## 158. *The Synthesis of Thyroxine and Related Substances. Part XII.* The Preparation of Some Simple Analogues of Thyroxine.*

By J. H. Barnes, J. Elks, F. F. Stephens, and G. J. Waller.

Several compounds in each of the following series were prepared by standard methods: (*a*) iodine-substituted phenoxyacetic acids, (*b*) benzyl and other ethers of 2 : 6-di-iodophenols, variously substituted in the 4-position, (*c*) 4-aryloxy-3 : 5-di-iodobenzoic acids, (*d*) 4-aryloxy-3 : 5-di-iodophenylalanines.

Several attempts to prepare 4-(4-hydroxy-3 : 5-di-iodobenzyloxy)-3 : 5-di-iodophenylalanine proved unsuccessful, owing to the great ease with which the ether linkage was cleaved.

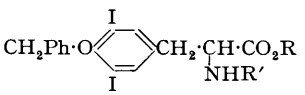
Antithyroid activities are reported for a number of compounds described in this and earlier papers.

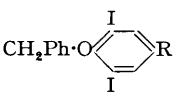
During the last few years, antithyroid activity has been found in a number of comparatively simple aromatic iodo-compounds bearing little structural resemblance to

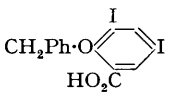
* Part XI, *J.*, 1953, 643.

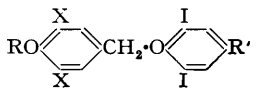
thyroxine. Barker and his co-workers (*Fed. Proc.*, 1950, **9**, 8; *J. Pharm. Exp. Ther.*, 1950, **99**, 202; *Endocrinology*, 1951, **48**, 525) have described one such series of compounds, the iodophenoxyacetic acids, several members of which possess appreciable activity. We have extended the series somewhat and, as shown in the Table, have confirmed Barker's discovery of antithyroid activity in this type of substance. The compounds were all prepared by reaction of the appropriate iodophenol with ethyl chloroacetate in alcoholic sodium ethoxide (Daniels and Lyons, *J. Amer. Chem. Soc.*, 1936, **58**, 2646) and alkaline hydrolysis of the ester, which was often not isolated.

The observation by Woolley (*J. Biol. Chem.*, 1946, **164**, 11) that certain alkyl and aralkyl ethers of *N*-acetyl-3 : 5-di-iodotyrosine possess antithyroid activity was confirmed by Frieden and Winzler (*ibid.*, 1949, **179**, 423), who found that the benzyl ether (I; R = R′ = H) of 3 : 5-di-iodotyrosine itself was considerably more effective than the *N*-acetyl derivative (I; R = H, R′ = Ac) and that the simple 4-benzyloxy-3 : 5-di-iodobenzoic acid (II; R = $CO_2H$) was more active than either. However, these reports were based on tests with tadpoles and it seemed desirable to test these and related compounds for antithyroid activity in mammals. More recently, Maclagan *et al.* (*Nature*, 1949, **164**, 699; *Biochem. J.*, 1951, **48**, 188; 1951, **49**, 710, 714) have prepared a large number of


(I)


(II)


(III)


(IV)

derivatives of 4-hydroxy-3 : 5-di-iodobenzoic acid and of 4-hydroxy-3 : 5-di-iodobenzaldehyde. Several of them showed activity when tested in mice by the oxygen-consumption method, the most active of their series being butyl 4-hydroxy-3 : 5-di-iodobenzoate. Barker *et al.* (*Proc. Soc. Exp. Biol. Med.*, 1951, **78**, 840; *J. Pharm. Exp. Ther.*, 1950, **99**, 202) used thyroidectomised rats as test animals and found some activity in a number of 4-hydroxy-3 : 5-di-iodophenylalkanecarboxylic acids and similar di-iodophenols, although when comparable their tests tended to show lower activity than those using tadpoles; a similar species variation has become apparent during the biological tests reported later in this paper.

Treatment of *N*-acetyl-3 : 5-di-iodo-DL-tyrosine with benzyl chloride in dilute sodium hydroxide solution (cf. Woolley, *loc. cit.*) produced a low yield of the benzyl ether (I; R = H, R′ = Ac), which was difficult to separate from unchanged phenolic material. The required compound was, however, obtained in satisfactory yield from *N*-acetyl-3 : 5-di-iodo-DL-tyrosine ethyl ester by benzylation in alcoholic sodium ethoxide and hydrolysis of the ester (I; R = Et, R′ = Ac) with dilute alcoholic sodium hydroxide. The acetamido-ester was hydrolysed to the free amino-acid (I; R = R′ = H) by prolonged treatment with boiling 40% sodium hydroxide solution; the milder treatment described by Frieden and Winzler (*loc. cit.*) proved unsatisfactory, as did the use of acid conditions.

When *N*-acetyl-3 : 5-di-iodo-L-tyrosine ethyl ester was treated with benzyl chloride in alcoholic sodium ethoxide, the resulting benzyl ether was optically inactive. It was then found that *N*-acetyl-3 : 5-di-iodo-L-tyrosine ethyl ester was rapidly and completely racemised by refluxing with 1·5 mols. of alcoholic sodium ethoxide, hydrolysis of the ester occurring simultaneously. On the other hand, similar treatment with 0·95 mol. of sodium ethoxide had no effect on the optical activity, and when these conditions were applied to the benzylation of the ester an optically active ether (I; R = Et, R′ = Ac) was obtained in 72% yield. A higher yield of material with very similar rotation resulted from benzylation of the ester by benzyl chloride in the presence of potassium carbonate in ethyl methyl ketone. The ester was hydrolysed to the L-acetamido-acid (I; R = H, R′ = Ac) by dilute alcoholic sodium hydroxide.

The benzyl ethers (II; R = $CH_2{\cdot}CO_2H$), (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$), (II; R = $SO_3H$), and (III) were prepared by benzylation of the appropriate di-iodophenols with excess of benzyl chloride in aqueous-alcoholic alkali and alkaline hydrolysis of the benzyl esters so formed. The sulphonic acid was converted into 4-benzyloxy-3 : 5-di-iodo-

benzenesulphonamide (II; R = $SO_2 \cdot NH_2$). An alternative method, applied to the preparation of (II; R = $CO_2H$) and (II; R = $CH{:}CH \cdot CO_2H$), involved esterification of the phenolic acid, benzylation in the presence of sodium ethoxide or potassium carbonate, and hydrolysis of the ester grouping. By similar methods, methyl, *n*-butyl, and *p*-nitrobenzyl ethers of *N*-acetyl-3 : 5-di-iodo-DL-tyrosine, and 3 : 5-di-iodo-4-methoxycinnamic and β-(3 : 5-di-iodo-4-methoxyphenyl)propionic acids were prepared.

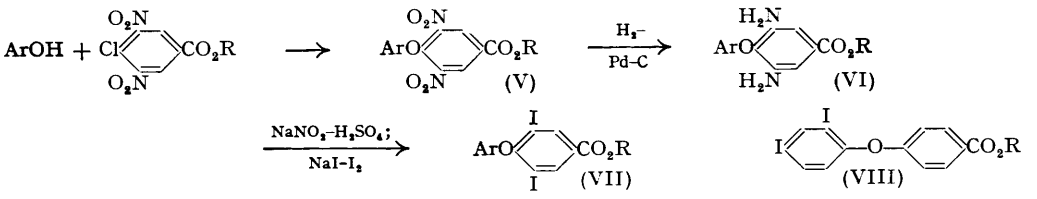
Our initial attempts to prepare 2-(4-benzyloxy-3 : 5-di-iodophenyl)ethylamine (II; R = $CH_2 \cdot CH_2 \cdot NH_2$) were defeated by our inability to obtain pure 3 : 5-di-iodotyramine by the method of G.P. 259,193. An attempt to prepare (II; R = $CH_2 \cdot CH_2 \cdot NH_2$) by decarboxylation of 4-benzyloxy-3 : 5-di-iodo-DL-tyrosine gave only an intractable black solid, but the amine was obtained by Curtius degradation of the propionic acid. Attempts to hydrolyse the crude *iso*cyanate (II; R = $CH_2 \cdot CH_2 \cdot NCO$) with hydrochloric acid led to loss of iodine, but either the *iso*cyanate or the urethane (II; R = $CH_2 \cdot CH_2 \cdot NH \cdot CO_2Et$) could be converted into the required amine by alkali.

Benzyl ethers of type (IV; X = I, R = H) and, in particular, the " homothyroxine " [IV; X = I, R = H, R′ = $CH_2 \cdot CH(NH_2) \cdot CO_2H$] seem of some interest as being more closely related to the hormone. Woolley (*loc. cit.*) sought this acid *via* the *p*-nitrobenzyl ether of *N*-acetyl-3 : 5-di-iodotyrosine, but his attempts to reduce the nitro- to an amino-group resulted in cleavage of the benzyl ether. To avoid the necessity for a reduction, we planned to protect the hydroxyl group by acylation.

4-Benzoyloxybenzyl bromide was best prepared by treating *p*-tolyl benzoate with *N*-bromosuccinimide; use of elementary bromine (Raiford and Milbery, *J. Amer. Chem. Soc.*, 1934, **56**, 2727) was less convenient and gave a much lower yield. The bromide could not be made to react with methyl 4-hydroxy-3 : 5-di-iodobenzoate in methanolic sodium methoxide, but both (IV; X = H, R = Bz, R′ = $CO_2Me$) and [IV; X = H, R = Bz, R′ = L-$CH_2 \cdot CH(NHAc) \cdot CO_2Et$] were prepared in high yield from the appropriate phenolic compound and 4-benzoyloxybenzyl bromide in ethyl methyl ketone containing potassium carbonate. However, all attempts to hydrolyse the benzoic ester groupings in these compounds, whether with acid or alkali, led to cleavage of the ether linkage. The lability of this linkage was shown strikingly by an experiment in which treatment of (IV; X = H, R = Bz, R′ = $CO_2Me$) with methanolic potassium hydroxide gave methyl 4-hydroxy-3 : 5-di-iodobenzoate, the ester group having survived under conditions that led to cleavage of the ether.

