130. *The Synthesis of Thyroxine and Related Substances. Part XI.* Diphenylamines.*

By R. C. Cookson.

In the presence of dimethylaniline *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester reacted with toluene-*p*-sulphonyl chloride followed by *p*-anisidine to give the dinitrodiarylamine (V; R = Me, R′ = H). Reduction of the last, tetrazotisation of the diamine, and treatment with tri-iodide solution produced the iodobenzotriazole (XI). The same series of operations with the derived *N*-acetyl derivative (V; R = Me, R′ = Ac) gave the related iodobenziminazole (XIII; R = Me, R′ = Et, R″ = Ac).

4′-Hydroxy-4-methyl-3 : 5-dinitrodiphenylamine underwent reversible oxidation to the quinone imine (VI), which added hydrogen chloride to form exclusively the 3′-chloro-4′-hydroxydiphenylamine (VII). With *n*-butylamine, however, the imine gave equimolecular quantities of the butylaminoquinone imine (X) and original hydroxydiphenylamine.

A series of *N*-benzoyl-2 : 6-di-iodo-diphenylamines (XV) was made by rearrangement of the imidates (XIV), easily got by condensation of the 2 : 6-di-iodophenols with *N*-*p*-methoxyphenylbenzimidoyl chloride. Preferential hydrolysis of the *N*-benzoyl group in (XV) was achieved by potassium hydroxide and of the *O*-methyl group by hydriodic acid.

THE only known analogue of thyroxine in which the central oxygen atom has been replaced is the sulphide prepared by Harington (*Biochem. J.*, 1948, **43**, 434), which had 1/5th the activity of thyroxine in the tadpole metamorphosis test and presumably no significant anti-thyroxine activity. Experiments on the synthesis of the " diphenylamine analogue," in which this oxygen atom is replaced by a secondary amino-group, have now been carried out.

A possible route to the necessary 2 : 6-di-iododiphenylamines seemed to be indicated by the synthesis of 2 : 6-di-iododiphenyl ethers from 2 : 6-dinitrophenols recently developed in these laboratories. In this the dinitrophenol is converted by toluene-*p*-sulphonyl chloride in pyridine into the 1-(2 : 6-dinitrophenyl)pyridinium toluene-*p*-sulphonate (I); this condenses with a phenol to give the 2 : 6-dinitrodiphenyl ether (Parts II, III, and V, *J.*, 1949, S 190, S 199, 3424) which can then be reduced to the diamine. This can be tetrazotised in sulphuric–acetic acids, and the diazonium groups replaced by iodine (Parts I and V, *J.*, 1949, S 185, 3424).

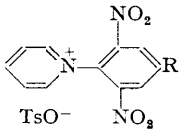
The pyridinium salt (I; R = Me) obtained from 3 : 5-dinitro-*p*-cresol (Me = 1) reacted vigorously with *p*-anisidine, to give 3 : 5-dinitro-*p*-toluidine and purple crystals of 5-*p*-anisidinopentadienal *p*-methoxyanil toluene-*p*-sulphonate (II); the latter, when heated, cyclised, with loss of *p*-anisidine, to 1-*p*-methoxyphenylpyridinium toluene-*p*-sulphonate, identified by comparison of the corresponding picrate with an authentic sample. This reaction is a variant of Zincke's method for opening the pyridine ring, in which 1-(2 : 4-dinitrophenyl)pyridinium halides react with primary aromatic amines to give 2 : 4-dinitroaniline and the hydrohalides of glutacondialdehyde " dianils " (Zincke *et al.*, *Annalen*, 1904, **330**, 361; **333**, 296; 1905, **338**, 107). Incidentally, it provides a much milder and more convenient method for converting dinitrophenyl toluene-*p*-sulphonates into dinitroanilines than the action of dry ammonia on the esters in boiling nitrobenzene or xylene (Ullmann and Nádai, *Ber.*, 1908, **41**, 1873; Ullmann and Sané, *ibid.*, 1911, **44**, 3730). The pyridinium toluene-*p*-sulphonate made from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester, for example, yielded (III) on treatment with *p*-anisidine.

In the absence of pyridine bases 2 : 4- and 2 : 6-dinitrophenyl toluene-*p*-sulphonates react with aromatic amines to form the dinitrodiphenylamines. The procedure may be simplified by allowing the amine to react with the ester (which may be the toluene-*p*-sulphonate or chloride, depending on the phenol) prepared *in situ* by treating the dinitro-

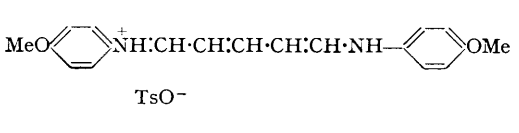
* Part X, *J.*, 1952, 2366.

phenol with toluene-*p*-sulphonyl chloride in diethylaniline (Ullmann *et al.*, *loc. cit.*; Sané and Joshi, *J. Indian Chem. Soc.*, 1932, **9**, 59; Joshi, *ibid.*, 1933, **10**, 677).

p-Anisidine reacted with 3 : 5-dinitro-*p*-cresol that had been treated with toluene-*p*-sulphonyl chloride in dimethylaniline, and the diphenylamine (IV; R = Me, R′ = H) was isolated from the dark red mixture. The yield of pure diphenylamine was disappointingly low compared with those reported by Ullmann *et al.* (*loc. cit.*) for the dinitrodiphenylamines made similarly from aniline and the toluidines (40% against 90—98%). The ester (V; R = Me, R′ = H) was prepared in the same way from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester in a yield of only 25%. This was raised to 59% by using chloroform as solvent instead of dimethylaniline, which was reduced to 2 mols. No strictly comparable experiments were done on the effect of diluents on the yield, but chloroform or dioxan were used in all later experiments.



(I)



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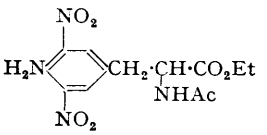

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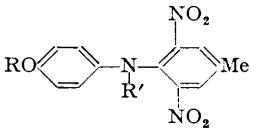
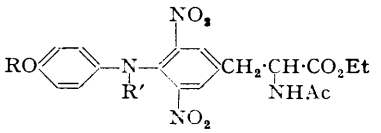


(IV)



(V)

(TsO = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$)

The 4′-hydroxydiphenylamines (IV; R = R′ = H) and (V; R = R′ = H) were prepared by essentially the same method from *p*-aminophenol. The possibility that the hydroxy- as well as the amino-group might react unless the dinitrophenyl ester was always presented with an excess of *p*-aminophenol, together with the sparing solubility of *p*-aminophenol in most organic solvents, made a slight modification in technique necessary; the dinitrophenol was caused to react with toluene-*p*-sulphonyl chloride as before, and the resulting solution was added slowly to an excess of *p*-aminophenol in boiling dioxan. In this way (IV; R = R′ = H) was obtained as dark red needles, but (V; R = R′ = H) was a gum, which was characterised as the crystalline *O*-acetate (V; R = Ac, R′ = H). In all these experiments the dinitrodiphenylamine was accompanied by a dark red oil, the original dinitrophenol, and (even in the absence of excess of toluene-*p*-sulphonyl chloride) the toluene-*p*-sulphonyl derivative of the amine.

