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119. *The Ullmann Biaryl Synthesis. Part III.*[1] *The Influence of Diluents on the Reaction between Iodobenzene and Copper.*

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The effect of compounds containing some of the commoner substituent groups on the rate and course of the Ullmann reaction of iodobenzene is described.

IN Part II [1] of this series it was shown that compounds containing the *m*-dinitro-grouping when used as diluents in the Ullmann reaction of iodobenzene, favoured formation of abnormal biaryls by condensation with the nitro-compound and reductive arylation of the nitro-group and impeded reaction of the iodo-compound with copper to a variable extent according to the additional substituents in the diluent. The present communication describes the influence of some common substituents on the rate and course of the reaction, here again the relatively slowly reacting iodobenzene, which might be expected to show the maximum effect of diluents, being primarily used.

Ullmann reactions of iodobenzene diluted with mononitro- or unnitrated compounds did not afford unsymmetrical biaryls by interaction with the diluent, as did similar condensations in *m*-dinitrated compounds. Thus, whereas reaction in a molar equivalent of nitrobenzene, as shown in Table 1, was slower by 20% and resulted in a loss of 50% of biphenyl in comparison with the unadulterated condensation, nitrobiphenyls were not formed although a small proportion of the nitro-compound was converted into triphenylamine. Further, the marked suppression of reaction by *m*-dinitrotoluenes was not encountered with the isomeric mononitrotoluenes, self-condensations of iodobenzene in such compounds and the corresponding nitroanisoles giving comparable results. Methyl benzoate, however, strongly impeded the aryl iodide–copper reaction, in the same way as its *m*-nitro-derivative and methyl isophthalate. In general the reaction was also powerfully suppressed by aromatic aldehydes, although *o*-methoxybenzaldehyde failed to influence the reaction rate to the same extent, presumably for steric reasons. Phenolic additives likewise strongly retarded the Ullmann condensation of iodobenzene. Primary amines, however, acted as the most powerful reaction inhibitors, less than 0·1 mol. of aniline suppressing biphenyl formation completely. In contrast, benzoic acid markedly promoted the aryl iodide–copper reaction.

Suppression of the self-condensation of aryl iodides such as iodobenzene or *p*-iodotoluene by the methoxycarbonyl group may be a general effect, as shown by comparative reactions of the iodides in methyl benzoate and 1,2,4-trichlorobenzene (cf. Table 1). The reaction rates of electronegative halides, such as 1-chloro-2,4-dinitrobenzene and *o*-bromonitrobenzene, however, did not appear to be specifically affected by the ester diluent.

Except in reactions in phenols, benzoic acid, and primary amines, which are described individually, the proportion of biphenyl in the products of these condensations was normally lower when nitrated diluents were present. Within the latter group, fractionally higher yields of biaryl were obtained from condensations in the isomeric nitroanisoles than in the corresponding nitrotoluenes. Despite the marked variation in the facility of reaction of iodobenzene in the isomeric methoxybenzaldehydes, the yield of biaryl in each case approached that afforded by the undiluted reaction. In contrast, the reaction of the iodo-compound in *p*-tolualdehyde furnished little biphenyl. Methyl benzoate afforded approximately the same proportion of biphenyl as did the nitrated diluents, in contrast to the specific suppression of normal reaction under similar conditions with the *m*-nitro-analogue or methyl isophthalate.

It has long been known that halogenated compounds containing unprotected amino-groups were unable to take part in Ullmann reactions.[2] In Part II it has been shown that

[1] Part II, preceding paper.

[2] Ullmann, *Annalen*, 1904, **332**, 38.

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small quantities of primary amines added during self-condensation of iodobenzene were fully *N*-arylated by the reactant halide, affording the corresponding triphenylamine derivatives. Further study of the effect of primary amines, exemplified by that of aniline on the reaction of iodobenzene, indicated that the initial reaction under these conditions was *N*-substitution of the base. Thus in the presence of 0·09 mol. of aniline triphenylamine alone was obtained, whereas in the presence of only 0·03 mol. under similar conditions both biphenyl and the tertiary amine were formed. In reaction with larger proportions of aniline (0·45 mol.) even the *N*-phenylation of the latter was impeded, only traces of triphenylamine being obtained. The product patterns in comparable preparations of the isomeric nitrotriphenylamines by this technique were influenced by the orientation of the nitro-group. Thus the *ortho*-isomer alone of the individual nitroanilines (0·1 mol.) strongly suppressed the aryl iodide–copper reaction and biphenyl formation, whereas the *meta*-isomer was converted mainly into *NNN'N'*-tetraphenyl-*m*-phenylenediamine (II) be additional reductive arylation of the nitro-group. In this reaction, however, the expected product, 3-nitrotriphenylamine (I), predominated when the concentration of the basic reactant was raised to 0·4 mol.

