. p. 110°, not depressed on admixture with a specimen prepared as described below (Found : I, 51·1. $C_{15}H_{12}O_3I_2$ requires I, 51·4%).

2 : 6-*Dinitro*-3′-*hydroxy*-4-*methyldiphenyl Ether*.—3 : 5-Dinitro-*p*-tolyl toluene-*p*-sulphonate (35 g.) was heated in boiling anhydrous pyridine (250 ml.) with resorcinol (110 g.) for 1 hour. The pyridine was removed under reduced pressure. The residue was extracted with chloroform and the extract washed with dilute hydrochloric acid. Free phenolic material was extracted into ice-cold N-sodium hydroxide, which was run immediately into an excess of hydrochloric acid, thus precipitating an oil. The chloroform layer was washed with acid and then water, dried ($MgSO_4$), and concentrated to a residue (7·1 g.) which crystallised from glacial acetic acid as slightly yellow needles of m-*di*-(2 : 6-*dinitro*-4-*methylphenoxy*)-*benzene*, m. p. 217° (Found : C, 50·7; H, 3·1; N, 12·3. $C_{20}H_{14}O_{10}N_4$ requires C, 51·0; H, 3·0; N, 11·9%).

The phenolic fraction was extracted into chloroform and washed with ice-cold 2N-sodium carbonate, then with dilute hydrochloric acid, and finally with water. The dried ($MgSO_4$) solution was evaporated to a gum (26 g.) which, on distillation at 5×10^{-4} mm., yielded only a small sublimate of 3 : 5-dinitro-*p*-cresol, m. p. 82°, identified by comparison with an authentic specimen. The gum (25 g.) was therefore boiled under reflux with acetic anhydride (90 ml.), containing fused sodium acetate (3 g.), for 2 hours. The sodium acetate was removed by filtration, and the solvent was removed from the filtrate by co-distillation under reduced pressure with xylene. The residual 2 : 6-*dinitro*-3′-*acetoxy*-4-*methyldiphenyl ether* crystallised from aqueous ethanol as white spikes (10 g.), m. p. 138° (Found : C, 54·5; H, 3·85; N, 8·2. $C_{15}H_{12}O_7N_2$ requires C, 54·2; H, 3·6; N, 8·4%).

The above acetoxy-compound (1·0 g.) was boiled under reflux with a mixture of ethanol (10 ml.) and concentrated hydrochloric acid (10 ml.) for 2 hours. The solvents were removed under reduced pressure and the residue was extracted into ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to an oil (0·9 g.) which could be crystallised at −30° from aqueous ethanol, but was better purified by distillation at $143°/10^{-4}$ mm.; 3 : 5-*dinitro*-3′-*hydroxy*-4-*methyldiphenyl ether* collected as an amber-coloured gum (Found : C, 53·9; H, 3·7; N, 9·9. $C_{13}H_{10}O_6N_2$ requires C, 53·8; H, 3·4; N, 9·7%).

2 : 6-*Di-iodo*-3′-*acetoxy*-4-*methyldiphenyl Ether*.—The foregoing acetoxy-ether (3·32 g.) in acetic acid (100 ml.) was shaken with palladised charcoal (10%; 1 g.) in the presence of hydrogen at atmospheric pressure and temperature. The diamine obtained by evaporation of the filtered solution was unstable in air and light, as were the hydrochloride, sulphate, picrate, and *m*-nitrobenzenesulphonate. The base was characterised by repeating the hydrogenation in the presence of acetic anhydride (3 ml.), removing the catalysts and solvent in the normal way, and crystallising the residual gum from ethanol; 2 : 6-*bis-acetamido*-3′-*acetoxy*-4-*methyldiphenyl ether* separated as white needles (2·8 g.), m. p. 195—196° (Found : C, 63·7; H, 5·6; N, 7·95. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6; N, 7·9%).

For the tetrazotisation, the freshly hydrogenated acetic acid solution of the diamine was concentrated under reduced pressure to small bulk (*ca.* 20 ml.) and added dropwise to a stirred ice-cold solution of sodium nitrite (1·7 g.) in concentrated sulphuric acid (25 ml.). The tetrazonium solution was stirred for a further hour at 0°, crystalline material separating. This slurry was then added slowly to an ice-cold solution of sodium iodide (4·5 g.) and iodine (3·7 g.) in water (70 ml.). The mixture was stirred overnight and the black tar was washed several times with boiling 10% aqueous sodium iodide. The pulverised product was dissolved in acetone and filtered on to an alumina pad, wet with light petroleum. An orange-brown zone, rapidly eluted with light petroleum, was collected. 3 : 5-*Di-iodo*-3′-*acetoxy*-4-*methyldiphenyl ether* (1·4 g., 28%) crystallised from ethanol as feathery white clusters, m. p. 111° (Found : C, 36·5; H, 2·7; I, 51·0. Calc. for $C_{15}H_{12}O_3I_2$: C, 36·5; H, 2·45; I, 51·4%).

This compound (1 g.) was hydrolysed in boiling ethanol (20 ml.) containing 10N-sodium hydroxide (10 ml.) for 90 minutes. The cooled solution was poured into ice-cold hydrochloric acid, and the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated to an oil (0·7 g.) distilling at $160°/5 \times 10^{-5}$ mm., consisting of 3 : 5-*di-iodo*-3′-*hydroxy*-4-*methyldiphenyl ether* (Found : C, 34·6; H, 2·5; I, 57·2. $C_{13}H_{10}O_2I_2$ requires C, 34·5; H, 2·2; I, 56·1%).

4-*Bromo*cyclo*hex*-2-*enone*.—*cyclo*Hex-2-enone (4·8 g.), *N*-bromosuccinimide (8·9 g.), benzoyl peroxide (100 mg.), and carbon tetrachloride (100 ml.) were boiled together under reflux for 45 minutes. The mixture was cooled to 0°, filtered, and evaporated to dryness under reduced pressure. The residual oil, which was extremely unstable, was used immediately, without further purification.

Reaction of 4-*Bromo*cyclo*hex*-2-*enone with* 3 : 5-*Di-iodo*-p-*cresol*.—A mixture of crude 4-bromo*cyclo*hex-2-enone, prepared as described above, with 3 : 5-di-iodo-*p*-cresol (18 g.), anhydrous potassium carbonate (20 g.), and methyl ethyl ketone was boiled under reflux for 18 hours. The mixture was then poured into water and extracted with ether, and the extract washed with dilute sodium hydroxide solution and then dilute hydrochloric acid. The dried ethereal extract on evaporation yielded an oil which, on distillation at very low pressure, gave two main fractions. The first, distilling at 83—85°/10^{-5} mm., has not been identified, but the second, distilling at 120—125°/10^{-5} mm., consisted of the ether contaminated with 3 : 5-di-iodo-*p*-cresol. This latter was removed by alkali-washing, and the ether was analysed as its 2 : 4-*dinitrophenylhydrazone*, which melted at 185° after crystallisation from benzene–ether (Found : N, 8·8; I, 39·9. $C_{19}H_{16}O_5N_4I_2$ requires N, 8·85; I, 40·0%). The yield was 10%.

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