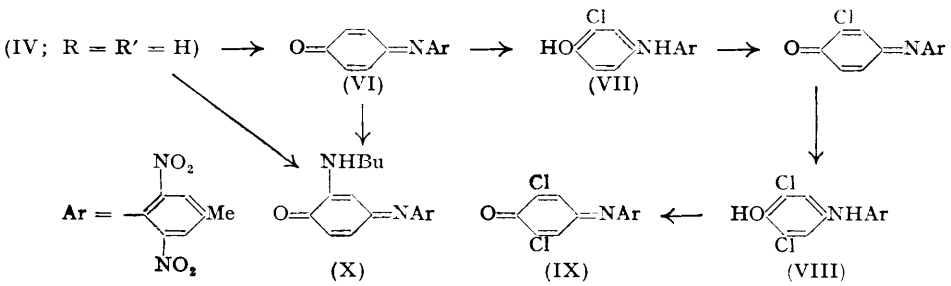
With acetic anhydride in pyridine the hydroxydiphenylamines rapidly gave the *O*-acetates, but much more drastic conditions were needed for formation of the *N*-acetates, namely, use of sulphuric or perchloric acid as catalyst in a large excess of acetic anhydride; toluene-*p*-sulphonic acid and sodium acetate were ineffective as catalysts. Unfortunately, the more important *N*-acetates (V; R = Me, R′ = Ac; R = R′ = Ac) were uncrystallisable. The *N*-benzoates could not be prepared by normal methods, such as long boiling of the amines with benzoyl chloride and pyridine in xylene. The *N*-acetate (IV; R = H, R′ = Ac) could be prepared indirectly from (IV; R = R′ = H) by hydrolysis of the *ON*-diacetate (IV; R = R′ = Ac) with one equivalent of methanolic alkali.

In an attempt at iodination, 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine (IV; R = R′ = H) and iodine monochloride in acetic acid gave the monochloro-derivative (VII) but no iodo-compound. Small proportions of chloro-compounds may be expected from the action of iodine monochloride on phenols, but such an extreme example appeared unique. However, the *N*-acetyl derivative (IV; R = H, R′ = Ac) with iodine in aqueous ethylamine gave a product analyses of which agreed fairly well for the di-iodo-compound.

The *p*-hydroxydiphenylamine (IV; R = R′ = H) was dehydrogenated by oxidising agents to *p*-benzoquinone 4-methyl-2 : 6-dinitroanil (as VI), which could be hydrolysed to *p*-benzoquinone and 3 : 5-dinitro-*p*-toluidine. Hydrosulphite (dithionite) or hydriodic acid reduced the quinone anil back to the hydroxydiphenylamine, although the latter

was oxidised by iodine in the presence of base (which removes hydrogen iodide from the equilibrium mixture).

Addition of hydrogen chloride to the quinone anil (VI) led to the chloro-compound produced by the action of iodine monochloride on the hydroxydiphenylamine (IV : R = R′ = H). The mechanism of the latter reaction thus becomes clear : there is first oxidation by iodine monochloride to (VI), most of which then adds hydrogen chloride to form (VII) while part is reduced back to (IV; R = R′ = H) by the resulting hydrogen iodide, with formation of iodine. These were indeed the products isolated. Successive dehydrogenation and addition of hydrogen chloride were applied to the synthesis of the 3 : 5-dichloro-4-hydroxy-compound (VIII), which could be further dehydrogenated to (IX). That the addition of hydrogen chloride to the quinones had occurred in the direction stated was confirmed by the production of the same diphenylamine (VIII) by condensation of 4-chloro-3 : 5-dinitrotoluene with 4-amino-2 : 6-dichlorophenol in the presence of sodium acetate.

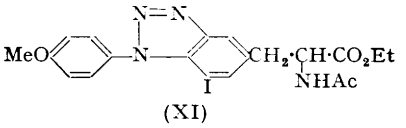


Orton (*J.*, 1908, 314; 1927, 2854) found that 2 : 6-dichlorobenzoquinone and 2 : 3 : 6-trichlorobenzoquinone 2′ : 4′ : 6′-trichloro-anils with hydrogen chloride formed respectively 2 : 3 : 6 : 2′ : 4′ : 6′-hexachloro- and 2 : 3 : 5 : 6 : 2′ : 4′ : 6′-heptachloro-4-hydroxydiphenylamine, and interpreted this reaction as partial reduction of the quinone anil by hydrogen chloride to the hydroxydiphenylamine, which was then chlorinated by the free chlorine produced, so that the reaction would eventually go to completion. However, in view of the probable reduction potentials of the quinone anils, the amount of free chlorine at equilibrium would be infinitesimal; direct 1 : 4-addition of hydrogen chloride to the quinone is much more likely. This explains why only one product is formed, and why the ethers of the hydroxydiphenylamines produced by reduction of the quinone anils are not chlorinated.

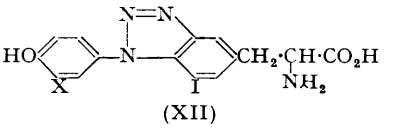
With *n*-butylamine, (VI) gave equimolecular quantities of (IV; R = R′ = H) and the butylaminoquinone anil (X). Addition of butylamine must initially give the butylamino-hydroxydiphenylamine. But the butylamino-group (unlike the chloro-group) is electron-releasing, and its substitution into a quinone lowers the reduction potential (Fieser and Fieser, *J. Amer. Chem. Soc.*, 1935, **57**, 491), so that the butylaminohydroxydiphenylamine is immediately oxidised to the butylaminoquinone anil (X) by unchanged quinone anil (VI), itself reduced to the hydroxydiphenylamine (IV; R = R′ = H). Provided that addition of butylamine is slow compared with establishment of the oxidation–reduction equilibrium, the products should be (X) and (IV; R = R′ = H), in agreement with experiment. Although (IV; R = R′ = H) did not react appreciably with iodine in organic solvents, in the presence of *n*-butylamine a vigorous reaction took place with production of the butylaminoquinone anil (X). Oxidation of the hydroxydiphenylamine by iodine proceeds in the presence of the amine, which adds on as before, but with the oxidising agent reaction can go to completion to give (X) and butylamine hydriodide. The structure (X), rather than that of the 2′-butylamino-isomer, is assigned to the product on theoretical grounds and by analogy with the products from addition of hydrogen chloride. The compound was dark purple and formed neither salts nor an acetyl derivative, owing to the conjugation of the butylamino- with the nitro-groups.

The dinitrodiphenylamine (V; R = Me, R′ = H) is less easily reduced than the comparable dinitrodiphenyl ethers, presumably owing to greater conjugation of the *o*-nitro-

groups with nitrogen than with oxygen. In the presence of palladium–charcoal at 110°/70 atm., but not at room temperature, reduction yielded the gummy diamine. The Sandmeyer reaction (Parts I and V), then gave the expected benzotriazole (XI) (cf. Saunders, "The Aromatic Diazo-Compounds," 2nd Edn., Arnold, 1944, pp. 247, 263), hydrolysed by hydriodic–acetic acid to the amino-acid (XII; X = H). Although several methods were tried, only one more atom of iodine could be introduced into this phenol, leading to (XII; X = I).



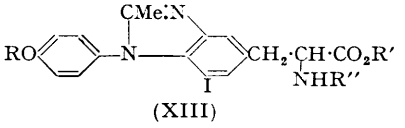
(XI)



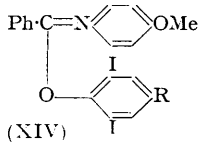
(XII)

In order to protect the imino-group (V; R = Me, R′ = H) was acetylated and then reduced to the diamine. Both compounds were gums. Under the influence of the strong acid used in the attempted tetrazotisation one of the amino-groups reacted with the acetyl group before diazotisation, so that the only solid product isolated after reaction with tri-iodide solution was the 2-methylbenziminazole (XIII; R = Me, R′ = Et, R″ = Ac). This could be hydrolysed to the hydroxy-amino-acid (XIII; R = R′ = R″ = H). Attachment of $R{\cdot}SO_2^-$ to the nitrogen atom of the diphenylamine should prevent such cylisation, but attempts to introduce this group failed.

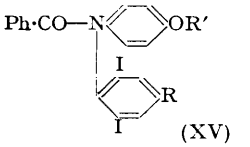
After the failure to convert 2 : 6-dinitrodiphenylamines into 2 : 6-di-iododiphenylamines, I investigated the isomerisation of aryl *N*-arylbenzimidates (XIV) to *N*-benzoyl-2 : 6-di-iododiphenylamines (XV) (cf. Chapman, *J.*, 1925, 1992; 1927, 1743; 1929, 569; Jamison and Turner, *J.*, 1937, 1954; Hall, *J.*, 1948, 1603). No iodo-compound has been subjected to this reaction, but electron-attracting groups in the migrating nucleus, and electron-releasing groups in the other nucleus, are known to facilitate it. Rearrangement of an ester such as (XIV) might well take place at a lower temperature than pyrolytic loss of iodine.