The acetates (IV; X = H, R = Ac, R′ = $CO_2Me$) and [IV; X = H, R = Ac, R′ = L-$CH_2 \cdot CH(NHAc) \cdot CO_2Et$] were prepared by methods similar to those used for the benzoates, but the same difficulty was encountered in hydrolysis. The instability of these *p*-acyloxybenzyl ethers is paralleled by that of *p*-aminobenzyl phenyl ether, the hydrochloride of which liberates phenol in aqueous solution at room temperature (Peak and Watkins, *J.*, 1950, 445).

As seen from the Table, some of the benzyl ethers described above show some anti-thyroid activity when tested by the oxygen consumption method in mice, though the



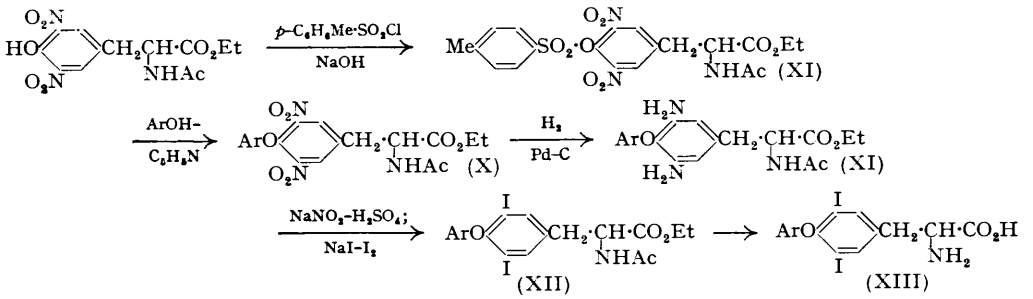

activites were considerably lower than those found by Frieden and Winzler (*loc. cit.*) with tadpoles. In the hope of finding more active compounds a series of 4-aryloxy-3 : 5-di-iodobenzoic acids was prepared.

4-Chloro-3 : 5-dinitrobenzoic acid reacted with phenol in aqueous potassium carbonate to yield 3 : 5-dinitro-4-phenoxybenzoic acid (V; Ar = Ph, R = H) which was reduced catalytically to the diamine (VI; Ar = Ph, R = H). This was converted into the

required 3 : 5-di-iodo-4-phenoxybenzoic acid (VII; Ar = Ph, R = H) by tetrazotisation and then by a Sandmeyer reaction under conditions similar to those described in earlier papers of this series. Since (VII; Ar = Ph, R = H) showed greater activity than the corresponding benzyl ether, a few compounds were prepared in which the phenoxy-group carried alkyl substituents. These compounds (VII; Ar = 3 : 4-$Me_2C_6H_3$, 3 : 5-$Me_2C_6H_3$, or 2-$C_{10}H_7$) were prepared in much the same way as the unsubstituted compound; they showed little or no antithyroid action.

Closely related to the above compounds is 4-(2 : 4-di-iodophenoxy)benzoic acid (VIII; R = H) the preparation of which was suggested by the high activity of 2 : 4-di-iodophenoxyacetic acid (Barker *et al.*, *locc. cit.*). It was prepared by the usual method from ethyl 4-(2 : 4-dinitrophenoxy)benzoate, itself obtained by reaction of 1-chloro-2 : 4-dinitrobenzene with ethyl *p*-hydroxybenzoate.

Finally, a few similarly substituted 4-aryloxy-3 : 5-di-iodophenylalanines (XIII) were prepared, in the hope that the closer structural resemblance to thyroxine might lead to greater activity. The compounds (XIII; Ar = Ph, 3 : 4-$Me_2C_6H_3$, 3 : 5-$Me_2C_6H_3$, and 3 : 5 : 1-$MeEtC_6H_3$) were prepared from *N*-acetyl-3 : 5-dinitrotyrosine ethyl ester by the method indicated, usually from the L-amino-acid derivative. The diamines (XI) could

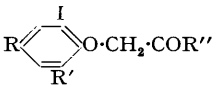



not be purified, but were generally characterised as acyl derivatives or salts; this behaviour contrasts with that of the 3 : 5-diamino-4-aryloxybenzoic acids and esters, of which most were comparatively stable crystalline solids. Since it seemed desirable that the final products should be racemic, the acetamido-esters (XII) were treated with alcoholic sodium ethoxide before hydrolysis. In the preparation of (XIII; Ar = 3 : 5 : 1-$C_6H_3MeEt$) the starting material was *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester, whose toluene-*p*-sulphonate, unlike the L-compound, was crystalline. The subsequent stages were as described above, with the racemisation stage omitted.

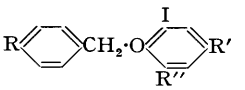
## Biological results

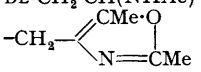
The compounds were tested in the Department of Chemical Pathology, Westminster Medical School, and in the Pharmacology Unit of this Company. With the exceptions indicated (see note 2), the method was that of Maclagan *et al.* (*J. Endocrinol.*, 1950, **6**, 456; *Biochem. J.*, 1951, **48**, 188) in which both the test-substance and the sodium salt of thyroxine are administered subcutaneously to mice and the rise in oxygen consumption is compared with that produced by thyroxine alone, the dosage of the latter being such as to produce a standard increase of 60—90%. A compound is regarded as being active at a particular dose level if it causes a decrease of at least 30% in the rise of oxygen consumption produced by thyroxine.

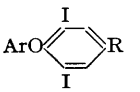
The compounds shown in the Tables are those described in this paper and in Part VIII (*J.*, 1951, 2467). The activities are indicated as follows: +++ active at a dose of 100 mg./kg. or less; ++ active at a dose of 200 mg./kg. but not at lower doses; + active at a dose of 400 mg./kg. but not at lower doses. Compounds found inactive at a dose of 400 mg./kg. have been omitted.

Iodophenoxyacetic acids: 

| R | R′ | R″ | Activity | Notes | R | R′ | R″ | Activity | Notes |
|---|---|---|---|---|---|---|---|---|---|
| Me | I | OH | + | — | I | Pr$^i$ | OEt | ++ | 1 |
| $CO_2H$ | I | OH | + | — | I | I | OH | ++ | 1 |
| I | Me | OH | ++ | 1 | I | I | OEt | +++ | — |
| I | Me | OEt | ++ | 1 | I | I | OBu | ++ | 1 |
| I | Me | $NH{\cdot}NH_2$ | ++ | 1 | I | I | $NH{\cdot}NH_2$ | — | 2 |

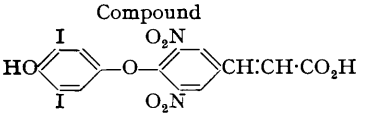
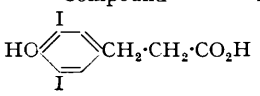
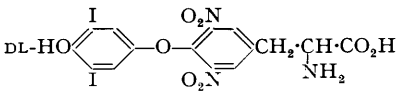
Benzyl ethers: 

| R | R′ | R″ | Activity | Notes |
|---|---|---|---|---|
| H | $CO_2H$ | I | + | 1 |
| H | I | $CO_2H$ | + | — |
| H | $CH_2{\cdot}CO_2H$ | I | — | 2 |
| H | DL-$CH_2{\cdot}CH(NHAc){\cdot}CO_2H$ | I | +++ | — |
| H | L-$CH_2{\cdot}CH(NHAc){\cdot}CO_2H$ | I | +++ | — |
| $NO_2$ | DL-$CH_2{\cdot}CH(NHAc){\cdot}CO_2H$ | I | + | — |
| H |  | I | — | 2, 3 |

Di-iododiphenyl ethers: 

| Ar | R | Activity | Notes |
|---|---|---|---|
| Ph | $CO_2H$ | +++ | — |
| Ph | $CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$ | + | — |
| *p*-$HO{\cdot}C_6H_4$ | $CO_2H$ | ++ | 4 |
| 3 : 5-$Me_2C_6H_3$ | $CO_2H$ | ++ | 1 |
| 3 : 5 : 1-$C_6H_3MeEt$ | DL-$CH_2{\cdot}CH(NH_2){\cdot}CO_2H$ | — | 2 |
| 3 : 4-$Me_2C_6H_3$ | DL-$CH_2{\cdot}CH(NH_2){\cdot}CO_2H$ | — | 2 |

Miscellaneous Compounds

| Compound | Activity | Notes | Compound | Activity | Notes |
|---|---|---|---|---|---|
|  | + | 4 |  | + | — |
|  | + | 4 | | | |

*Notes:* 1, Not tested at dose levels lower than 200 mg./kg. 2, Active when fed along with thyroxine in the diet at a wt. ratio of 100 : 1. 3, Prep.: *J.*, 1952, 827. 4, Prep.: *J.*, 1951, 2467.

## Experimental

[α] are for chloroform solutions, unless otherwise specified.

2 : 6-*Di-iodo*-4-*methylphenoxyacetic Acid*.—Sodium (1·3 g.) was dissolved in ethanol (150 c.c.), 3 : 5-di-iodo-*p*-cresol (18·0 g.) and ethyl chloroacetate (7·5 c.c.) were added, and the solution was boiled for 6 hours. 10N-Sodium hydroxide (56 c.c.) was added and the solution was boiled for 2 hours more. Concentration gave a brownish solid, which was removed and treated with hydrochloric acid. Recrystallisation of the resulting acid from aqueous acetic acid produced colourless crystals (6·7 g., 32%), m. p. 167° (Found: I, 60·3. Calc. for $C_9H_8O_3I_2$: I, 60·7%). Wawzonek and Wang (*J. Org. Chem.*, 1951, **16**, 1271) give m. p. 168—169°.