TABLE 1.

Aryl halide	Diluent	Reaction time (hr.)	Reaction (%) (based on Cu halide)	Yield of biaryl (%) *
C_6H_5I	—	5	70 †	80
,,	$C_6H_5{\cdot}NO_2$	,,	50	40
,,	*o*-$C_6H_4Me{\cdot}NO_2$	,,	55	35
,,	*m*-$C_6H_4Me{\cdot}NO_2$	,,	55	30
,,	*p*-$C_6H_4Me{\cdot}NO_2$	,,	55	35
,,	*o*-$C_6H_4OMe{\cdot}NO_2$	,,	55	45
,,	*m*-$C_6H_4OMe{\cdot}NO_2$	,,	55	40
,,	*p*-$C_6H_4OMe{\cdot}NO_2$	,,	60	40
,,	*o*-$C_6H_4OMe{\cdot}CHO$	,,	75	70
,,	*m*-$C_6H_4OMe{\cdot}CHO$	,,	20	70
,,	*p*-$C_6H_4OMe{\cdot}CHO$	,,	15	75
,,	*p*-$C_6H_4Me{\cdot}CHO$	,,	15	<10
,,	$C_6H_5{\cdot}OH$	6	20	0
,,	*p*-$C_6H_4(OH){\cdot}OMe$	7	25	0
,,	$C_6H_5{\cdot}NH_2$ (0·09 mol.)	6	30	0
,,	$C_6H_5{\cdot}CO_2H$	2	95	0
,,	$C_6H_5{\cdot}CO_2Me$	5	25	40
p-$C_6H_4I{\cdot}OMe$	,,	,,	25	30
p-C_6H_4IMe	,,	,,	15	25
p-C_6H_4ClI	,,	,,	30	50
o-$C_6H_4Br{\cdot}NO_2$	,,	3	95	75
1,2,4-$C_6H_3Cl(NO_2)_2$	,,	5	70	25
C_6H_5I	1,2,4-$C_6H_3Cl_3$	,,	45	65
p-$C_6H_4I{\cdot}OMe$	,,	,,	60	75
p-C_6H_4IMe	,,	,,	40	35
p-C_6H_4ClI	,,	,,	55	55
o-$C_6H_4Br{\cdot}NO_2$	,,	3	95	75
1,2,4-$C_6H_3Cl(NO_2)_2$	,,	5	65	25

* Based on reacted material. † Cf. Part II.

The reaction of iodobenzene with copper was impeded by phenol or *p*-methoxyphenol approximately to the same extent as by methyl benzoate or by an aromatic aldehyde. Under these conditions dehalogenation of the reactant, as indicated by previous work in this field,[3] was the major reaction. Phenolic additives in sub-molar concentrations, however, were etherified to a certain extent, probably as a secondary effect. For example, the addition of *p*-methoxyphenol (0·25 mol.) in the iodobenzene reaction afforded a mixture of biphenyl and 4-methoxydiphenyl ether, whereas under the same conditions adding twice the amount of the phenol yielded the biaryl ether alone. A similar product pattern was obtained when phenol was used in place of its *p*-methoxy-derivative.

[3] Nursten, *J.*, 1955, 3081.

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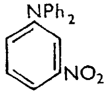
Etherification by this means appeared a fairly general reaction although as a preparative route to diaryl ethers it compared unfavourably with established methods [4] owing to the loss of at least 50% of the aryl halide by dehalogenation, etc. Moreover, etherification of nitrophenols was restricted in specific instances by preferential attack on the nitro-group. For example, 2-nitrodiphenyl ether (III) was better prepared by the Ullmann reaction of *o*-bromonitrobenzene in phenol, the alternative route from iodobenzene in *o*-nitrophenol affording predominantly the reductive arylation product, 2-hydroxytriphenylamine (IV). Catechol did not react in the same way as did the monohydric phenols: a dark, finely divided solid, sparingly soluble in the commoner organic solvents, was the major product; this material resembled that obtained by Nursten [3] in a similar condensation of *p*-iodonitrobenzene in catechol; it was not further investigated.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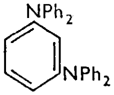
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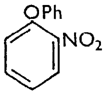
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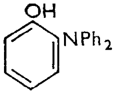
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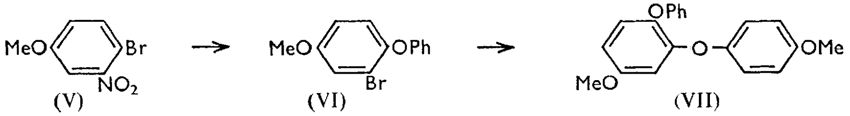
(V) (VI) (VII)