(XIII)



(XIV)



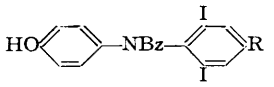
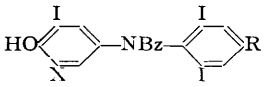
(XV)

The esters (XIV) were prepared in the conventional way, by condensing the imidoyl chloride with the sodium salt of the di-iodophenol in an anhydrous solvent or, more conveniently, with the free di-iodophenol in pyridine. The ester (XIV; R = Me) was selected as a model for a trial of the rearrangement, because of its electronic similarity with [XIV; R = $CH_2{\cdot}CH(NHAc){\cdot}CO_2Et$]. In the first attempts, at 190° to 250° without a solvent, the products were gums. Three hours' boiling in nitrobenzene (b. p. 209°) gave the rearranged compound (XV; R = R′ = Me) in 50% yield. After various trials (see Experimental section) it was found that ten minutes' boiling in diphenyl ether (b. p. 259°) or diphenyl (254°) and extraction with light petroleum afforded the amide in about 55% yield without chromatography. Hydriodic acid in acetic acid demethylated (XV; R = R′ = Me), leaving the hindered amide group intact—a fortunate selectivity in view of the ability of iodine in alkaline solution, involved in the next stage, to dehydrogenate *p*-hydroxydiphenylamines to quinone anils. Treatment of (XVI; R = Me) with iodine in ethylamine then led to the tetraiodo-compound (XVII; R = Me, X = I) in high yield.

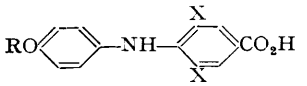
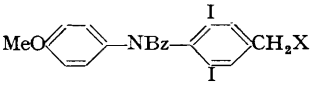
However, the *N*-*p*-methoxyphenylbenzimidic esters from *N*-acetyl-3 : 5-di-iodo-DL- or -L-tyrosine ethyl ester were gums, as also were the products obtained by their isomerisation. 3 : 5-Di-iodo-DL-tyrosine hydantoin and the imidoyl chloride gave a gel, from which only unchanged hydantoin and benz-*p*-anisidide could be isolated.

After the failure of this direct synthesis the work was concentrated on preparing amides (XV) in which R could later be elaborated into the alanine side chain. In agreement with the effect of electron-attracting groups in this position, the ester (XIV; R = CO_2Me)

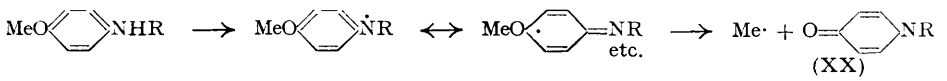
changed into (XV; R = CO_2Me, R′ = Me) almost quantitatively on 1·5 hours' boiling in *o*-dichlorobenzene (b. p. 179°). Hydriodic acid in acetic acid then gave the hydroxy-acid (XVI; R = CO_2H), but the action of 2 mols. of iodine in potassium carbonate solution led only to the tri-iodo-compound (XVII; R = CO_2H, X = H).

(XVI)   (XVII)

The *N*-benzoyl-4′-methoxydiphenylamine ester (XV; R = CO_2Me, R′ = Me) was hydrolysed by dilute alkali to the acid (XV; R = CO_2H, R′ = Me), from which the benzoyl group was removed by 40% potassium hydroxide, yielding (XVIII; R = Me, X = I). The corresponding 4′-hydroxy-compound (XV; R = CO_2H, R′ = H), however, was recovered unchanged from boiling 40% potassium hydroxide, perhaps owing to the negative charge conferred on the second benzene ring by the phenoxide ion. On the other hand, although the 4′-methoxy-amide (XV; R = CO_2Me, R′ = Me) was smoothly demethylated to the 4′-hydroxy-amide (XV; R = CO_2H, R′ = H) by hydriodic acid, the 4′-methoxy-amine (XVIII; R = Me, X = I), in which the electron pair of the nitrogen atom is no longer prevented by the benzoyl group from spreading to the 2 and the 6 position of the benzene ring, underwent reduction as well as demethylation to give 4′-hydroxydiphenylamine-4-carboxylic acid (XVIII; R = X = H).

(XVIII)   (XIX)

This investigation was ended before alternative methods of demethylating 2 : 6-di-iodo-4′-methoxydiphenylamines had been explored, but one method that might be applicable to the iodo-compounds was used to demethylate the 4′-methoxy-2 : 6-dinitrodiphenylamine (V; R = Me, R′ = H), at the same time leaving the acetyl and the ester group in the side chain intact. It utilised the susceptibility of the *p*-aminophenyl ether system to oxidation. *N*-Bromosuccinimide in dioxan oxidised (V; R = Me, R′ = H) to the quinone anil (XX), which on reduction and acetylation yielded (V; R = Ac, R′ = H), identical with the sample described previously. This reaction, which proceeded in good yield at room temperature, may involve diphenylimine radicals :



Heating the ester (XV; R = CO_2Me, R′ = Me) with lithium aluminium hydride in ether or dioxan was without effect or caused loss of iodine. The bromide (XIX; X = Br) resulted from the action of *N*-bromosuccinimide in the presence of benzoyl peroxide on (XV; R = R′ = Me), but the yield was low and erratic. Only gums could be isolated after the aldehyde (XIV; R = CHO), which should rearrange relatively easily, had been heated.

Experimental

N-Acetyl-4-amino-3 : 5-dinitro-DL-phenylalanine Ethyl Ester.—*N*-Acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (3 g.) and toluene-*p*-sulphonyl chloride (1·8 g., 1·1 mols.) in pyridine (15 c.c.) were heated at 110° for ½ hour. *p*-Anisidine (4·3 g., 4 mols.) in pyridine (4·3 g.) was added to the cooled solution, which immediately became deep purplish-red, changing to reddish-brown on heating. After 1 hour at 110° the mixture was cooled and poured into chloroform, which was washed with water and then 2N-hydrochloric acid, dried (Na_2SO_4–Na_2CO_3), and distilled. The dark reddish-brown residue of the p-*amino*-compound crystallised when scratched. Recrystallised from alcohol, it (1·9 g., 63%) had m. p. 152—153°. Another crystallisation from benzene in the presence of charcoal yielded the pure compound as golden-yellow blades, m. p. 153—154° (Found : C, 46·1; H, 5·0. $C_{13}H_{16}O_7N_4$ requires C, 45·9; H, 4·7%).

This amine (0·3 g.), pyridine (0·65 c.c., 1·2 mols.), benzoyl chloride (0·85 c.c., 1·1 mols.), and toluene (1·5 c.c.) were boiled for ¾ hours. The cooled mixture was filtered from pyridine

hydrochloride, which was washed with more toluene. The toluene solution was washed with water, dried, and concentrated. The yellow crystals of the p-*benzamido*-compound which separated on cooling were filtered off and washed (yield, 0·19 g.). Recrystallisation from toluene gave yellow needles, m. p. 175—176° (Found : C, 53·8; H, 4·4. $C_{20}H_{20}O_8N_4$ requires C, 54·1; H, 4·5%).

Reaction between 1-(4-*Methyl*-2 : 6-*dinitrophenyl*)*pyridinium Toluene*-p-*sulphonate and* p-*Anisidine*.—3 : 5-Dinitro-*p*-cresol (10 g.), toluene-*p*-sulphonyl chloride (10 g., 1 mol.), and pyridine (30 c.c.) were hreated at 110° for ½ hour and then cooled. Addition of *p*-anisidine (18 g., 3 mols.) in pyridine (9 c.c.) caused immediate development of a deep purple-red colour and evolution of heat. After 1 hour the mixture, containing a mass of dark purplish-blue crystals, was poured into water. The solid was filtered off, and thoroughly extracted with acetone, leaving 5-p-*anisidinopentadienal* p-*methoxyanil toluene*-p-*sulphonate* (20·8 g., 86%). It separated from methanol in metallic, purple-blue crystals, m. p. 149° (Found : C, 64·7; H, 6·0; N, 5·7. $C_{26}H_{28}O_5N_2S$ requires C, 65·1; H, 5·8; N, 5·8%). Concentration of the acetone solution gave orange-yellow needles of 3 : 5-dinitro-*p*-toluidine (8·0 g., 80%), m. p. 171° after recrystallisation from alcohol.