4-tert.-*Butyl*-2 : 6-*di-iodophenoxyacetic Acid*.—Sodium (0·23 g.) was dissolved in ethanol (30 c.c.), 4-*tert.*-butyl-3 : 5-di-iodophenol (Burger *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 1416) (4·02 g.) and ethyl chloroacetate (1·05 c.c.) were added, and the solution was boiled for 4 hours. The crude ester was extracted with ethyl acetate from the diluted mixture and the extract was washed with sodium carbonate solution and water and evaporated to dryness. The residue

was boiled for 2 hours with sodium hydroxide (30%; 15 c.c.) and sufficient alcohol to give a clear solution. Acidification precipitated the *acid* as an oil that later crystallised. Recrystallisation once from alcohol and twice from aqueous acetic acid gave colourless crystals, m. p. 183—184° (Found: I, 55·2. $C_{12}H_{14}O_3I_2$ requires I, 55·2%).

*4-Carboxy-2 : 6-di-iodophenoxyacetic Acid.*—This was prepared from methyl 4-hydroxy-3 : 5-di-iodobenzoate (4·0 g.) and ethyl chloroacetate (2·4 g.) as described for 2 : 6-di-iodo-4-methylphenoxyacetic acid. After the hydrolysis, the solution was diluted and acidified. The precipitated *acid*, crystallised from acetic acid, had m. p. 253° (decomp.) (Found: I, 56·0. $C_9H_6O_5I_2$ requires I, 56·7%).

*3 : 5-Di-iodo-o-cresol* (Me = 1).—The following method was much more satisfactory than those described in the literature. A solution of *o*-cresol (10·8 g.) in a mixture of 20% aqueous methylamine (80 c.c.) and methanol (50 c.c.) was stirred while a solution of iodine (50·8 g.) and sodium iodide (60 g.) in water (60 c.c.) was added gradually. A yellow solid began to separate after a short time. The mixture was stirred for a further hour and the solid was then filtered off and treated with dilute hydrochloric acid containing a little sodium metabisulphite. It was then filtered off, washed with water, and dried. The material (32·8 g., 91%) melted at 56—59°; crystallisation from acetic acid raised the m. p. to 65—66° (Datta and Prosad, *J. Amer. Chem. Soc.*, 1917, **39**, 441, give m. p. 67°). The acetate, after crystallisation from aqueous ethanol, had m. p. 72—74° (cf. 56° given by Willgerodt and Kornblum, *J. pr. Chem.*, 1889, **39**, 289) (Found: C, 27·05; H, 2·2; I, 62·7. Calc. for $C_9H_8O_2I_2$: C, 26·9; H, 2·0; I, 63·1%).

*4 : 6-Di-iodo-2-methylphenoxyacetic Acid.*—Sodium (1·3 g.) was dissolved in ethanol (150 c.c.), 3 : 5-di-iodo-*o*-cresol (18·0 g.) and ethyl chloroacetate (7·5 c.c.) were added and the solution was boiled for 6 hours. Most of the alcohol was distilled off, the residue was dissolved in chloroform and the solution was washed with water. After evaporation of the chloroform, the residue was crystallised from alcohol. The *ethyl* ester (15·1 g., 68%) was obtained as needles, m. p. 72—73° (Found: I, 57·1. $C_{11}H_{12}O_3I_2$ requires I, 56·95%).

The free acid, obtained in 81% yield by hydrolysis with aqueous-alcoholic sodium hydroxide, melted at 205—206° after crystallisation from acetic acid (Found: C, 25·8; H, 1·7; I, 60·5. Calc. for $C_9H_8O_3I_2$: C, 25·8; H, 1·9; I, 60·7%) (Wawzonek and Wang, *loc. cit.*, give m. p. 205°).

The ester (3·0 g.) was dissolved in saturated alcoholic ammonia. After 5 days the solution was evaporated and the solid crystallised from alcohol; the *amide* (2·6 g., 93%) melted at 162° (Found: N, 3·2; I, 60·5. $C_9H_9O_2NI_2$ requires N, 3·4; I, 60·9%).

The ester (10 g.) was boiled for 6 hours in 50% hydrazine hydrate (50 c.c.) and ethanol (20 c.c.). After cooling, the *hydrazide* (4·7 g., 48%) was filtered off and crystallised from alcohol; it had m. p. 141° (Found: N, 6·5; I, 58·6. $C_9H_{10}O_2N_2I_2$ requires N, 6·5; I, 58·8%).

*4 : 6-Di-iodo-2-propylphenol.*—A solution of 2-*n*-propylphenol (Farinholt, Harden, and Twiss, *J. Amer. Chem. Soc.*, 1933, **55**, 3383) (6·8 g.) in aqueous methylamine (30%; 55 c.c.) and methanol (100 c.c.) was treated during 45 minutes, while being stirred, with a solution of iodine (25·4 g.) and sodium iodide (50 g.) in water (30 c.c.). The mixture was stirred for a further 30 minutes and, after removal of some insoluble material, was acidified with concentrated hydrochloric acid (external cooling to <5°). The 4 : 6-di-iodo-2-propylphenol (16·3 g., 84%) separated as an oil, which solidified and then had m. p. 51—52°. This crude material was used for the subsequent stages, but for characterisation it was acetylated (acetyl chloride–pyridine). After distillation under high vacuum and crystallisation from methanol the *acetate* melted at 39·5—40·5° (Found: C, 31·1; H, 2·8; I, 58·6. $C_{11}H_{12}O_2I_2$ requires C, 30·7; H, 2·8; I, 59·0%).

*Ethyl 4 : 6-Di-iodo-2-propylphenoxyacetate.*—This was prepared in the usual way from 4 : 6-di-iodo-2-*n*-propylphenol (2·0 g.) and was purified by passage in chloroform through alumina. The *ester* crystallised from aqueous alcohol in needles, m. p. 63—65° (Found: C, 33·9; H, 3·5; I, 51·1. $C_{13}H_{16}O_3I_2,\frac{1}{2}C_2H_6O$ requires C, 33·8; H, 3·8; I, 51·2%).

*Butyl 2 : 4 : 6-Tri-iodophenoxyacetate.*—A solution of ethyl 2 : 4 : 6-tri-iodophenoxyacetate (Daniels and Lyons, *J. Amer. Chem. Soc.*, 1936, **58**, 2646) (11·2 g.) in *n*-butanol (70 c.c.) containing toluene-*p*-sulphonic acid (1·0 g.) was boiled for 5 hours. After cooling, the solid was filtered off and washed with 2N-sodium carbonate and water. The *ester* (8·5 g., 72%) crystallised from *cyclo*hexane as needles, m. p. 80—82° (Found: C, 24·4; H, 2·3; I, 64·9. $C_{12}H_{13}O_3I_3$ requires C, 24·6; H, 2·2; I, 65·0%).

*2 : 4 : 6-Tri-iodophenoxyacetohydrazide.*—Ethyl 2 : 4 : 6-tri-iodophenoxyacetate (5·0 g.) was boiled under reflux for 6 hours with hydrazine hydrate (25%; 100 c.c.) and sufficient alcohol

to give a clear solution. After cooling, the *hydrazide* was filtered off and crystallised from alcohol. The colourless crystals (2·5 g., 51%) melted with effervescence at 190—191°, resolidified, and finally melted with loss of iodine at 210°. After further crystallisation from methanol the substance melted at 192° and 211° (Found: N, 5·1; I, 69·4. $C_8H_7O_2N_2I_3$ requires N, 5·15; I, 70·0%).

*N-Acetyl-4-benzyloxy-3 : 5-di-iodo-*DL*-phenylalanine Ethyl Ester* (I; R = Et, R′ = Ac).—Sodium (1·03 g.) was dissolved in anhydrous ethanol (55 c.c.), and *N*-acetyl-3 : 5-di-iodo-DL-tyrosine ethyl ester (*J.*, 1950, 2824) (13·65 g.) was added. Benzyl chloride (4·7 c.c.) was added dropwise and the mixture was then boiled under reflux for 90 minutes. Most of the alcohol was distilled off, water was added, and the solution was acidified and extracted with ether. The extract was washed with sodium carbonate solution and water, then dried ($MgSO_4$), and the ether was removed. Crystallisation of the residue from aqueous alcohol yielded the *benzyl ether* (9·6 g., 60%), m. p. 126—129° (Found: N, 2·4; I, 42·2. $C_{20}H_{21}O_4NI_2$ requires N, 2·4; I, 42·8%).

A solution of this ester (3 g.) in 40% aqueous sodium hydroxide (9 c.c.) and ethanol (45 c.c.) was left at room temperature for 100 minutes, at the end of which a test portion gave no precipitate on dilution with water. The solution was filtered and acidified to Congo-red with 2N-hydrochloric acid. The resulting oil solidified and was crystallised from methanol. The *acetamido-acid* (2·36 g.; 82%) melted at 78—88°, resolidified, and finally melted at 176—179°. For analysis it was dried at 120° under reduced pressure (Found: N, 2·5; I, 45·0. $C_{18}H_{17}O_4NI_2$ requires N, 2·5; I, 44·9%).