The formation of small quantities of high-boiling products was a characteristic feature of Ullmann reactions in the presence of phenols. Condensation of iodobenzene in *p*-methoxyphenol afforded abnormally large quantities of such material, from which a second product, 5,4'-dimethoxy-2-phenoxydiphenyl ether (VII), was isolated in unexpectedly good yield. The structure of the polyether was confirmed by synthesis from 4-bromo-3-nitroanisole (V) *via* 2-bromo-4-methoxydiphenyl ether (VI). The compound (VII) was not obtained by reaction of iodobenzene to which preformed 4-methoxydiphenyl ether had been added.

Addition of an excess of benzoic acid in Ullmann condensations of certain halogeno-nitro-compounds has been described as a convenient method for the dehalogenation of these materials.[5] Further experiment in this field with the more slowly reacting iodobenzene and *p*-iodoanisole has shown that alongside the dehalogenation the halide–copper reaction became materially faster. Moreover, aryl benzoates were also produced, to a variable extent, particularly when relative small amounts of the carboxylic acid were used. For example, 0·25 mol. of benzoic acid added in the reaction of *p*-iodoanisole was almost completely converted into *p*-methoxyphenyl benzoate, whereas use of 1 mol. of the acid led to but little ester.

The esterification mechanism presumably involved the intermediate formation of a copper salt of benzoic acid although under the conditions of reaction benzoic acid alone was unattacked by copper. Thus, reaction of the chloroform-insoluble products from the condensation of an aryl halide in a molar equivalent of benzoic acid with either iodobenzene or *p*-iodoanisole readily afforded the corresponding aryl ester of benzoic acid. Visual evidence of the reaction (cf. p. 587), together with the failure of cupric benzoate to react under the same conditions, indicated that the cuprous salt might well be the functional intermediate.

EXPERIMENTAL

General directions are as in Part II.[1]

General Technique.—The reactants were heated with stirring in a metal-bath, the temperature of which was maintained at *ca.* 5° above that of the mixture. The products were worked up as described in Part I of this series. Where practicable the aryl halide was recovered

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[4] Ullmann and Sponagel, *Ber.*, 1905, **38**, 2211.

[5] Smith and Camparo, *J. Amer. Chem. Soc.*, 1953, **75**, 3602.

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to provide a check on the quantity which reacted. The figures so obtained were fractionally higher than those based on the weight increase of inorganic material, probably owing to experimental losses. Except where stated otherwise, molar equivalents of the diluents were used.

Ullmann Reactions of Iodobenzene in Organic Diluents.—(1) *In nitrobenzene.* Iodobenzene (12·5 g.), nitrobenzene (7·7 g.), and copper (5·5 g.) were caused to react at 190—195° for 5 hr., and furnished copper salts, etc. (9·5 g.), unchanged iodobenzene and nitrobenzene (12·25 g.), b. p. 40—50°/0·8 mm., crude biphenyl (1·2 g.), b. p. 72—78°/0·8 mm., and a viscous oil (0·5 g.), b. p. 120—130°/0·8 mm., which solidified. Crystallisation of the last from methanol gave colourless prisms of triphenylamine (0·3 g.), m. p. and mixed m. p. 124—125° (Found: N, 5·5. Calc. for $C_{18}H_{15}N$: N, 5·7%). Pure biphenyl (1 g.) was obtained from the crude fraction on crystallisation from 90% methanol.

In a similar reaction of iodobenzene to which nitrobenzene (2·75 g.) was added, inorganic material (9·5 g.), recovered diluent and iodobenzene (9 g.), and biphenyl (1·4 g.) were obtained. A small higher-boiling residue (*ca.* 0·1 g.) gave a deep blue colour in warm concentrated sulphuric acid, indicating the presence of triphenylamine. The yields of biphenyl (1·7 g.) and copper halides, etc. (10·3 g.), were increased in a comparable reaction with 0·5 g. of nitrobenzene. Triphenylamine could not be identified in the distillation residues.