When the salt of the dianil (3·0 g.) was boiled in chlorobenzene (14 c.c.) for about 1·5 minutes the colour began to fade rapidly and an oil to separate. After 10 minutes the mixture was cooled, and the oil, which had crystallised, was filtered off (2·0 g., 90%). 1-p-*Methoxyphenyl*-*pyridinium toluene*-p-*sulphonate* separated from ethyl alcohol–acetate in colourless plates, m. p. 180° (Found : C, 64·0; H, 5·5. $C_{19}H_{19}O_4NS$ requires C, 63·9; H, 5·3%). This reaction proceeded also in boiling *n*-butanol, pyridine, or nitrobenzene. Addition of aqueous sodium picrate to a solution of the salt in water precipitated the pyridinium picrate as pale yellow needles, m. p. 162—164°, unchanged by admixture of the picrate with an authentic sample.

4′-*Methoxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—3 : 5-Dinitro-*p*-cresol (10 g.) was heated with toluene-*p*-sulphonyl chloride (10 g., 1 mol.) in dimethylaniline (30 c.c.) at 110° for ½ hour. *p*-Anisidine (18 g., 3 mols.) in dimethylaniline (9 c.c.) was added to the cooled mixture, which immediately became dark red with the separation of much solid and evolution of heat. After 1 hour the pasty mass was dissolved in chloroform, which was washed with 2N-hydrochloric acid, and water, dried, and distilled. The residue set to a sticky mass on scratching, but recrystallisation from various solvents did not yield a clean product. Chromatography in benzene on alumina led to the pure *diphenylamine*, deep red plates [from light petroleum (b. p. 100—120°)], m. p. 132—134° (6 g., 39%) (Found : C, 55·45; H, 4·3; N, 13·8. $C_{14}H_{13}O_5N_3$ requires C, 55·45; H, 4·3; N, 13·9%). The broad, brick-red, very strongly adsorbed band at the top of the chromatogram was extruded and boiled with water, yielding red needles of the sodium salt of 3 : 5-dinitro-*p*-cresol, evidently formed from the phenol by reaction with sodium ions on the highly alkaline grade of alumina used.

When the diphenylamine (1 g.) was boiled for 1 hour in acetic anhydride (5 c.c.) containing sulphuric or perchloric acid (1 drop), and the resulting mixture was poured into water the N-*acetyl* derivative was precipitated (1·05 g., 92%). After recrystallisation from alcohol–benzene and then alcohol the yellow needles melted at 189° (Found : N, 12·2. $C_{16}H_{15}O_6N_3$ requires N, 12·3%).

N-*Acetyl*-4-p-*anisidino*-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester*.—*N*-Acetyl-3 : 5-dinitro-DL-phenylalanine ethyl ester (30 g.), toluene-*p*-sulphonyl chloride (18 g., 1·1 mols.), and dimethylaniline (25 c.c., 2·2 mols.) in chloroform (100 c.c.) were boiled for 1 hour. *p*-Anisidine (16 g., 1·5 mols.) in chloroform (25 c.c.) was added. A dark red colour very rapidly developed and colourless, water-soluble crystals separated (probably a salt of dimethylaniline). After an hour's boiling the chloroform solution was washed with N-hydrochloric acid, dried (Na_2SO_4), and distilled. The viscous oil which remained was dissolved in alcohol and very carefully diluted with water. The red needles of the *diphenylamine* (23·0 g., 59%) melted at 142—145°. Later crops were contaminated with toluene-*p*-sulphon-*p*′-anisidide, m. p. 114° after purification. Further recrystallisation of the diphenylamine raised the m. p. to 146° (Found : C, 53·9; H, 4·8; N, 12·8. $C_{20}H_{22}O_8N_4$ requires C, 53·8; H, 4·9; N, 12·6%).

When dimethylaniline was used as solvent and the second stage of the reaction was allowed to proceed at room temperature (with spontaneous heating), the yield of diphenylamine after chromatography was only 25%.

Acetylation of the diphenylamine in hot acetic anhydride containing sulphuric or perchloric acid produced a yellow oil, uncrystallisable even after chromatography.

4′-*Hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—3 : 5-Dinitro-*p*-cresol (10 g., 0·96 mol.), toluene-*p*-sulphonyl chloride (10 g., 1 mol.), dimethylaniline (13·3 c.c., 2 mols.), and dioxan

(35 c.c.) were boiled for ½ hour. This solution was dropped, during 10 minutes, into a vigorously boiling solution of *p*-aminophenol (11 g., 1·9 mols.) in dioxan (60 c.c.). A colourless solid separated from the red solution. After another 20 minutes' boiling the mixture was poured into dilute hydrochloric acid. The precipitate was washed with water and recrystallised from alcohol, yielding dark red needles (9·9 g., 68%), m. p. 160—168°. Repeated recrystallisation gave a sample of *amine* melting at 174—175° (Found: C, 52·0; H, 3·9; N, 13·3. $C_{13}H_{11}O_5N_3,\frac{1}{2}H_2O$ requires C, 52·3; H, 4·1; N, 14·1%).

Acetic anhydride (0·072 c.c., 1·1 mols.) was added to the amine (0·2 g.) in pyridine. The dark red colour faded to orange. After 1 hour the solution was diluted with water and the orange needles of the O-*acetate* were filtered off (0·23 g., 100%). They separated from alcohol or benzene–*cyclo*hexane as compact, bright red crystals, m. p. 157° (Found: C, 54·6; H, 4·0. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9%).

Acetic anhydride (2 c.c. per 0·3 g. of amine) containing a trace of sulphuric acid on the steam-bath for a few minutes led to the *diacetate* (0·32 g., 83%), pale yellow needles (from acetone–alcohol), m. p. 186° (Found: C, 54·65; H, 4·0; N, 11·15. $C_{17}H_{15}O_7N_3$ requires C, 54·7; H, 4·0; N, 11·3%). Half the above amount of acetic anhydride led to, mainly, the *O*-acetate, which with more acetic anhydride–sulphuric acid gave the diacetate.

The diacetate (0·15 g.) was suspended in warm methanol (1 c.c.) and acetone was added until it dissolved (*ca.* 2 c.c.). Methanolic potassium hydroxide (1·07 c.c.; 21 g./l.; 1 mol.) was added, causing an immediate darkening in colour of the solution. After 2 hours at 45°, the solution was poured into water. Addition of acetic acid (2 drops) to the clear brownish-orange solution precipitated crystals of the *amide* (0·12 g., 90%), m. p. 192—193°. Recrystallisation from alcohol–*cyclo*hexane gave yellow needles, m. p. 245° (Found: C, 54·3; H, 4·0. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9%). Repetition of this preparation yielded the high-melting form at once.

N-*Acetyl*-4′-*hydroxy*-3′ : 5′-*di*-*iodo*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—To the above *N*-acetyldiphenylamine (250 mg.) in 33% aqueous ethylamine (4 c.c.), iodine in aqueous potassium iodide solution (1·6 c.c.; 244 g./l.; 2 mols.) was slowly added with shaking. After 2 hours the pale yellowish-brown crystals that had separated were filtered off, washed with water, and dried (230 mg.). They could not be recrystallised and were, therefore, dissolved in aqueous alcohol and decomposed by dilute hydrochloric acid. On scratching, the yellow emulsion formed deposited the solid *iodo*-compound (120 mg.). After two recrystallisations from alcohol the yellow crystals melted at 140—144° to a brown liquid (Found: C, 31·6; H, 2·15; N, 6·5; I, 41·6. $C_{15}H_{11}O_6N_3I_2$ requires C, 30·9; H, 1·9; N, 7·2; I, 43·5%).