*4-Benzyloxy-3 : 5-di-iodo-*DL*-phenylalanine* (I; R = R′ = H).—*N*-Acetyl-4-benzyloxy-3 : 5-di-iodo-DL-phenylalanine ethyl ester (5 g.) was boiled under reflux for 16 hours with 40% sodium hydroxide solution (50 c.c.) in a stainless steel vessel. The resulting mixture was diluted with water, warmed to dissolve the solid, filtered, and brought to pH 5 with acetic acid. After cooling, the solid was filtered off, washed with water, and dried. It was extracted with a large volume of boiling 0·2N-hydrochloric acid, and the liquid was decanted from a little gum and cooled, whereupon the hydrochloride crystallised. The solid was dissolved in N-sodium hydroxide, filtered and brought to pH 5 with acetic acid. The free base was filtered off, washed well with water, and dried. The amino-acid (3·2 g., 69%) melted at 208—209° and gave a positive ninhydrin test and a negative Kendall reaction (Found: N, 2·5; I, 48·5. Calc. for $C_{16}H_{15}O_3NI_2$: N, 2·7; I, 48·5%). Frieden and Winzler (*J. Biol. Chem.*, 1949, **179**, 423) give m. p. 203—205° (decomp.).

*N-Acetyl-4-benzyloxy-3 : 5-di-iodo-*L*-phenylalanine Ethyl Ester* (I; R = Et, R′ = Ac).—(*a*) Sodium (0·09 g.; 0·95 mols.) was dissolved in absolute ethanol (13 c.c.), and *N*-acetyl-3 : 5-di-iodo-L-tyrosine ethyl ester (*J.*, 1950, 2824) (2 g.) was added, followed by benzyl chloride (0·69 c.c.). The mixture was boiled under reflux for 90 minutes and most of the alcohol was then distilled off. Addition of water gave an oil which solidified. This material was shown by the Kendall test to contain some unchanged starting material and this was removed by washing the material in chloroform with sodium carbonate solution and then with water. Removal of the chloroform and crystallisation of the residue from aqueous ethanol gave the *acetamido-ester* (1·7 g., 72%), m. p. 152—154°, $[\alpha]_D^{20}$ +53° (*c*, 1·0) (Found: N, 2·2; I, 42·4. $C_{20}H_{21}O_4NI_2$ requires N, 2·4; I, 42·8%).

(*b*) *N*-Acetyl-3 : 5-di-iodo-L-tyrosine ethyl ester (15 g.) in ethyl methyl ketone (180 c.c.) was boiled under reflux for 3 hours with potassium carbonate (12·4 g.) and benzyl chloride (5·2 c.c.). After removal of potassium chloride by filtration, the solution was evaporated and the solid residue was crystallised from aqueous alcohol. The product (15·7 g., 89%) had m. p. 152—155° and $[\alpha]_D^{20}$ +54° (*c*, 1·0).

A solution of the ester (10 g.) in ethyl alcohol (150 c.c.) and aqueous sodium hydroxide (10N; 30 c.c.) was left at room temperature for 30 minutes. The ester, which was not completely soluble in the mixture, went into solution as hydrolysis took place. Acidification to Congo-red gave the acid (7 g., 74%; from methanol), m. p. between 65° and 85° with gas evolution, $[\alpha]_D^{20}$ +70° (*c*, 1·0) (Found, in material dried at 110°/5 mm.: I, 45·0. Calc. for $C_{18}H_{17}O_4NI_2$: I, 44·9%). Woolley (*J. Biol. Chem.*, 1946, **164**, 11) gives m. p. 84—90° but the specific rotation is not quoted.

*N-Acetyl-3 : 5-di-iodo-4-methoxy-*DL*-phenylalanine Ethyl Ester.*—Sodium (0·35 g.) was dissolved in anhydrous ethanol (20 c.c.), *N*-acetyl-3 : 5-di-iodo-DL-tyrosine ethyl ester (5 g.) was added followed by methyl iodide (1 c.c.) and the mixture was boiled under reflux for 2 hours. Most of the alcohol was distilled off, water was added, and the mixture was left overnight in the refrigerator. The gummy solid was filtered off and crystallised from aqueous alcohol, giving

the *methyl ether* (4·0 g., 78%), m. p. 127—129° (Found : N, 2·6; I, 49·2. $C_{14}H_{17}O_4NI_2$ requires N, 2·7; I, 49·0%).

Hydrolysis of the ester (3·25 g.) in ethanol (50 c.c.) and 40% sodium hydroxide (10 c.c.) until a portion gave no precipitate on dilution with water (about 1 hour) yielded the *acetamido-acid* (2·6 g.; 85%), m. p. 215—218° (from aqueous alcohol) (Found : N, 2·8; I, 51·8. $C_{12}H_{13}O_4NI_2$ requires N, 2·9; I, 51·9%).

N-*Acetyl*-4-*butoxy*-3 : 5-*di-iodo*-DL-*phenylalanine*.—(*a*) The method described by Woolley (*loc. cit.*) for the L-isomer gave the required *ether* (58% yield), m. p. 160—163° (from aqueous alcohol) (Found : N, 2·7; I, 47·2. $C_{15}H_{19}O_4NI_2$ requires N, 2·6; I, 47·8%).

(*b*) *N*-Acetyl-3 : 5-di-iodo-DL-tyrosine ethyl ester in alcoholic sodium ethoxide was treated with butyl bromide as described for the methyl ether. The crude product, in chloroform solution, was washed with aqueous sodium carbonate to remove some phenolic material. Evaporation of the chloroform solution and crystallisation of the residue from aqueous alcohol gave N-*acetyl*-4-*butoxy*-3 : 5-*di-iodo*-DL-*phenylalanine ethyl ester*, m. p. 98—100° (Found : N, 2·55; I, 45·0. $C_{17}H_{23}O_4NI_2$ requires N, 2·5; I, 45·4%).

The free acid, obtained in 51% overall yield by hydrolysis with cold 6% alcoholic sodium hydroxide, melted at 160—161°.

N-*Acetyl*-3 : 5-*di-iodo*-4-p-*nitrobenzyloxy*-DL-*phenylalanine*.—A solution of *N*-acetyl-3 : 5-di-iodo-DL-tyrosine (11·9 g.) in N-sodium hydroxide (55 c.c.) was heated on the steam-bath and stirred vigorously while *p*-nitrobenzyl chloride (4·25 g.) was added in portions during about 5 minutes. The mixture was heated and stirred for 2 hours and then left overnight in the refrigerator. The sodium salt was filtered off and washed with a little cold water. It was dissolved in water (375 c.c.) and the solution was extracted with ether. Acidification of the aqueous layer with 2N-hydrochloric acid gave a solid, which was crystallised from aqueous acetone. The *ether* (7·6 g., 50%) melted between 77° and 100° with gas-evolution, resolidified, and melted finally at 184—186°. After being dried under reduced pressure at 140° the compound melted at 182—185° (Found : N, 4·5; I, 41·2. $C_{18}H_{16}O_6N_2I_2$ requires N, 4·6; I, 41·6%).

4-*Benzyloxy*-3 : 5-*di-iodobenzoic Acid* (II; R = $CO_2H$).—Sodium (0·12 g.) was dissolved in anhydrous ethanol (10 c.c.), methyl 4-hydroxy-3 : 5-di-iodobenzoate (2 g.) was added, and the mixture was boiled under reflux on the water-bath until all the solid dissolved. Benzyl chloride (0·63 c.c.) was added portionwise to the boiling solution which was then boiled for a further 2 hours. Sodium hydroxide solution (10N; 10 c.c.) was added and the mixture boiled under reflux for 3 hours. The alcohol was distilled off, water added to the residue, and the solution extracted with ether. Acidification, etc., gave the acid (1·0 g.; 42%), m. p. 227—229° (from aqueous methanol; charcoal) (Frieden and Winzler, *loc. cit.*, give m. p. 227—228°).

2-*Benzyloxy*-3 : 5-*di-iodobenzoic Acid* (III).—To a boiling solution of 2-hydroxy-3 : 5-di-iodobenzoic acid (*Org. Synth.*, Coll. Vol. II, p. 343) (11·7 g.) and potassium hydroxide (3·36 g.) in 50% aqueous ethanol (80 c.c.), benzyl chloride (22·8 g.) was added dropwise. Refluxing was continued for 2 hours and the solvent was then removed on the water-bath. Potassium hydroxide (20 g.) and ethanol (50 c.c.) were added to the oily residue and the mixture was refluxed for 3 hours. The ethanol was then removed and water added to the residue which was extracted with ether. The aqueous layer contained an insoluble oil, which dissolved on warming. The warm aqueous solution was then acidified to Congo-red with concentrated hydrochloric acid and the resulting solid was crystallised from benzene. The *acid* (6·85 g., 48%) melted at 149—153° (Found : C, 34·8; H, 2·3; I, 53·5. $C_{14}H_{10}O_3I_2$ requires C, 35·0; H, 2·1; I, 52·9%).

4-*Benzyloxy*-3 : 5-*di-iodophenylacetic Acid* (II; R = $CH_2{\cdot}CO_2H$).—4-Hydroxy-3 : 5-di-iodophenylacetic acid (Papa *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 2619) (4·04 g.), in aqueous-alcoholic potassium hydroxide was treated with benzyl chloride as in the foregoing preparation. After crystallisation from aqueous alcohol, 4-*benzyloxy*-3 : 5-*di-iodophenylacetic acid* (3·25 g., 66%) melted at 196—197·5° (Found : C, 36·5; H, 2·75; I, 51·5. $C_{15}H_{12}O_3I_2$ requires C, 36·5; H, 2·45; I, 51·4%).

β-(4-*Benzyloxy*-3 : 5-*di-iodophenyl*)*propionic Acid* (II; R = $CH_2{\cdot}CH_2{\cdot}CO_2H$).—β-(4-Hydroxy-3 : 5-di-iodophenyl)propionic acid (*J.*, 1950, 2824) (4·18 g.) in aqueous-alcoholic potassium hydroxide was benzylated in the usual way. After crystallisation from ethanol the *ether* (2·8 g., 55%) melted at 162—164° (Found : I, 49·4. $C_{16}H_{14}O_3I_2$ requires I, 50·0%).