(2) *In derivatives of nitrobenzene. General procedure.* Iodobenzene (0·185 mol.), the nitro-diluent (0·185 mol.), and copper (0·28 mol.) reacted at 195° for 5 hr. Normally, fractional distillation failed to separate the main bulk of the organic products. The middle fractions were therefore combined and reductively acetylated with zinc dust in acetic acid–acetic anhydride by standard techniques. After separation of suspended excess of zinc, etc., water (5 vols.) was added to the liquor, which after being warmed to decompose unchanged anhydride, was cooled and extracted with light petroleum. The extracts were washed with water, then fractionally distilled to obtain the biphenyl.

A small high-boiling fraction was normally obtained on distillation of the original reaction product. The corresponding derivative of triphenylamine could in some cases be isolated therefrom either (A) by direct crystallisation from methanol–ethyl acetate or (B) by similar treatment of the first eluate on chromatography of the crude fraction in benzene–light petroleum (1 : 3). In the remaining examples the crude oil proved intractable.

(*a*) In *o*-nitrotoluene (copper salts, etc., 30 g.). A crude fraction, treated as described, gave biphenyl (2·5 g.). A viscous top fraction (1 g.), b. p. 175—200°/0·5 mm., failed to yield characterisable material even after chromatography.

(*b*) In *m*-nitrotoluene (copper salts, etc., 35 g.). Biphenyl (2·35 g.) was obtained from a crude fraction (41 g.), of boiling range 90—140°/25 mm. A higher-boiling fraction (1·5 g.), b. p. 180—200°/1 mm., gave (method B) rosettes of needles of 3-methyltriphenylamine (0·35 g.), m. p. 69° (lit., 69—70°) (Found: C, 87·8; H, 6·6; N, 5·2. Calc. for $C_{19}H_{17}N$: C, 88·0; H, 6·6; N, 5·4%).

(*c*) In *p*-nitrotoluene (copper salts, etc., 30 g.). Biphenyl (2·5 g.) was obtained from a crude fraction (43 g.), of boiling range 85—145°/20 mm. A top cut (1·5 g.), b. p. 170—200°/1 mm., gave (method A) colourless prisms of 4-methyltriphenylamine (0·3 g.), m. p. 67—68° (lit., 68°) (Found: C, 87·9; H, 6·5; N, 5·4%).

(*d*) In *o*-nitroanisole (copper salts, etc., 31 g.). Fractionation of the organic product gave iodobenzene (12·5 g.), a fraction (29·5 g.) of boiling range 120—160°/30 mm. [which afforded biphenyl (3·75 g.)] and a residue (1·5 g.), b. p. >160°/1 mm.

(*e*) In *m*-nitroanisole (copper salts, etc., 30·5 g.). Fractionation of the organic material (46·7 g.) gave iodobenzene (13·5 g.) and fractions, b. p. 130—160°/50 mm. (31·5 g.) [which afforded biphenyl (3·2 g.)], and b. p. 170—210°/1 mm. (1·5 g.).

(*f*) In *p*-nitroanisole (copper salts, etc., 32 g.). Distillation of the products (42·5 g.) gave iodobenzene (8·2 g.), a fraction (32 g.), b. p. 120—150°/20 mm., and a residue (2·5 g.), b. p. >170°/20 mm. Treatment of the main fraction furnished biphenyl (3·6 g.). The high-boiling material afforded (method B) 4-methoxytriphenylamine (0·35 g.), m. p. 102° (lit., 104°) (Found: C, 83·1; H, 6·3; N, 5·3. Calc. for $C_{19}H_{17}ON$: C, 82·9; H, 6·2; N, 5·1%). Further elution of the chromatogram with ethyl acetate gave a small quantity (0·35 g.) of a red oil which crystallised from methanol in yellow needles of 4,4′-dimethoxyazobenzene (0·05 g.), m. p. 161° (lit., 161°) (Found: C, 69·6; H, 5·8; N, 11·4. Calc. for $C_{14}H_{14}O_2N_2$: C, 69·4; H, 5·8; N, 11·6%).

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(3) *In unnitrated diluents.* (*a*) In methyl benzoate. Iodobenzene (50 g.), methyl benzoate (34 g.), and copper (23·5 g.), reacting at 190° for 5 hr., gave inorganic material (30·8 g.), unchanged reactants (63 g.), b. p. 40—50°/0·3 mm., and an oily solid (2·7 g.), b. p. 60—85°/0·3 mm. There was no distillation residue. The oily solid was treated with 5% methanolic potassium hydroxide (100 ml.) for 18 hr. at 20°, then the solvent was removed and water (50 ml.) added. Extraction of the liquor with light petroleum gave, after removal of solvent, biphenyl (1·8 g.) (from 90% methanol). The original alkaline residue gave, on acidification and extraction with chloroform, etc., a small quantity (0·15 g.) of intractable oil.