4-(p-*Acetoxyanilino*)-N-*acetyl*-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester*.—*N*-Acetyl-3 : 5-dinitro-DL-phenylalanine ethyl ester (13·9 g.), toluene-*p*-sulphonyl chloride (8·0 g., 1·05 mols.), and dimethylaniline (10·3 c.c., 2 mols.) were boiled in dioxan (60 c.c.) for ½ hour. This solution was dropped during 20 minutes into *p*-aminophenol (14 g.) in boiling dioxan (80 c.c.). After a further ½ hour's boiling the mixture was poured into dilute acid, which was extracted with chloroform. Evaporation of the chloroform left a dark red syrup (23 g.). A previous experiment had shown that this did not crystallise after chromatography on alumina and reprecipitation from various solvents, but that the *O*-acetate was crystalline. The product was, therefore, dissolved in pyridine (100 c.c.), to which acetic anhydride (7·5 c.c.) was added. After ½ hour the solution was diluted with chloroform, washed with dilute hydrochloric acid, and evaporated. The oily residue was dissolved in alcohol. Addition of water until cloudiness appeared caused the separation of only oil. Excess of water was therefore added and the whole extracted with chloroform. The dried extract was passed down a 2-ft. column of activated alumina. The red oil resulting from the evaporation of the first eluate was dissolved in hot alcohol. Orange-yellow needles of the *acetoxy-amine* (4·6 g.) separated on cooling. A second crop (4·8 g.) was obtained by dilution of the mother-liquors with water. After two recrystallisations from alcohol the needles melted at 184° (Found: C, 52·6; H, 4·2; N, 11·85. $C_{21}H_{22}O_9N_4$ requires C, 53·2; H, 4·6; N, 11·8%).

The fraction immediately following the diphenylamine (still with chloroform as eluant) separated from alcohol, after treatment with charcoal, as plates (0·5 g.), m. p. 141°, undepressed by *p*-toluene-*p*′-sulphonamidophenyl acetate prepared by treatment of *p*-aminophenol in pyridine with toluene-*p*-sulphonyl chloride followed by acetic anhydride and recrystallisation from toluene.

The eluate obtained by using chloroform–methanol (2 : 1) left a dark red syrup of unacetylated hydroxydiphenylamine on evaporation. This was dissolved in pyridine and treated with more acetic anhydride (10 c.c.). Dilution with water after ½ hour produced needles of the acetoxy-compound (2·0 g.) (total yield, 59%).

Treatment of the acetoxydiphenylamine with a large excess of acetic anhydride containing perchloric acid gave a yellow gum, which did not crystallise.

p-*Benzoquinone* 4-*Methyl*-2 : 6-*dinitroanil*.—Addition of a solution of *N*-bromosuccinimide (0·31 g., 2 mols.) in dioxan (10 c.c.) to the dark red solution of 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine (0·25 g.) in dioxan (10 c.c.) caused the colour to fade to orange-yellow in a few minutes. After ½ hour the mixture was poured into water and the pale yellow precipitate, m. p. 185—187°, was filtered off. Recrystallisation from alcohol gave golden-yellow needles of the *quinone anil* (0·23 g., 90%), m. p. 193° (Found : C, 54·4; H, 3·2; N, 14·6. $C_{13}H_9O_5N_3$ requires C, 54·4; H, 3·1; N, 14·6%). The reaction could also be carried out in boiling carbon tetrachloride, but this was less convenient because of the low solubility of the diphenylamine.

Other agents used successfully for the oxidation were chromic acid in acetic acid, alcoholic ferric chloride, iodine in dioxan containing tri-*n*-propylamine, and mercuric oxide.

For preparative purposes the most convenient oxidant was mercuric oxide; a benzene solution of the diphenylamine was boiled with a slight excess of mercuric oxide for 10 minutes after the colour indicated that dehydrogenation was complete. After filtration from mercury and unchanged oxide and concentration of the solution, *cyclo*hexane was added to the boiling solution until crystals appeared. On cooling, needles of the pure anil separated in almost quantitative yield.

Reduction. Sodium dithionite solution (1 c.c.; 66 g./l.; 1 mol.) was added dropwise to a well-shaken solution of the anil (110 mg.) in dioxan (3 c.c.). Dilution with water precipitated red needles of 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine (100 mg., 90%), m. p. and mixed m. p. 169—172°. Hydriodic acid or *p*-aminophenol also effected the reduction.

Hydrolysis. When the anil was boiled with sulphuric acid the pungent smell of benzoquinone could be detected. The anil (100 mg.) was boiled for 1 hour in a mixture of 2N-sulphuric acid (3 c.c.) and dioxan (2 c.c.). The orange blades of 3 : 5-dinitro-*p*-toluidine which separated on cooling (65 mg., 95%) had m. p. and mixed m. p. 170—171°.

3′-*Chloro*-4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—(a) *From* 4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*. The diphenylamine (1 g.) in acetic acid (10 c.c.) was treated with 15% iodine monochloride in acetic acid (7·5 c.c., 2 mols.). Having been heated on the steam-bath for 1 hour the mixture was poured into sodium hydrogen sulphite solution and extracted with ethyl acetate, which was then washed with sodium hydrogen carbonate solution. The residue after evaporation of the solvent recrystallised from alcohol. The red plates (0·7 g.) began to sinter at 156° and melted at 182—188°. Three recrystallisations from alcohol raised the m. p. of the *chlorodiphenylamine* to 193—195° (Found : C, 48·3; H, 3·0; N, 13·2. $C_{13}H_{10}O_5N_3Cl$ requires C, 48·25; H, 3·1; N, 13·0%). A small amount of unchanged 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine was isolated by fractional crystallisation of the material remaining in the first two mother-liquors.

Acetylation (acetic anhydride–pyridine) gave an almost quantitative yield of the *acetate*, bright orange needles, m. p. 182—184° (from alcohol) (Found : N, 11·7. $C_{15}H_{12}O_6N_3Cl$ requires N, 11·5%).

(b) *From* p-*benzoquinone* 4-*methyl*-2 : 6-*dinitroanil*. A solution of the anil (1·5 g.) in dioxan (25 c.c.) was saturated with dry hydrogen chloride. After ½ hour the solution was poured into water, precipitating a red oil, which crystallised when scratched (1·7 g., 100%). After one recrystallisation from alcohol the m. p. was 193—195°, unchanged by the specimen described above. The product obtained by adding concentrated hydrochloric acid to a solution of the anil in acetic acid was less pure.

3-*Chloro*-p-*benzoquinone* 4′-*Methyl*-2′ : 6′-*dinitroanil*.—A solution of the chlorodiphenylamine (1·5 g.) in benzene (25 c.c.) was boiled with mercuric oxide (1·5 g., 1·5 mols.) for ½ hour, filtered, and evaporated. The residue was recrystallised from acetone–alcohol (charcoal). The orange-yellow needles of the *chloroquinone-anil* melted at 198° (1·4 g., 94%) (Found : N, 12·8; Cl, 10·8. $C_{13}H_8O_5N_3Cl$ requires N, 13·1; Cl, 11·0%).

3′ : 5′-*Dichloro*-4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—Dioxan saturated with hydrogen chloride (5 c.c.) was added to a solution of the monochloroquinone anil (0·7 g.) in dioxan (10 c.c.). The oil obtained by diluting the solution with water crystallised later (yield 0·75 g., 96%). The *dichlorodiphenylamine* crystallised from benzene in red needles, m. p. 240—241° (Found : C, 43·5; H, 2·5; Cl, 19·6. $C_{13}H_9O_5N_3Cl_2$ requires C, 43·6; H, 2·5; Cl, 19·8%).

3 : 5-*Dichloro*-p-*benzoquinone* 4′-*Methyl*-2′ : 6′-*dinitroanil*.—The dichlorodiphenylamine (0·25 g.) was boiled with mercuric oxide (0·25 g., 1·7 mols.) in benzene (15 c.c.) for 1 hour. On cooling, orange crystals of the *quinone-anil* (0·16 g., 64%) separated. A second crop, obtained

by concentration of the mother-liquor, was contaminated by some unchanged diphenylamine. The first crop crystallised from benzene–*cyclo*hexane in orange-yellow fibres, m. p. 208° (Found : C, 43·5; H, 2·25; Cl, 20·3. $C_{13}H_7O_5N_3Cl_2$ requires C, 43·8; H, 2·0; Cl, 19·95%).