β-(3 : 5-*Di-iodo*-4-*methoxyphenyl*)*propionic Acid*.—A mixture of β-(4-hydroxy-3 : 5-di-iodophenyl)propionic acid (6 g.), methyl iodide (6·6 c.c.), potassium hydroxide (4·1 g.), water (5 c.c.), and methanol (100 c.c.) was left overnight at room temperature and then boiled under reflux for 150 minutes. Aqueous sodium hydroxide (40%; 50 c.c.) was added and the mixture

refluxed for 2 hours more. The methanol was distilled off, the residual sodium salt dissolved in water, and the solution acidified with concentrated hydrochloric acid. The resulting oil solidified on standing. Crystallisation, first from aqueous alcohol, then from light petroleum (b. p. 80—100°), gave the *ether* (2·5 g., 40%), m. p. 116—119° (Found: C, 27·9; H, 2·0. $C_{10}H_{10}O_3I_2$ requires C, 27·8; H, 2·3%).

*Ethyl* 4-*Benzyloxy*-3 : 5-*di-iodocinnamate* (II; R = CH:CH·$CO_2$Et).—Methyl 4-hydroxy-3 : 5-di-iodocinnamate (Paal and Mohr, *Ber.*, 1896, **29**, 2302) had m. p. 169—171°, whereas these authors quote m. p. 107° (Found: I, 59·5. Calc. for $C_{10}H_8O_3I_2$: I, 59·0%). Sodium (0·5 g.) was dissolved in ethanol (40 c.c.), methyl 4-hydroxy-3 : 5-di-iodocinnamate (6·1 g.) was added and the mixture was boiled under reflux while benzyl chloride (5·24 c.c.) was added dropwise and then for 3 hours more. The alcohol was distilled off, water added to the residue, and the solid was crystallised from methanol (charcoal), giving the *ethyl* ester (3·2 g., 42%), m. p. 131—133°.

The compound was shown to be the ethyl ester by comparison with the authentic methyl ester prepared as described below and with an authentic specimen of the ethyl ester prepared by Fischer–Speier esterification of the free acid. The specimen so obtained melted at 133—134° (Found: C, 40·7; H, 3·1; I, 47·8. $C_{18}H_{16}O_3I_2$ requires C, 40·5; H, 3·0; I, 47·5%).

The free *acid* obtained by hydrolysis of the ethyl ester with alcoholic sodium hydroxide melted at 235—237° after crystallisation from ethyl acetate (Found: C, 37·9; H, 2·35; I, 50·4. $C_{16}H_{12}O_3I_2$ requires C, 38·0; H, 2·4; I, 50·15%).

*Methyl* 4-*Benzyloxy*-3 : 5-*di-iodocinnamate* (II; R = CH:CH·$CO_2$Me).—Methyl 4-hydroxy-3 : 5-di-iodocinnamate (1 g.), anhydrous potassium carbonate (0·7 g.), benzyl chloride (0·4 c.c.), and ethyl methyl ketone (10 c.c.) were boiled under reflux for 3 hours. After removal of potassium chloride and solvent, the residue crystallised from methanol (charcoal). The *methyl* ester (0·23 g., 19%) had m. p. 122—124° (Found: C, 39·2; H, 2·6; I, 48·2. $C_{17}H_{14}O_3I_2$ requires C, 39·25; H, 2·7; I, 48·8%).

3 : 5-*Di-iodo*-4-*methoxycinnamic Acid*.—This was prepared from the phenol by the method used for the propionic acid. The methyl ether, obtained in 32% yield, melted at 202—204° after crystallisation from chloroform (Wheeler and Johns, *Amer. Chem. J.*, 1910, **43**, 11, give m. p. 202—203°).

4-*Benzyloxy*-3 : 5-*di-iodobenzenesulphonic Acid* (II; R = $SO_3$H).—Benzyl chloride (13·7 c.c.) was added dropwise to a boiling solution of sodium 4-hydroxy-3 : 5-di-iodobenzenesulphonate (Kehrmann, *J. pr. Chem.*, 1888, **37**, 9) (8·64 g.) and sodium hydroxide (0·8 g.) in alcohol (20 c.c.) and water (20 c.c.). The mixture was then refluxed for 3 hours more and the alcohol distilled off. The residue was diluted with water and extracted with ether. On concentration of the aqueous layer and cooling, the *sulphonic acid* (5·4 g., 52%) separated in needles; it decomposed gradually on heating, with loss of iodine (Found: C, 29·6; H, 2·4; S, 6·1; I, 47·4. $C_{13}H_{10}O_4I_2S,H_2O$ requires C, 29·2; H, 2·3; S, 6·0; I, 47·5%).

The acid (2·9 g.), phosphorus pentachloride (3·5 g.), and xylene (30 c.c.) were heated together on the water-bath for 90 minutes. The xylene was removed under reduced pressure and the oily residue dissolved in acetone (40 c.c.), a little insoluble material being filtered off. The solution was then poured into ammonia solution (*d* 0·88; 75 c.c.), and after 1 hour in the refrigerator the solid was filtered off and washed with water. Crystallisation from benzene (charcoal) gave the *sulphonamide* (1·1 g., 39%), m. p. 205—206° (Found: N, 2·7; I, 50·0; S, 5·7. $C_{13}H_{11}O_3NI_2S$ requires N, 2·7; I, 49·3; S, 6·2%).

Attempts to prepare the sulphonyl chloride by means of thionyl chloride led only to unchanged starting material, while chlorosulphonic acid gave materials which could not be purified.

*Ethyl* 2-(4-*Benzyloxy*-3 : 5-*di-iodophenyl*)*ethylcarbamate* (II; R = $CH_2$·$CH_2$·NH·$CO_2$Et).—β-(4-Benzyloxy-3 : 5-di-iodophenyl)propionic acid (6·48 g.) and thionyl chloride (24 c.c.) were boiled under reflux for 1 hour. The excess of thionyl chloride was removed under reduced pressure and the residual crude acid chloride, which solidified, was dissolved in acetone (36 c.c.) and stirred vigorously while a solution of sodium azide (0·78 g.) in water (6 c.c.) was added. After a further 15 minutes, the solution was cooled in an ice-bath, and the azide was precipitated by the addition of water (120 c.c.). The azide was extracted into ether and the extract was treated briefly with calcium chloride and added to anhydrous ethanol (120 c.c.). The ether was removed by distillation and the alcoholic solution boiled under reflux until evolution of nitrogen ceased. The solution was evaporated to dryness on the steam-bath and the residual gum was chromatographed in benzene on alumina. The first benzene eluate gave 1·98 g. of oil which, after chromatography on a second column, followed by crystallisation from light

petroleum (b. p. 60—80°), gave 0·4 g. of the *carbamate*, m. p. 96—97°. Subsequent benzene eluates from the first column yielded a further 1·87 g. of material which, after crystallisation from light petroleum, gave 1·31 g. of the carbamate, m. p. 96—97°. Recrystallisation of the combined solids (1·7 g., 24%) did not affect the m. p. (Found: N, 2·5; I, 46·1. $C_{18}H_{19}O_3NI_2$ requires N, 2·5; I, 46·0%).

2-(4-*Benzoyloxy*-3 : 5-*di-iodophenyl*)*ethylamine Hydrochloride* (II; R = $CH_2$·$CH_2$·$NH_2$,HCl).—The crude unchromatographed carbamate (1·88 g., from 2·16 g. of acid) was boiled under reflux for 16 hours with sodium hydroxide (5 g.) in water (5 c.c.) and ethanol (20 c.c.). Addition of water precipitated an oil which was extracted into chloroform. The extract was dried ($CaCl_2$) and evaporated. The residual brown gum was extracted with boiling 0·25N-hydrochloric acid (4 × 80 c.c.). Overnight, these extracts deposited a solid, which, after crystallisation from alcohol, gave the *amine hydrochloride* (0·31 g., 14%), m. p. 213—214° (Found: C, 34·8; H, 3·4; N, 2·6. $C_{15}H_{15}ONI_2$,HCl requires C, 35·0; H, 3·1; N, 2·7%).

Hydrolysis of the pure carbamate gave the same material in 49% yield.

The amine hydrochloride was also obtained in 17% yield (based on the propionic acid) by decomposition of the azide in boiling benzene and hydrolysis of the resulting crude *iso*cyanate as described for hydrolysis of the carbamate.

4-*Benzoyloxybenzyl Bromide*.—*p*-Tolyl benzoate (10·5 g., 1 mol.), *N*-bromosuccinimide (8·9 g., 1 mol.), carbon tetrachloride (50 c.c.), and benzoyl peroxide (0·05 g.) were heated under reflux for 2 hours. After cooling, the solid was filtered off and washed with carbon tetrachloride. The combined filtrate and washings were evaporated to dryness on the water-bath, leaving an oil (12·9 g.) which solidified (m. p. 102—106°). After crystallisation from light petroleum (b. p. 60—80°) it (10·9 g., 76%) melted at 108—111° (Raiford and Milbery, *J. Amer. Chem. Soc.*, 1934, **56**, 2727, give m. p. 109—110°).

*Methyl* 4-(4-*Benzoyloxybenzyloxy*)-3 : 5-*di-iodobenzoate* (IV; R = Bz, R′ = $CO_2Me$, X = H).—Methyl 4-hydroxy-3 : 5-di-iodobenzoate (4·04 g.), 4-benzoyloxybenzyl bromide (4·38 g.), anhydrous potassium carbonate (4·14 g.), and ethyl methyl ketone (60 c.c.) were boiled under reflux for 3 hours. The solid was filtered off and washed with a little hot ethyl methyl ketone, and the combined filtrate and washings were concentrated to about 20 c.c. and allowed to cool. The resulting solid was filtered off and washed with a little ethyl methyl ketone. After crystallisation from ethyl alcohol, the *ether* (5·3 g., 86%) melted at 138—140° (Found: C, 42·8; H, 2·8; I, 41·2. $C_{22}H_{16}O_5I_2$ requires C, 43·0; H, 2·6; I, 41·3%).