(*b*) In 1,2,4-trichlorobenzene. The product from iodobenzene (37·5 g.), the chloro-compound (33·5 g.), and copper (17·5 g.) at 190° (5 hr.) gave inorganic material (27·5 g.), a mixture of chloro- and iodo-hydrocarbons (51 g.), b. p. 40—50°/0·5 mm., and biphenyl (4 g.). There was no distillation residue.

(*c*) In *o*-methoxybenzaldehyde. Iodobenzene (12·5 g.), *o*-methoxybenzaldehyde (8·8 g.), and copper (6 g.), reacting at 195° for 5 hr., gave inorganic material (12·1 g.), unchanged aryl iodide (2·5 g.), and a mixed fraction (6·8 g.), b. p. 65—80°/0·3 mm. The last was shaken for 15—20 min. with excess of sodium hydrogen sulphite solution. The precipitated solid was filtered off, washed with water, and extracted with light petroleum. Removal of the solvent left biphenyl (2·7 g.). A similar condensation with 4·4 g. of methoxy-aldehyde gave an almost identical result.

(*d*) In *m*-methoxybenzaldehyde. A reaction similar to (*c*) with *m*-methoxybenzaldehyde (8·8 g.) as diluent gave inorganic material (7·7 g.), iodobenzene (8·5 g.), and a mixed fraction (9 g.), b. p. 60—75°/0·5 mm., which afforded biphenyl (0·7 g.) on treatment as before.

(*e*) In *p*-methoxybenzaldehyde. Reaction in *p*-methoxybenzaldehyde (8·8 g.) gave inorganic material (7·3 g.), iodobenzene (8·8 g.), and biphenyl (0·6 g.). Little variation of the product pattern was obtained on repetition of the condensation with 4·4 g. of the ether.

(*f*) In *p*-tolualdehyde. The aldehyde (24 g.), iodobenzene (37·5 g.), and copper (17·5 g.), reacting as in (*c*), afforded inorganic material (20·5 g.), a mixed fraction (53 g.), b. p. 45—50°/0·5 mm., and a fraction (1 g.), b. p. 75—90°/0·5 mm., which partly solidified. A higher-boiling residue (1 g.) was discarded. Iodobenzene (29 g.) was obtained from the major fraction after removal of the aldehyde with aqueous sodium hydrogen sulphite. The higher-boiling distillate appeared to contain some biphenyl, but as purification could not be easily achieved, the oily solid was not further investigated. Repetition of the reaction with 12 g. of the aldehyde gave inorganic material (21·5 g.), iodobenzene and *p*-tolualdehyde (34 g.), and a fraction (1·5 g.), b. p. 75—90°/0·5 mm., from which biphenyl (0·5 g.) crystallised slowly at 0° in 90% methanolic solution.

(4) *In primary amines.* (*a*) In aniline. Iodobenzene (37·5 g.), aniline (0·5 g., 0·03 mol.), and copper (17·5 g.), reacting at 195° for 6 hr., gave inorganic material (34·5 g.), iodobenzene (9·5 g.), biphenyl (7·8 g.), and a fraction (1·2 g.), b. p. 120—130°/0·4 mm., which solidified readily. Crystallisation of the solid gave colourless prisms of triphenylamine (1 g.), m. p. and mixed m. p. 124—125° (from methanol) (Found: N, 5·5. Calc. for $C_{18}H_{15}N$: N, 5·7%). Repetition of the condensation with aniline (1·7 g., 0·09 mol.) gave copper salts, etc. (25 g.), iodobenzene (22 g.), and triphenylamine (3·5 g.). No biphenyl could be isolated. A similar reaction in aniline (7·5 g., 0·44 mol.) afforded copper salts (22 g.), iodobenzene (31·5 g.) [after separation of unchanged aniline from a mixed fraction (37 g.) with dilute mineral acid], and triphenylamine (1·9 g.).