Direct Chlorination of 4′-Hydroxy-4-methyl-2 : 6-dinitrodiphenylamine.—Chlorine was passed into a solution of the diphenylamine (0·5 g.) in acetic acid (15 c.c.) for 8 minutes. After about ½ minute the colour had faded to yellow. 20 Minutes later the solution was poured into water. The precipitate was filtered off, washed, and recrystallised from alcohol (*ca.* 100 c.c.). Rather brownish orange-yellow needles (0·36 g.) formed, more being obtainable by dilution of the mother-liquor with water (0·16 g.). Two more crystallisations from alcohol gave the *trichloro*-compound, m. p. 208—212° (Found : C, 40·0; H, 1·5; Cl, 25·75. $C_{13}H_6O_5N_3Cl_3$ requires C, 40·0; H, 1·5; Cl, 27·2%).

The only compound isolated after 1 hour's boiling with dioxan–2N-sulphuric acid (1 : 1) was unchanged chloro-compound.

*3-Butylamino-*p*-benzoquinone 4′-Methyl-2′ : 6′-dinitroanil.*—(a) *From 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine.* Iodine (1·55 g., 4 g.-atoms) in pyridine (10 c.c.) was added with shaking to a solution of the diphenylamine (0·88 g.) in pyridine (5 c.c.) and *n*-butylamine (3 c.c.). The mixture became hot, and very dark, greenish-brown. After a few minutes the mixture was gradually diluted with water (*ca.* 200 c.c.), and the purplish-black precipitate produced was filtered off (1·05 g.). Recrystallisation twice from alcohol and once from *cyclo*hexane containing a little benzene gave purple needles of the *butylaminoquinone anil*, m. p. 184° (Found : C, 57·0; H, 5·8; N, 15·6. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·0; N, 15·6%).

A small-scale experiment indicated that dioxan as solvent instead of pyridine gave a purer product.

A similar reaction took place when piperidine or morpholine was substituted for butylamine, but the products failed to crystallise.

(b) *From* p-*benzoquinone 4-methyl-2 : 6-dinitroanil. n*-Butylamine (1·5 c.c.) in dioxan (5 c.c.) was added to a solution of the anil (1·0 g.) in dioxan (20 c.c.). The mixture rapidly became deep red. After ½ hour it was cautiously diluted with water, and thus separated into two fractions. The first crop (0·48 g.) began to sinter at 173° and melted at 183—185°. After recrystallisation from *cyclo*hexane containing a little benzene, the purple needles (0·35 g.) melted at 186—187°, unchanged when mixed with the previous sample of butylaminoquinone anil. The second crop (0·62 g.) crystallised from alcohol as red needles (0·3 g.), m. p., alone and mixed with 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine, 169—171°.

*N-Acetyl-4-(4-ketocyclohexa-2 : 5-dienylideneamino)-3 : 5-dinitrophenyl-*DL*-alanine Ethyl Ester.*—A freshly made solution of *N*-bromosuccinimide (0·8 g., 2 mols.) in dioxan (15 c.c.) was added to one of *N*-acetyl-4-*p*-anisidino-3 : 5-dinitrophenyl-DL-alanine ethyl ester (1·0 g.) in dioxan (20 c.c.). After having been kept for 1·5 hours at *ca.* 45° the mixture was diluted with water. The resulting yellow emulsion gradually deposited the *quinone imine* (0·7 g.), m. p. 184° after two recrystallisations from alcohol (Found : C, 52·9; H, 4·3; N, 13·1. $C_{19}H_{18}O_8N_4$ requires C, 53·0; H, 4·2; N, 13·0%).

1-p-Methoxyphenyl-6′-iodobenzotriazole-4′-(*N-acetyl-*DL*-alanine Ethyl Ester*) (XI).—*N*-Acetyl-4-*p*-anisidino-3 : 5-dinitro-DL-phenylalanine ethyl ester (5·0 g.) in dioxan (100 c.c.) was hydrogenated in the presence of palladium–charcoal (6%, 1·0 g.) at 110°/75 atm. for 2 hours. The catalyst and solvent were removed in an atmosphere of carbon dioxide, leaving the diamine as an almost colourless gum. This was slowly added in acetic acid (15 c.c.) to sulphuric acid (8 c.c.) at <15°. The resulting solution was added during ¾ hour to a stirred solution of sodium nitrite (1·6 g., 2·1 mols.) in sulphuric acid (30 c.c.) and acetic acid (50 c.c.) kept below −2°. After the very dark solution had stood at 0° for 1 hour it was allowed to run into a solution of sodium iodide (18 g.), iodine (15 g.), and urea (2 g.) in water (300 c.c.) and chloroform (100 c.c.) at 35—40°. After ½ hour the lowest, black, tarry layer was separated, dissolved in alcohol, treated with sodium hydrogen sulphite, and poured into water. The black tar was extracted with ethyl acetate, which was then washed with water, dried ($MgSO_4$), and evaporated. The residual syrup was later induced to crystallise (4·9 g.). The chloroform extract from the reaction mixture after removal of iodine and evaporation yielded a gum from which more solid material (0·5 g.) separated on scratching under warm alcohol (total crude yield, 95%). Two recrystallisations from alcohol and one from toluene gave colourless crystals of the *benzotriazole*, m. p. 152—154° (2·9 g., 51%) (Found : C, 47·1; H, 4·1; N, 10·7. $C_{20}H_{21}O_4N_4I$ requires C, 47·2; H, 4·1; N, 11·0%).

1′-p-Hydroxyphenyl-7′-iodobenzotriazole-5′-alanine.—The preceding compound (1·6 g.) was boiled in acetic acid (8 c.c.) and hydriodic acid (5 c.c.) for 1 hour. The cooled solution was

diluted with water and neutralised with dilute ammonia solution. The precipitated *amino-acid* crystallised from hot water in colourless blades (1·1 g., 82%) (Found : C, 40·5; H, 3·75; N, 12·6 $C_{15}H_{13}O_3N_4I,H_2O$ requires C, 40·7; H, 3·4; N, 12·7%).

1′-(4-*Hydroxy*-3-*iodophenyl*)-7′-*iodobenzotriazole*-5′-*alanine* (XII; X = I).—The preceding amino-acid (55 mg.) in 33% ethylamine (1 c.c.) was treated with iodine (4·2 g.-atoms) in aqueous potassium iodide (0·27 c.c., 244 g./l.). After 1 hour the solution was diluted to 5 c.c. and made neutral with dilute acetic acid. The flocculent, pale brown precipitate was washed, and dissolved in a large volume of boiling water. The colloidal solution formed on cooling had deposited the *di-iodo*-compound, m. p. 210—214° (decomp.), as a fine, colourless powder by next morning (Found : I, 46·4. $C_{15}H_{12}O_3N_4I_2$ requires I, 46·2%).

Iodine monochloride (2 mols.) in acetic acid also produced the di-iodo-compound.

7′-*Iodo*-1-p-*methoxyphenyl*-2-*methylbenziminazole*-5′-(N-*acetyl*-DL-*alanine Ethyl Ester*) (XIII; R = Me, R′ = Et, R″ = Ac).—The product from the acetylation of *N*-acetyl-4-*p*-anisidino-3 : 5-dinitro-DL-phenylalanine ethyl ester (12 g.) with hot acetic anhydride and perchloric acid was purified by chromatography in chloroform on alumina. The resulting yellow gum was hydrogenated in alcohol containing palladium–charcoal at 70°/60 atm. After removal of the catalyst and solvent under carbon dioxide the diamine remained as an almost colourless glass (11·3 g.).