N-*Acetyl*-4-(4-*benzoyloxybenzyloxy*)-3 : 5-*di-iodo*-L-*phenylalanine Ethyl Ester* [IV; R = Bz, R′ = $CH_2$·$CH(NHAc)$·$CO_2Et$, X = H].—*N*-Acetyl-3 : 5-di-iodo-L-tyrosine ethyl ester (2·51 g.), as in the foregoing experiment, yielded the *ether* (3·03 g., 85%), m. p. 195—196°, $[\alpha]_D^{20}$ +22·2° (*c*, 0·4 in EtOH–$CHCl_3$, 1 : 1 by vol.) (Found: C, 45·7; H, 3·6; N, 1·8; I, 36·1. $C_{27}H_{25}O_6NI_2$ requires C, 45·45; H, 3·5; N, 2·0; I, 35·6%).

4-*Acetoxybenzyl Bromide*.—*p*-Tolyl acetate (7·5 g.), *N*-bromosuccinimide (8·9 g.), benzoyl peroxide (0·05 g.), and carbon tetrachloride (50 c.c.) gave, as above, the *bromide* (5·75 g., 50%) melting at 49—55° [from light petroleum (b. p. 60—80°)] (Found: C, 47·8; H, 4·4; Br, 34·7. $C_9H_9O_2Br$ requires C, 47·2; H, 4·0; Br, 34·9%). Recrystallisation gave material melting at 53—56°, but this decomposed whilst being dried in a vacuum-desiccator at room temperature. The material was used with the smallest possible delay.

*Methyl* 4-(4-*Acetoxybenzyloxy*)-3 : 5-*di-iodobenzoate* (IV; R = Ac, R′ = $CO_2Me$, X = H).—Methyl 4-hydroxy-3 : 5-di-iodobenzoate (2·02 g.), 4-acetoxybenzyl bromide (1·72 g.), anhydrous potassium carbonate (2·07 g.) and ethyl methyl ketone (30 c.c.) were heated under reflux for 3 hours. The *ether* (2·4 g., 87%; from ethyl alcohol) melted at 103—105° (Found: C, 36·5; H, 2·6; I, 45·7. $C_{17}H_{14}O_5I_2$ requires C, 37·0; H, 2·55; I, 46·0%).

*N*-Acetyl-3 : 5-di-iodo-L-tyrosine ethyl ester similarly gave 4-(4-*acetoxybenzyloxy*)-N-*acetyl*-3 : 5-*di-iodo*-L-*phenylalanine ethyl ester* [IV; R = Ac, R′ = $CH_2$·$CH(NHAc)$·$CO_2Et$, X = H] (4·6 g., 84%), m. p. 187—189° (from ethyl alcohol) (Found: N, 2·1; I, 39·2. $C_{22}H_{23}O_6NI_2$ requires N, 2·15; I, 39·0%).

3 : 5-*Dinitro*-4-*phenoxybenzoic Acid* (V; Ar = Ph, R = H).—4-Chloro-3 : 5-dinitrobenzoic acid (26 g.), phenol (37·6 g.), potassium carbonate (13·8 g.), and water (40 c.c.) were heated at 140—150° for 1 hour, then poured into an excess of 2N-hydrochloric acid; the precipitated solid was filtered off, washed with water, dried, and crystallised from alcohol. The *diphenyl ether* (22·7 g., 71%) melted at 219—222° (Found: N, 9·0. $C_{13}H_8O_7N_2$ requires N, 9·2%).

3 : 5-*Diamino*-4-*phenoxybenzoic Acid* (VI; Ar = Ph, R = H).—A suspension of 3 : 5-dinitro-4-phenoxybenzoic acid (21·5 g.) in anhydrous ethanol (210 c.c.) was hydrogenated at atmospheric temperature and pressure over palladised charcoal (4·2 g.) in 1½ hours. The

catalyst was then filtered off and the filtrate concentrated to small bulk, under carbon dioxide. The *diamine* (6·0 g.) crystallised overnight. A further quantity (4·9 g.) was obtained by extraction of the catalyst with alcohol. By concentration of the combined mother-liquors from both crops, the yield was brought to 14·0 g. (81%). Recrystallisation from ethyl alcohol gave material melting at 229—231° (Found: N, 11·6. $C_{13}H_{12}O_3N_2$ requires N, 11·5%).

3 : 5-*Di-iodo*-4-*phenoxybenzoic Acid* (VII; Ar = Ph, R = H).—Sodium nitrite (1·94 g.) was dissolved in concentrated sulphuric acid (25 c.c.) and the solution was stirred, and kept at 0—2°, whilst a solution of 3 : 5-diamino-4-phenoxybenzoic acid (2·58 g.) in acetic acid (50 c.c.) and concentrated sulphuric acid (25 c.c.) was added dropwise. The mixture was then stirred for a further hour at about 0°. The tetrazonium solution was added, from a cooled dropping funnel during about 30 minutes, to a stirred solution of iodine (7·45 g.) and sodium iodide (14·9 g.) in water (150 c.c.). The mixture was stirred for a further hour and set aside overnight. The solid was filtered off and washed with water. Excess of iodine was removed by shaking an aqueous suspension of the solid with a little sodium metabisulphite. The *di-iodo*-compound was washed with water, dried, and crystallised twice from benzene (charcoal), giving needles (3·46 g., 70%), m. p. 230—232° (Found: C, 33·3; H, 2·0; I, 54·9. $C_{13}H_8O_3I_2$ requires C, 33·5; H, 1·7; I, 54·5%).

The *methyl* ester, prepared by methanolic hydrogen chloride, had m. p. 148—149° (from methanol) (Found: C, 35·0; H, 2·0. $C_{14}H_{10}O_3I_2$ requires C, 35·0; H, 2·1%). The n-*butyl* ester, prepared similarly, melted at 95—97° (from methanol) (Found: C, 39·3; H, 3·1. $C_{17}H_{16}O_3I_2$ requires C, 39·1; H, 3·1%).

2-*Dimethylaminoethyl* 3 : 5-*Di-iodo*-4-*phenoxybenzoate* (VII; Ar = Ph, R = $CH_2{\cdot}CH_2{\cdot}NMe_2$).—3 : 5-Di-iodo-4-phenoxybenzoic acid (4 g.) and thionyl chloride (8 c.c.) were boiled together under reflux for 1 hour. Excess of thionyl chloride was distilled off, finally with benzene. The residue solidified and crystallised from light petroleum (b. p. 40—60°) as needles (1·78 g., 43%), m. p. 100—103°.

This acid chloride (1·5 g.) was treated in benzene (10 c.c.) with dimethylaminoethanol (0·63 c.c.) and the mixture boiled under reflux for 1 hour. The solution was extracted with 2N-sodium carbonate, the benzene layer dried ($Na_2SO_4$), the solvent removed, and the residue crystallised from light petroleum (b. p. 60—80°) (charcoal). The *ester* (0·9 g., 54%) melted at 95—98° (Found: N, 2·35. $C_{17}H_{17}O_3NI_2$ requires N, 2·6%).

*Methyl* 4-(3 : 5-*Dimethylphenoxy*)-3 : 5-*dinitrobenzoate* (V; Ar = 3 : 5-$Me_2C_6H_3$, R = Me).—Methyl 4-chloro-3 : 5-dinitrobenzoate (26·1 g.), 3 : 5-dimethylphenol (12·2 g.), ethyl methyl ketone (100 c.c.), and anhydrous potassium carbonate (27·7 g.) were heated under reflux for 2 hours, then filtered, and the residue was thoroughly extracted with hot acetone. The combined filtrate and washings yielded on evaporation a reddish semi-solid which was washed in chloroform with N-sodium hydroxide and water. Evaporation of the chloroform afforded a yellow solid which, after crystallisation from ethanol, gave the *ester* (25·2 g., 73%), m. p. 142—143°. Further crystallisation gave rise to lemon-yellow blades, darkening on exposure to light, m. p. 146—148° (Found: C, 55·5; H, 4·3; N, 7·8. $C_{16}H_{14}O_7N_2$ requires C, 55·5; H, 4·1; N, 8·1%).

The *acid*, obtained by hydrolysis with boiling hydrochloric–acetic acid, crystallised from aqueous acetic acid in yellow prisms, m. p. 216—221° (Found: C, 53·8; H, 3·5. $C_{15}H_{12}O_7N_2$ requires C, 54·2; H, 3·6%).

*Methyl* 3 : 5-*Diamino*-4-(3 : 5-*dimethylphenoxy*)*benzoate* (VI; Ar = 3 : 5-$Me_2C_6H_3$, R = Me). The foregoing ester (10 g.) in glacial acetic acid (250 c.c.) was hydrogenated at room temperature and 90 atm., in the presence of 6% palladised charcoal (2 g.). After filtration and evaporation, the residual pale syrup crystallised and, on recrystallisation from ethanol (charcoal), yielded the *diamine* (5 g., 60%) as almost colourless prisms, m. p. 163—164° (Found: C, 67·0; H, 6·1; N, 9·9. $C_{16}H_{18}O_3N_2$ requires C, 67·1; H, 6·3; N, 9·8%).