(*b*) In *o*-nitroaniline. The nitro-amine (1 g., 0·1 mol.), iodobenzene (15 g.), and copper (7·5 g.), reacting as in (*a*), gave inorganic material (12·5 g.), unchanged iodobenzene (6·5 g.), and a crimson viscous oil (2 g.), b. p. 165—185°/0·5 mm. An undistillable dark resin (2 g.) was discarded. No fraction corresponding to biphenyl was obtained. The red oil crystallised readily from light petroleum containing a few drops of benzene in orange needles of 2-nitrotriphenylamine (0·75 g.), m. p. 102—103° (lit., 102—103°) (Found: N, 9·8. Calc. for $C_{18}H_{14}O_2N_2$: N, 9·7%).

(*c*) In *m*-nitroaniline. A similar reaction with *m*-nitroaniline (1 g.) gave inorganic material (15·5 g.), biphenyl (2·1 g.), and a viscous red oil (2·5 g.), b. p. 170—225°/0·3 mm. An undistillable dark resin (2 g.) was discarded. The viscous oil was chromatographed in benzene–light petroleum (1 : 2), yielding successively, on elution with the same solvent, (1) a red oil (1·2 g.) which crystallised from ethanol in feathery white needles of *NNN'N'*-tetraphenyl-*m*-phenylenediamine (0·7 g.), m. p. 137° (lit., 137·5°) (Found: C, 87·1; H, 6·0; N, 6·5. Calc. for $C_{30}H_{24}N_2$:

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C, 87·4; H, 5·8; N, 6·8%), (2) an uncrystallisable red oil (0·3 g.), and (3) a red oil (0·7 g.) which crystallised slowly from methanol in orange prisms of 3-nitrotriphenylamine (0·3 g.), m. p. and mixed m. p. 78° (Found: N, 9·3. Calc. for $C_{18}H_{14}O_2N_2$: 9·7%). Repetition of the condensation with 4 g. (0·4 mol.) of *m*-nitroaniline gave inorganic material (15·4 g.), iodobenzene (2·5 g.), and a red oil (6 g.), b. p. 185—195°/0·6 mm. A small quantity of higher-boiling material ($<$1 g.) was discarded. No fraction corresponding to biphenyl was obtained. The red oil crystallised slowly from methanol, yielding 3-nitrotriphenylamine (4·1 g.).

(*d*) In *p*-nitroaniline. A similar reaction with *p*-nitroaniline (1 g.) gave inorganic material (15 g.), iodobenzene (3 g.), biphenyl (1·5 g.), and a viscous red-brown oil (2·1 g.), b. p. 195—200°/0·6 mm., which solidified. A small distillation residue (0·5 g.) was discarded. Crystallisation of the crude solid from methanol–ethyl acetate furnished golden prisms of 4-nitrotriphenylamine (1·7 g.), m. p. 143—144° (lit., 144°) (Found: N, 9·8%).

(5) *In phenols.* (*a*) In phenol. Iodobenzene (25 g.), phenol (12 g.), and copper (12 g.), reacting at 195° for 6 hr., gave inorganic material (15·5 g.), a mixture of phenol and iodobenzene (25 g.), b. p. 40—50°/0·5 mm., and diphenyl ether (3 g.), b. p. 70—75°/0·3 mm. (Found: C, 84·4; H, 5·8. Calc. for $C_{12}H_{10}O$: C, 84·7; H, 5·9%). There was no higher-boiling fraction. Repetition of the condensation with phenol (6 g., 0·5 mol.) gave inorganic material (17·5 g.), the mixed organic reactants (19 g.), and diphenyl ether (3 g.). A similar reaction with 3 g. (0·25 mol.) of phenol afforded inorganic material (23·7 g.), iodobenzene and phenol (6·5 g.), and a mixture of biphenyl and diphenyl ether (6·2 g.), b. p. 75—85°/0·6 mm. (Found: C, 89·2; H, 6·45. Calc. for $C_{12}H_{10}$: C, 93·5; H, 6·5%). A small higher-boiling residue (0·75 g.) was not further examined.