A solution of the diamine (11·3 g.) in acetic acid (30 c.c.) was added to sulphuric acid (15 c.c.) at 0°. The mixture was then dropped into a solution of sodium nitrite (42 g., 2·3 mols.) in sulphuric (30 c.c.) and acetic (50 c.c.) acids at <0°, during 1 hour. After another ½ hour at 0° the mixture was run into a solution of sodium iodide (25 g.), iodine (18 g.), and urea (3 g.) in water (380 c.c.) at 35°. An hour later the dark tarry lower layer, containing some free iodine, was separated and dissolved in 85% alcohol. Free iodine was eliminated by addition of sodium hydrogen sulphite. Dilution with a large volume of water produced a cloudy solution which was neutralised with sodium carbonate and extracted repeatedly with ethyl acetate. After being washed with water and dried (Na_2SO_4), the extract was evaporated to a syrup which was dissolved in alcohol. Cautious dilution with water then caused separation of the *benziminazole* (2·5 g., 19% from the dinitrophenylamine). Further dilution precipitated a little gum from which no solid could be separated. The product was recrystallised from aqueous alcohol (charcoal). Careful attention to the concentration and temperature was necessary to avoid its deposition as an oil. Two more crystallisations from benzene yielded colourless needles, m. p. 189—191° (1·6 g.) (Found : N, 7·9; I, 24·8. $C_{22}H_{24}O_4N_3I$ requires N, 8·1; I, 24·4%).

1′-*p*-*Hydroxyphenyl*-7′-*iodo*-2-*methylbenziminazole*-4′-DL-*alanine*.—The foregoing ester (250 mg.) in acetic acid–hydriodic acid (2 : 1, 3 c.c.) was boiled for 1·5 hours. Slow neutralisation of the diluted liquid with ammonia precipitated the *amino-acid* as an amorphous solid (140 mg., 67%). After long boiling in water it crystallised, but then could not be redissolved even in a large volume. It was, therefore, reprecipitated from hot dilute ammonia solution by dilute acetic acid. Great care was necessary to avoid its separation as an emulsion or gum; it had m. p. 234—236° (decomp.) (Found : I, 29·0. $C_{17}H_{16}O_3N_3I$ requires I, 29·1%).

Iodophenyl Imidates.—2 : 6-*Di-iodo*-4-*methylphenyl* N-p-*methoxyphenylbenzimidate*. Benzanisidide (25 g.) and phosphorus pentachloride (23 g., 1 mol.) were heated on the steam-bath till no more hydrogen chloride was evolved. After the phosphoryl chloride produced had been removed at the water pump, the imidoyl chloride crystallised on cooling. A solution of this in dioxan (75 c.c.) was added to one of di-iodocresol (61 g., 1·2 mols.) in alcohol (150 c.c.) containing sodium (2·8 g., 1·1 g.-atoms). Sodium chloride was immediately precipitated and the *ester* soon crystallised. It was washed with alcohol and water (yield, 47 g., 75%). Recrystallisation from alcohol–dioxan gave colourless crystals, m. p. 158—160° (Found : I, 44·7. $C_{21}H_{17}O_2NI_2$ requires I, 44·6%).

4-*Carbomethoxy*-2 : 6-*di-iodophenyl* N-p-*methoxyphenylbenzimidate*. Sodium (0·28 g., 1 g.-atom) in methanol (10 c.c.) was added to methyl 4-hydroxy-3 : 5-di-iodobenzoate (4·9 g., 1·1 mols.) in dioxan (20 c.c.), immediately followed by a solution of the imidoyl chloride from benzanisidide (2·5 g.) in dioxan (10 c.c.). After 1 hour the mixture was poured into water and the oil which crystallised on being scratched was recrystallised from carbon tetrachloride. The colourless rhombohedra of *ester* (4·0 g.) melted at 184°. Light petroleum (b. p. 100—120°) was added to the mother-liquors, and most of the carbon tetrachloride was distilled off. The solvent was decanted from the heavy crystals of ester (0·8 g., total yield, 71%), before the needles of unchanged ester separated (Found : C, 43·3; H, 2·9; I, 41·2. $C_{22}H_{17}O_4NI_2$ requires C, 43·1; H, 2·8; I, 41·4%).

4-*Formyl*-2 : 6-*di-iodophenyl* N-p-*methoxyphenylbenzimidate*. A solution of this *ester* in alcohol–dioxan made as above from benzanisidide (2·5 g., 1 mol.) and 4-hydroxy-3 : 5-di-iodo-

benzaldehyde (5·0 g., 1·2 mols.) was poured into water. The syrup was extracted with benzene, evaporation of which gave an oil that later solidified. After crystallisation from carbon tetrachloride–light petroleum and then *cyclo*hexane the blades melted at 134° (Found: C, 43·0; H, 2·9; I, 43·9. $C_{21}H_{15}O_3NI_2$ requires C, 43·25; H, 2·6; I, 43·5%).

Condensation in pyridine. To get a clean product by this method it seemed important to use imidoyl chloride free from phosphoryl chloride. Since the recrystallisation of such a low-melting solid was difficult and wasteful it was purified by removing as much phosphoryl chloride as possible at the pump, adding benzene, concentrating the mixture, adding light petroleum (b. p. 40—60°), and removing the solvent again from the filtered solution.

4-*Carbo*-n-*butoxy*-2 : 6-*di*-*iodophenyl* N-p-*methoxyphenylbenzimidate*. The imidoyl chloride (1·2 g., 1·1 mols.) and *n*-butyl 4-hydroxy-3 : 5-di-iodobenzoate (2·0 g., 1 mol.) were dissolved in pyridine (10 c.c.). 3 Hours later the solution was poured into water and the brown oil extracted with ethyl acetate, which was washed with dilute hydrochloric acid and then water. Evaporation left a gum that crystallised. The *ester* separated from methyl cyanide as large rhombohedra (2·7 g., 92%), m. p. 170—172° (Found: I, 38·9. $C_{25}H_{23}O_4NI_2$ requires I, 38·7%).

2 : 4 : 6-*Tri*-*iodophenyl* N-p-*methoxyphenylbenzimidate*. This *compound*, made by the same method, formed colourless plates (65%) (from acetone–alcohol), m. p. 135—136° (Found: I, 56·1. $C_{20}H_{14}O_2NI_3$ requires I, 55·9%).

The 4 : 6-*di*-*iodo*-2-*methylphenyl ester* crystallised from ethyl acetate–alcohol in colourless needles (90%), m. p. 145—146° (Found: I, 44·2. $C_{21}H_{17}O_2NI_2$ requires I, 44·6%).

Rearrangements.—N-*Benzoyl*-2 : 6-*di*-*iodo*-4′-*methoxy*-4-*methyldiphenylamine*—*In nitrobenzene.* 2 : 6-Di-iodo-4-methylphenyl *N*-*p*-methoxyphenylbenzimidate (4·0 g.) in nitrobenzene (6 c.c.) was boiled under reflux for 3 hours. A little free iodine and the nitrobenzene were removed at 160° (bath) at the water-pump. The residue was extracted from some tar with benzene (110 c.c.) and chromatographed on alumina. The first fractions, crystallised from alcohol, gave the pale brown *amide* (2·0 g., 50%). A colourless sample for analysis, got by crystallisation from light petroleum (b. p. 100—120°) (charcoal), had m. p. 191° (Found: C, 43·7; H, 3·6; I, 43·9. $C_{21}H_{17}O_2NI_2$ requires C, 44·3; H, 3·0; I, 44·6%).

In diphenyl ether. The ester (4·0 g.) in diphenyl ether (10·0 g.) was boiled for 10 minutes. The solution became very dark and iodine vapour appeared. The cooled mixture was extracted twice with boiling light petroleum (b. p. 100—120°) leaving a dark tar. On cooling, the petroleum deposited crystals (2·25 g., 56%) of the rearranged compound. It was best finally purified by crystallisation from 90% acetic acid with charcoal.

Effect of solvent. Samples of the ester (2·0 g.) were boiled in various solvents (5 c.c.) and the amide produced was extracted from the product with light petroleum (b. p. 100—120°). The table shows the yields (%) of rearranged compound.