*Methyl* 4-(3 : 5-*Dimethylphenoxy*)-3 : 5-*di-iodobenzoate* (VII; Ar = 3 : 5-$Me_2C_6H_3$, R = Me).—Sodium nitrite (2·5 g.) was added gradually with stirring to concentrated sulphuric acid (20 c.c.) below 60°; glacial acetic acid (30 c.c.) was then added gradually with cooling. The foregoing diamine (4·2 g.) in glacial acetic acid (15 c.c.) was slowly added to concentrated sulphuric acid (8 c.c.) with cooling in a stream of water. This solution was added dropwise with stirring during 45 minutes to the nitrosylsulphuric acid solution. After a further hour's stirring the tetrazonium solution was added to a well-stirred solution of sodium iodide (13·4 g.), iodine (11·3 g.), and urea (1 g.) in water (200 c.c.), covering a layer of chloroform (200 c.c.). After 2 hours' stirring the mixture was filtered from free iodine, and the chloroform layer was washed successively with sodium metabisulphite solution, sodium hydrogen carbonate solution, and water. On evapor-

ation it gave a dark syrup which was poured in the minimum of chloroform on to alumina. Elution with more chloroform afforded a pale pink solid. Crystallisation from aqueous acetic acid gave the *di-iodo*-ester (3·0 g., 40%) as almost colourless prisms, m. p. 160—161° (Found : C, 38·1; H, 3·0; I, 49·6. $C_{16}H_{14}O_3I_2$ requires C, 37·8; H, 2·8; I, 50·0%).

The *acid* was prepared by heating the ester (1·5 g.) in acetic acid (50 c.c.)–concentrated hydrochloric acid (20 c.c.) for 2 hours, and when crystallised from aqueous acetic acid and then from methyl cyanide, was obtained as almost colourless prisms, m. p. 265° (Found : I, 51·0. $C_{15}H_{12}O_3I_2$ requires I, 51·4%).

*Methyl* 4-(3 : 4-*Dimethylphenoxy*)-3 : 5-*dinitrobenzoate* (V; Ar = 3 : 4-$Me_2C_6H_3$, R = Me).—Prepared in the same way as the 3 : 5-dimethyl compound in 81% yield, this *ester* crystallised from ethanol in lemon-yellow platelets, m. p. 125—127°, darkening on exposure to light (Found : C, 55·4; H, 4·3; N, 7·8%).

The corresponding *acid* crystallised from aqueous acetic acid in lemon-yellow needles, m. p. 235—240° (Found : C, 53·7; H, 3·45%).

*Methyl* 3 : 5-*Diamino*-4-(3 : 4-*dimethylphenoxy*)*benzoate* (VI; Ar = 3 : 4-$Me_2C_6H_3$, R = Me).—Hydrogenation of the dinitro-compound as described for the 3 : 5-dimethyl analogue afforded a 74% yield of the *diamine*, colourless prisms (from ethanol), m. p. 123—124° (Found : C, 66·85; H, 6·4; N, 10·2%).

*Methyl* 4-(3 : 4-*dimethylphenoxy*)-3 : 5-*di-iodobenzoate* (VII; Ar = 3 : 4-$Me_2C_6H_3$, R = Me), prepared from the diamine as described for the 3 : 5-dimethyl analogue, in 58% yield, and crystallised from acetone, had m. p. 165—166° (Found : C, 38·0; H, 2·7; I, 50·3%). The *acid*, obtained as described above, formed prisms, m. p. 267°, from methyl cyanide (Found : C, 36·8; H, 2·7; I, 51·8. $C_{15}H_{12}O_3I_2$ requires C, 36·5; H, 2·45; I, 51·4%).

4-β-*Naphthoxy*-3 : 5-*dinitrobenzoic Acid* (V; Ar = 2-$C_{10}H_7$, R = H).—4-Chloro-3 : 5-dinitrobenzoic acid (26 g.), β-naphthol (58 g.), and anhydrous potassium carbonate (13·8 g.) were mixed into a paste with water and heated at 140—150° under reflux for 1 hour. After cooling, the solid was filtered off and twice extracted with a small volume of ether. Recrystallisation of the residue from ethanol afforded the *acid* (22·6 g., 61%) as yellow prisms, m. p. 258° (decomp.) (Found : C, 57·5; H, 2·7; N, 8·0. $C_{17}H_{10}O_7N_2$ requires C, 57·6; H, 2·85; N, 7·9%).

3 : 5-*Di-iodo*-4-β-*naphthoxybenzoic Acid* (VII; Ar = 2-$C_{10}H_7$, R = H).—The above dinitro-compound (10 g.) in glacial acetic acid (250 c.c.) was hydrogenated at 80°/100 atm. for 4 hours in the presence of 6% palladised charcoal (1 g.). The liquid was evaporated under reduced pressure and the residue extracted with benzene, whence the crude diamine (4·3 g., 52%) was precipitated by addition of *cyclo*hexane. A solution of this material in acetic acid (50 c.c.) was added at −5° with stirring to sodium nitrite (3 g.) in sulphuric acid (50 c.c.) and acetic acid (50 c.c.) and treated with iodine–sodium iodide in the usual way. Evaporation of the chloroform solution afforded a gummy product which was poured in acetone on to alumina. The product was readily eluted with acetic acid (not acetone). Recrystallisation from aqueous acetic acid gave the *di-iodo-acid* (7·3 g., 50%) as off-white prisms, m. p. 260—266° (Found : C, 39·85; H, 2·1; I, 48·6. $C_{17}H_{10}O_3I_2$ requires C, 39·6; H, 1·9; I, 49·2%).

*Ethyl* 4-(2 : 4-*Dinitrophenoxy*)*benzoate*.—This *ester* was prepared in the usual way from 1-chloro-2 : 4-dinitrobenzene (61 g.), ethyl *p*-hydroxybenzoate (50 g.), and anhydrous potassium carbonate (83 g.) in ethyl methyl ketone (150 c.c.). Crystallisation from acetic acid gave yellow prisms (90 g.; 90%) m. p. 150—152° (Found : C, 54·1; H, 3·8; N, 8·4. $C_{15}H_{12}O_7N_2$ requires C, 54·2; H, 3·6; N, 8·4%).

*Ethyl* 4-(2 : 4-*Di-iodophenoxy*)*benzoate* (VIII; R = Et).—The foregoing dinitro-compound (10 g.) in glacial acetic acid (250 c.c.) was hydrogenated at room temperature and 100 atm. pressure in the presence of palladised charcoal (2 g.). Filtration and evaporation under reduced pressure in carbon dioxide, afforded a dark, air-sensitive oil which could not be crystallised.

This crude material was diazotised and subjected to the Sandmeyer reaction as described above for the preparation of methyl 4-(3 : 5-dimethylphenoxy)-3 : 5-di-iodobenzoate. The *di-iodo*-ester was obtained from the chromatogram as a straw-coloured oil, which crystallised from ethanol as plates (5·5 g., 37%), m. p. 67—68° (Found : C, 36·8; H, 2·5; I, 51·1. $C_{15}H_{12}O_3I_2$ requires C, 36·5; H, 2·4; I, 51·4%).

The *acid*, prepared in the usual way, melted at 250° (from acetic acid) (Found : C, 33·3; H, 1·8. $C_{13}H_8O_3I_2$ requires C, 33·5; H, 1·7%).

*N-Acetyl*-3 : 5-*dinitro*-4-*phenoxy*-L-*phenylalanine Ethyl Ester* (X; Ar = Ph).—*N*-Acetyl-3 : 5-dinitro-L-tyrosine ethyl ester (*J.*, 1949, 3424) (34·1 g.) in acetone (250 c.c.) and N-sodium hydroxide (100 c.c.) was treated with toluene-*p*-sulphonyl chloride (20 g.) in acetone (250 c.c.).

The mixture was boiled under reflux for 1 hour, most of the acetone was boiled off, and the resulting oil taken up in chloroform. The extract was washed with 2N-sodium carbonate and with water, then dried ($CaCl_2$), and the solvent removed under reduced pressure. The crude toluene-*p*-sulphonyl ester (42 g., 85%) was obtained as a brownish-yellow gum.

This was boiled in dry chloroform (100 c.c.) and pyridine (20 c.c.) under reflux for 30 minutes. Phenol (28·2 g.) was then added and the mixture refluxed for a further hour. After cooling, the chloroform solution was washed successively with 2N-hydrochloric acid, 2N-sodium carbonate, and water, dried ($CaCl_2$), and evaporated. Crystallisation from ethanol gave the *diphenyl ether* (13 g., 37% based on toluenesulphonyl ester), m. p. 136—137°, $[\alpha]_D^{22}$ +44·9° (*c*, 2·1) (Found: C, 54·8; H, 4·75; N, 9·8. $C_{19}H_{19}O_8N_3$ requires C, 54·7; H, 4·6; N, 10·1%).

N-*Acetyl*-3 : 5-*diamino*-4-*phenoxy*-L-*phenylalanine Ethyl Ester* (XI; Ar = Ph).—The foregoing dinitro-compound (9 g.) in methanol (200 c.c.) was hydrogenated at room temperature and pressure in the presence of 10% palladised charcoal (1·8 g.). The catalyst and solvent were removed, leaving a glass (7·5 g.) which did not crystallise. The material was characterised as its *diacetyl* derivative, m. p. 209—209·5° (from ethanol), $[\alpha]_D^{23}$ +72·9° (*c*, 1·1) (Found: C, 62·6; H, 6·2; N, 9·6. $C_{23}H_{27}O_6N_3$ requires C, 62·6; H, 6·2; N, 9·5%).

N-*Acetyl*-3 : 5-*di-iodo*-4-*phenoxy*-L-*phenylalanine Ethyl Ester* (XII; Ar = Ph).—The above diamine (7·5 g.) was treated with nitrosylsulphuric acid and the tetrazonium solution decomposed with iodide as described above for the preparation of methyl 4-(3 : 5-dimethylphenoxy)-3 : 5-di-iodobenzoate. After removal of excess of iodine, the chloroform solution was evaporated, to give an amorphous solid (9·7 g., 78% based on dinitro-compound), m. p. 104—105°. Recrystallisation from *cyclo*hexane, followed by benzene–light petroleum, gave the *di-iodo*-compound as white crystals, m. p. 106—107°, $[\alpha]_D^{20}$ +50·2° (*c*, 1·6) (Found: N, 2·6; I, 43·4. $C_{19}H_{19}O_4NI_2$ requires N, 2·4; I, 43·9%).