(*b*) In *p*-methoxyphenol. Iodobenzene (37·5 g.), *p*-methoxyphenol (11·5 g., 0·5 mol.), and copper (17·5 g.), reacting as in (*a*) above, gave inorganic material (23·5 g.), iodobenzene (27·5 g.), *p*-methoxyphenol (7 g.), b. p. 85—90°/0·5 mm., 4-methoxydiphenyl ether (2 g.), b. p. 105—115°/0·5 mm., and a viscous oil (1·75 g.), b. p. 180—200°/0·5 mm. Redistillation of the crude diaryl ether gave the pure material (1·5 g.), b. p. 112—115°/0·8 mm.; m. p. 14° (Found: C, 77·8; H, 6·2; OMe, 15·3. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·0; OMe, 15·5%). The viscous oil crystallised slowly from methanol at 0° in colourless rhombs, m. p. 61—63°. After 2 further crystallisations from the same solvent 5,4′-*dimethoxy*-2-*phenoxydiphenyl ether* (VII) was obtained in prisms, m. p. 67—68° (Found: C, 74·3; H, 5·4; OMe, 19·7. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6; OMe, 19·3%). Repetition of the reaction with 23 g. of *p*-methoxyphenol gave, after 7 hr. at 195°, inorganic material (24 g.), iodobenzene (25 g.), *p*-methoxyphenol (17 g.), 4-methoxydiphenyl ether (2·5 g.), and the polyether (VII) (0·35 g.). A similar reaction with 5·75 g. (0·25 mol.) of *p*-methoxyphenol gave inorganic material (33·5 g.), iodobenzene (9 g.), biphenyl (2·7 g.), 4-methoxydiphenyl ether (3·75 g.), and the polyether (VII) (2·6 g.). The compound (VII), however, was not isolated after reaction of iodobenzene (12·5 g.), 4-methoxydiphenyl ether (4 g.), and copper (6 g.) under similar conditions, biphenyl (3 g.) being the sole product.

(*c*) In *o*-nitrophenol. Iodobenzene (12·5 g.), *o*-nitrophenol (2·1 g., 0·25 mol.), and copper (6 g.) at 195° (5 hr.) gave copper salts, etc. (10·7 g.), iodobenzene (3·7 g.), a viscous oil (2·5 g.), b. p. 150—170°/0·3 mm., which solidified, and a dark resin (2·5 g.), b. p. $>$180°/0·3 mm., which was not further examined. Crystallisation of the solid product from methanol–ethyl acetate (twice) gave stout flesh-coloured needles of 2-*hydroxytriphenylamine* (1·1 g.), m. p. 138—139° (Found: C, 83·0; H, 5·4; N, 5·6. $C_{18}H_{15}ON$ requires C, 82·8; H, 5·7; N, 5·4%). After removal of solvent from the mother-liquors distillation of the residue *in vacuo* gave 2-nitrodiphenyl ether (0·65 g.), b. p. 138—145°/0·5 mm. (Found: N, 6·9. Calc. for $C_{12}H_9O_3N$: N, 6·5%).

(*d*) In *p*-nitrophenol. Iodobenzene (12·5 g.), *p*-nitrophenol (2·1 g., 0·25 mol.), and copper (6 g.), treated as in (*c*) above, gave inorganic material (12·2 g.), iodobenzene (3·2 g.), and an orange viscous oil (1·5 g.), b. p. 130—140°/0·7 mm., which partly solidified. A dark resin (1 g.) was discarded. Crystallisation of the oily solid from methanol (twice) gave pale yellow prisms of 4-nitrodiphenyl ether (0·75 g.), m. p. 60° (lit., 61°) (Found: N, 6·7%).

(*e*) In catechol. Iodobenzene (12·5 g.), catechol (1·5 g., 0·22 mol.), and copper (6 g.) were allowed to react as in (*c*) above. Filtration of chloroform extracts from insoluble material (13·5 g.) was greatly impeded by a blue-black suspension. Distillation of the organic product gave iodobenzene (4·5 g.), and a mixed inseparable fraction (0·7 g.) of boiling range 110—160°/0·5 mm.

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Ullmann Reactions of Other Aryl Halides in Phenols.—p-*Iodoanisole in phenol.* The inorganic products (40 g.) of the reaction between *p*-iodoanisole (45 g.), phenol (8·8 g., 0·5 mol.), and copper (17·5 g.) at 195° (5 hr.) were additionally extracted with boiling acetone to ensure complete elimination of organic material. Fractional distillation of the latter, after removal of the combined solvents, yielded anisole (6·5 g.), b. p. 75—85°/35 mm., crude 4-methoxydiphenyl ether (7·8 g.), b. p. 90—100°/0·2 mm., 4,4′-dimethoxybiphenyl (6 g.), b. p. 115—130°/0·3 mm., m. p. 172°, and a fraction (3 g.), of boiling range 140—200°/0·5 mm. The crude aryl ether was freed from traces of diether by dissolution in 90% methanol and cooling to 5° for 4 hr., after which the deposited biaryl (0·1 g.) was filtered off. The mother-liquors were concentrated, then the residue fractionally distilled to give pure 4-methoxydiphenyl ether (6·5 g.), b. p. 175—178°/35 mm. (Found: OMe, 15·3%).