Solvent	B. p.	Time of boiling (min.) 1	5	10	15	30	90
Ph_2O	259°	30	45	55	—	43	—
Ph_2	254	—	—	53	—	—	—
Ph_2O–$PhNO_2$ (4 : 1)	240	—	—	—	45	—	—
o-$C_6H_4Me{\cdot}NO_2$	224	—	—	—	—	34	—
$PhNO_2$	209	—	—	—	—	30	—
o-$C_6H_4Cl_2$	180	—	—	—	—	—	0

Methyl N-*Benzoyl*-2 : 6-*di*-*iodo*-4′-*methoxydiphenylamine*-4-*carboxylate*.—A solution of 4-carbomethoxy-2 : 6-di-iodophenyl *N*-*p*-methoxyphenylbenzimidate (4·0 g.) in *o*-dichlorobenzene (12 c.c.) was boiled for 80 minutes. Light petroleum (b. p. 100—120°) was then added until crystals began to separate from the boiling solution. On cooling, the *amide* (3·8 g., 95%) was filtered off; it had m. p. 205° [from toluene–light petroleum (b. p. 100—120°)] (Found: C, 42·9; H, 2·7; I, 40·8. $C_{22}H_{17}O_4NI_2$ requires C, 43·1; H, 2·8; I, 41·4%).

N-*Benzoyl*-4′-*hydroxy*-2 : 6-*di*-*iodo*-4-*methyldiphenylamine*.—The 4′-methoxy-compound (3·1 g.) in acetic acid (15 c.c.) and hydriodic acid (10 c.c.) was boiled for ½ hour. The solid 4′-*hydroxy*-compound was filtered from the cooled solution and recrystallised from acetic acid–dioxan as colourless crystals (2·8 g., 93%), decomp. from 296°, m. p. 306—307° (Found: C, 43·2; H, 2·9; I, 45·8. $C_{20}H_{15}O_2NI_2$ requires C, 43·2; H, 2·7; I, 45·8%).

N-*Benzoyl*-4′-*hydroxy*-2 : 6 : 3′ : 5′-*tetraiodo*-4-*methyldiphenylamine*.—The preceding phenol (1·8 g.) in dioxan (40 c.c.) and ethylamine (30 c.c.; 40%) was treated dropwise with iodine (4 g.-atoms) in potassium iodide solution (6·9 c.c.; 245 g. I_2/l.). After 3 hours the solution was neutralised with dilute acetic acid. The precipitated *tetraiodide* crystallised from alcohol–

dioxan in colourless needles (2·3 g., 88%), m. p. 260—275° (decomp.) (Found : I, 62·6. $C_{20}H_{13}O_2NI_4$ requires I, 62·9%).

N-*Benzoyl*-4-*bromomethyl*-2 : 6-*di*-*iodo*-4′-*methoxydiphenylamine*.—The 4-methyl compound (1·63 g.) and *N*-bromosuccinimide (0·56 g., 1·1 mols.) in carbon tetrachloride (25 c.c.) containing a trace of benzoyl peroxide were boiled for an hour. A little more peroxide was then added and the boiling continued for 4 hours. The hot solution was filtered and then mixed with *cyclo*hexane. The solid was filtered off and recrystallised from benzene containing some *cyclo*hexane. The succinimide (m. p. 122—124°) that first separated were removed and the solution then deposited small crystals (0·9 g.), m. p. 187—197° After another crystallisation from benzene–*cyclo*hexane there still appeared to be some succinimide, so the solid was washed with water and crystallised again. The needles of the *bromide* melted at 198—201° (Found : C, 38·7; H, 2·5. $C_{21}H_{16}O_2NBrI_2$ requires C, 38·9; H, 2·5%).

N-*Benzoyl*-4′-*hydroxy*-2 : 6-*di*-*iododiphenylamine*-4-*carboxylic Acid*.—The 4′-methoxy-4-methyl ester (3·0 g.) in acetic acid (15 c.c.) and hydriodic acid (10 c.c.) was boiled for 1·5 hours. The colourless crystals of *hydroxy-acid* which formed when the solution was diluted with water were recrystallised from aqueous acetic acid, and then had m. p. 278—280° after sintering from 270° (2·3 g., 80%) (Found : C, 41·3; H, 2·5; I, 43·4. $C_{20}H_{13}O_4NI_2$ requires C, 41·05; H, 2·2; I, 43·4%).

N-*Benzoyl*-4′-*hydroxy*-2 : 6 : 3′-*tri*-*iododiphenylamine*-4-*carboxylic Acid*.—Potassium carbonate solution was added to a suspension of the preceding hydroxy-acid (0·5 g.) in hot water (5 c.c.) until a clear solution was obtained. This solution was kept at *ca.* 60° while iodine solution (1·85 c.c., 245 g./l. ; 4·2 atoms) was added slowly, potassium carbonate being added occasionally to keep the solution clear and alkaline. After a trace of metabisulphite had been added the solution was acidified. Recrystallisation of the precipitate from acetic acid containing a little water gave the colourless *tri-iodo-acid*, which began to lose iodine at 264°, sintered at 270°, and decomposed at 292° (Found : C, 33·7; H, 2·0; I, 53·2. $C_{20}H_{12}O_4NI_3$ requires C, 33·8; H, 1·7; I, 53·6%).

N-*Benzoyl*-2 : 6-*di*-*iodo*-4′-*methoxydiphenylamine*-4-*carboxylic Acid*.—A solution of methyl *N*-benzoyl-2 : 6-di-iodo-4′-methoxydiphenylamine-4-carboxylate (4·39 g.) in alcohol (40 c.c.) and 10N-sodium hydroxide (5 c.c.) was refluxed for 1 hour. Acidification of the solution with hydrochloric acid precipitated a sticky solid. This was washed with alcohol and crystallised from aqueous acetic acid to yield a solid (3·07 g.), m. p. 145—150° (frothing), probably a hydrate. A sample crystallised from toluene yielded the colourless *acid*, m. p. 230° (Found : N, 2·35; I, 41·9. $C_{21}H_{15}O_4NI_2$ requires N, 2·35; I, 42·4%).

2 : 6-*Di*-*iodo*-4′-*methoxydiphenylamine*-4-*carboxylic Acid*.—A solution of the above acid (1 g.) and potassium hydroxide (10 g.) in 50% ethanol (20 c.c.) was refluxed for 2 hours under nitrogen. The cooled solution was acidified and the yellow-brown solid separated, dried, and recrystallised from toluene as yellow crystals (0·61 g.), m. p. 201°. Repeated crystallisation from toluene raised the m. p. of the *diphenylamine* to 210° (Found : N, 2·9; I, 51·2. $C_{14}H_{11}O_3NI_2$ requires N, 2·8; I, 51·3%).

4′-*Hydroxydiphenylamine*-4-*carboxylic Acid*.—A solution of the foregoing acid (1 g.) in glacial acetic acid (5 c.c.) and hydriodic acid (constant-boiling; 3·3 c.c.) was boiled for 1 hour. The solution, which became very dark owing to evolution of iodine, was diluted with water and extracted with ether. The extract was washed with water, sodium hydrogen sulphite solution, sodium hydrogen carbonate solution, and water. The ether was evaporated, to leave the *acid* which, crystallised from a large volume of water, had m. p. 226° (0·22 g.), unchanged after recrystallisation from aqueous acetic acid (Found : C, 68·1; H, 4·95; N, 6·05. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·85; N, 6·1%).

Methyl 2 : 6-*Di*-*iodo*-4′-*methoxydiphenylamine*-4-*carboxylate*.—2 : 6-Di-iodo-4′-methoxydiphenylamine-4-carboxylic acid (0·80 g.) was heated in methanol (10 c.c.) and saturated with hydrogen chloride for 10 minutes. Evaporation left an oily *ester* which was redissolved in methanol and precipitated on the addition of water as a pale yellow solid. Chromatography on alumina in ether and two crystallisations from *cyclo*hexane gave colourless crystals (0·53 g.), m. p. 111° (Found : C, 35·4; H, 2·6; N, 2·85; I, 50·05. $C_{15}H_{13}O_3NI_2$ requires C, 35·4; H, 2·6; N, 2·75; I, 49·85%).

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