3 : 5-*Di-iodo*-4-*phenoxy*-DL-*phenylalanine* (XIII; Ar = Ph).—The above acetamido-ester (6·75 g.) was racemised by boiling it in absolute ethanol (70 c.c.) containing sodium (0·45 g.) for 90 minutes. After cooling, the mixture was poured on ice and hydrochloric acid, diluted, and set aside. The solid which separated was boiled under reflux with acetic acid (35 c.c.)–concentrated hydrochloric acid (35 c.c.) for 75 minutes; the mixture was cooled, diluted, and partially neutralised, and the crude amino-acid filtered off. Crystallisation from aqueous pyridine, then from aqueous acetic acid, gave the *amino-acid* (4 g., 67%), m. p. 237—238° (Found: C, 35·5; H, 2·9; I, 49·5. $C_{15}H_{13}O_3NI_2$ requires C, 35·4; H, 2·55; I, 49·9%).

N-*Acetyl*-4-(3 : 5-*dimethylphenoxy*)-3 : 5-*dinitro*-L-*phenylalanine Ethyl Ester* (X; Ar = 3 : 5-$Me_2C_6H_3$).—A solution of crude *N*-acetyl-3 : 5-dinitro-4-toluene-*p*-sulphonyloxy-L-phenylalanine ethyl ester (31 g.), prepared as already described, in dry pyridine (200 c.c.), was boiled for 10 minutes under reflux, 3 : 5-dimethylphenol (36·6 g.) was added, and the mixture refluxed for 1 hour. Pyridine (120 c.c.) was then removed by distillation, the residue poured into an excess of 2N-hydrochloric acid, and the oil so formed extracted into chloroform. The chloroform solution was washed with 2N-hydrochloric acid, 2N-sodium hydroxide, and water. After being dried ($CaCl_2$), the chloroform was distilled off and the residual gum (25 g.) triturated with a small quantity of ethanol. Crystallisation of the resulting solid from ethanol gave the *dinitro*-compound (22·2 g., 80%), m. p. 131—132°, $[\alpha]_D^{22}$ +43·1° (*c*, 2·0) (Found: C, 56·1; H, 5·15; N, 9·4. $C_{21}H_{23}O_8N_3$ requires C, 56·6; H, 5·2; N, 9·4%).

N-*Acetyl*-3 : 5-*diamino*-4-(3 : 5-*dimethylphenoxy*)-L-*phenylalanine Ethyl Ester* (XI; Ar = 3 : 5-$Me_2C_6H_3$).—The preceding dinitro-compound (12 g.) in methanol (300 c.c.) was hydrogenated at atmospheric temperature and pressure in the presence of 10% palladised charcoal (2·4 g.). After removal of the catalyst, evaporation gave a pale brown gum (10 g.) which did not crystallise. The diamine formed a *dihydrochloride*, m. p. 214—215° (Found: N, 9·4; Cl, 15·3. $C_{21}H_{27}O_4N_3$,2HCl requires N, 9·2; Cl, 15·5%), and a *diacetyl* derivative, m. p. 207°, $[\alpha]_D^{24}$ +66·8° (*c*, 1·0) (Found: C, 63·9; H, 6·7; N, 8·9. $C_{25}H_{31}O_6N_3$ requires C, 63·9; H, 6·7; N, 8·95%).

N-*Acetyl*-4-(3 : 5-*dimethylphenoxy*)-3 : 5-*di-iodo*-L-*phenylalanine Ethyl Ester* (XII; Ar = 3 : 5-$Me_2C_6H_3$).—The above crude diamine (10 g.) was tetrazotised and treated with iodine in the usual way. The *di-iodo*-ester (10·0 g., 61% based on dinitro-compound) was recrystallised from ethanol and finally from *cyclo*hexane, forming needles, m. p. 158·5—159°, $[\alpha]_D^{20}$ +50·0° (*c*, 2·0) (Found: I, 41·6. $C_{21}H_{23}O_4NI_2$ requires I, 41·8%).

4-(3 : 5-*Dimethylphenoxy*)-3 : 5-*di-iodo*-DL-*phenylalanine* (XIII; Ar = 3 : 5-$Me_2C_6H_3$).—The above compound (8 g.) was racemised and then hydrolysed as described above for the phenoxy-compound. After crystallisation from aqueous acetic acid, the *amino-acid* (7·0 g., 99%) melted

at 237—238° (decomp.) (Found : C, 38·2; H, 3·4; I, 46·9. $C_{17}H_{17}O_3NI_2$ requires C, 38·0; H, 3·2; I, 47·3%).

N-*Acetyl*-4-(3 : 4-*dimethylphenoxy*)-3 : 5-*dinitro*-L-*phenylalanine Ethyl Ester* (X; Ar = 3 : 4-$Me_2C_6H_3$).—Crude *N*-acetyl-3 : 5-dinitro-4-toluene-*p*-sulphonyloxy-L-phenylalanine ethyl ester (30 g.) was treated with 3 : 4-dimethylphenol (36·6 g.) and dry pyridine (200 c.c.) and the product was isolated as described for the isomeric 3 : 5-dimethylphenoxy-compound. The *diphenyl ether* separated from ethanol as pale yellow needles, m. p. 114·5—115·5°, $[\alpha]_D^{22}$ +44·7° (*c*, 1·9) (Found : C, 56·7; H, 5·4; N, 9·4%).

N-*Acetyl*-3 : 5-*diamino*-4-(3 : 4-*dimethylphenoxy*)-L-*phenylalanine Ethyl Ester* (XI; Ar = 3 : 4-$Me_2C_6H_3$).—Hydrogenation of the foregoing dinitro-compound in methanol with palladised charcoal gave the crude diamine which was characterised as its *diacetyl* derivative, m. p. 190° (from aqueous acetic acid), $[\alpha]_D^{22}$ +70° (*c*, 2·1) (Found : C, 63·8; H, 6·5; N, 8·9%), and *dihydrochloride*, m. p. 213—214° (decomp.) (Found : Cl, 15·4%).

N-*Acetyl*-4-(3 : 4-*dimethylphenoxy*)-3 : 5-*di-iodo*-L-*phenylalanine Ethyl Ester* (XII; Ar = 3 : 4-$Me_2C_6H_3$).—The above diamine gave an 88% yield of the *di-iodo*-compound, m. p. 117—118° [from light petroleum (b. p. 80—100°)], $[\alpha]_D^{20}$ +49·5° (*c*, 1·3) (Found : I, 41·7%).

4-(3 : 4-*Dimethylphenoxy*)-3 : 5-*di-iodo*-DL-*phenylalanine* (XIII; Ar = 3 : 4-$Me_2C_6H_3$).—Racemisation and hydrolysis of the above acetamido-ester as already described gave the *amino-acid* (68%), m. p. 234—235° (from acetic acid) (Found : C, 37·8; H, 3·5; I, 46·7%).

N-*Acetyl*-3 : 5-*dinitro*-4-*toluene*-p-*sulphonyloxy*-DL-*phenylalanine Ethyl Ester* (IX).—This *compound* was prepared from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (*J.*, 1951, 2467) (22 g.) as for the L-compound. It (yield, 56%) separated readily from chloroform as pale yellow needles, m. p. 157—158° (Found : C, 48·7; H, 4·4; N, 8·3. $C_{20}H_{21}O_{10}N_3S$ requires C, 48·5; H, 4·2; N, 8·5%).

N-*Acetyl*-4-(5-*ethyl*-3-*methylphenoxy*)-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester* (X; Ar = 3 : 5 : 1-MeEt$C_6H_3$).—The above toluene-*p*-sulphonyl ester (16·5 g.) was heated on the steam-bath with dry pyridine (80 c.c.) for 20 minutes. Removal of excess of pyridine *in vacuo* gave a gum which was boiled under reflux with 3-ethyl-5-methylphenol (14 g.) in chloroform (100 c.c.) and pyridine (10 c.c.) for 2 hours. The chloroform solution was washed successively with 2N-hydrochloric acid, 2N-sodium hydroxide, and water, dried ($CaCl_2$), and evaporated and the residue crystallised from ethanol. The *diphenyl ether* (4·25 g., 28%) melted at 118—119° (Found : C, 57·4; H, 5·6; N, 9·0. $C_{22}H_{25}O_8N_3$ requires C, 57·5; H, 5·5; N, 9·15%).

4-(5-*Ethyl*-3-*methylphenoxy*)-3 : 5-*di-iodo*-DL-*phenylalanine* (XIII; Ar = 3 : 5 : 1-MeEt$C_6H_3$).—The above dinitro-compound (4·25 g.) in methanol (100 c.c.) was reduced with hydrogen in the presence of 10% palladised charcoal (1 g.), and the crude diamine tetrazotised and converted into the 3 : 5-di-iodo-compound as above. Hydrolysis of the product with acetic acid–hydrochloric acid gave the *amino-acid* (1·7 g., 33%), m. p. 226—227° (from acetic acid) (Found : C, 39·1; H, 3·2; N, 2·3; I, 46·0. $C_{18}H_{19}O_3NI_2$ requires C, 39·2; H, 3·45; N, 2·5; I, 46·1%).

The authors acknowledge gratefully the help of Professor N. F. Maclagan in arranging for the testing of many of the compounds and of Mr. E. G. Tomich, Head of the Pharmacology Unit, Glaxo Laboratories, for testing the others. Thanks are due also to the late Mr. A. Busby and Mr. W. F. Wall for their assistance in the experimental work.

GLAXO LABORATORIES, LTD.,
GREENFORD, MIDDLESEX.

[*Received, October 15th*, 1952.]