p-*Iodonitrobenzene in Phenol.*—*p*-Iodonitrobenzene (15·5 g.), phenol (3 g., 0·5 mol.), and copper (6 g.) reacted at 195° for 5 hr. The organic material was extracted from copper salts, etc. (13 g.), with boiling acetone in addition to the chloroform normally used. Fractional distillation of the residue obtained on removal of the combined solvents afforded nitrobenzene (2·5 g.), b. p. 40—45°/0·3 mm., followed by a fraction (5·5 g.), of boiling range 110—180°/0·6 mm., which solidified. An undistillable black residue (2 g.) was discarded. The crude solid was treated with piperidine (20 ml.) at 100° for 4 hr. to convert unchanged *p*-iodonitrobenzene. The filtrate liquor was then poured into water (200 ml.), and the organic material extracted with benzene (2 × 100 ml.). The combined extracts were shaken with concentrated hydrochloric acid (2 × 100 ml.), then the benzene layer was separated and washed with water, and the solvent was removed. Distillation of the residue *in vacuo* gave an orange oil (0·75 g.), b. p. 135—145°/0·5 mm., which readily crystallised from methanol in yellow prisms of 4-nitrodiphenyl ether (0·5 g.), m. p. and mixed m. p. 60° (Found: N, 6·2. Calc. for $C_{12}H_9O_3N$: N, 6·5%).

o-*Bromonitrobenzene in Phenol.*—Copper (6 g.) was added portionwise in 30 min. to a stirred mixture of *o*-bromonitrobenzene (12·3 g.) and phenol (3 g., 0·5 mol.) at 195°. Heating and stirring were continued for a further 2·5 hr. This led to inorganic material (10·5 g.), nitrobenzene (2 g.), and a mixed fraction (5·5 g.), b. p. 140—170°/0·5 mm. A residual tar (1·2 g.) was discarded. The semi-solid main fraction was crystallised exhaustively from benzene–light petroleum, affording 2,2′-dinitrobiphenyl (2·3 g.), m. p. 124°. The final mother-liquors, after removal of solvent, were distilled *in vacuo* to yield 2-nitrodiphenyl ether (2·75 g.), 135—140°/0·4 mm. (Found: N, 6·7%).

Ullmann Reactions of Aryl Halides in Methyl Benzoate and 1,2,4-*Trichlorobenzene.*—The general procedure described for the reaction of iodobenzene in these diluents was adhered to. The biaryls obtained from such condensations were isolated by distillation and/or crystallisation of the residue after removal of solvent and unchanged halide. The symmetrical biaryls, being known, are not further described. The results are detailed in Table 1.

Ullmann Reactions in Benzoic Acid.—*Iodobenzene.* Iodobenzene (12·5 g.), benzoic acid (7·5 g.), and copper (6 g.) were heated in a hard-glass tube without stirring to 195°. After a few min. a vigorous reaction occurred, and the metal swelled and was converted into a white solid which rapidly became bright blue in contact with air. After 2 hr. the reaction mass was cooled and repeatedly extracted with dry ether, leaving grey insoluble copper salts, etc. (18·2 g.). Concentration of the combined ethereal extracts, followed by re-extraction of the residue with a little chloroform, gave cupric benzoate (*ca.* 0·3 g.) which was filtered off. Extraction of the chloroform liquor with aqueous sodium hydroxide furnished benzoic acid (2 g.) on acidification of the aqueous layer. Fractional distillation of the organic extracts gave, after a small fore-run (0·4 g.) which was not further investigated, phenyl benzoate (0·8 g.), b. p. 110—115°/0·4 mm., m. p. 61° (Found: C, 78·6; H, 5·1. Calc. for $C_{13}H_{10}O_2$: C, 78·8; H, 5·1%). Repetition of the reaction with benzoic acid (3·75 g.; 0·5 mol.) gave copper salts, etc. (14 g.), iodobenzene (1 g.), benzoic acid (0·15 g.), biphenyl (0·4 g.) (isolated during the distillation), and phenyl benzoate (3·3 g.). A similar reaction with benzoic acid (1·9 g., 0·25 mol.) gave copper salts, etc. (12 g.), unchanged iodobenzene (2·5 g.), biphenyl (1 g.), and the aryl ester (2·7 g.).

p-*Iodoanisole.* The iodo-ether (14·5 g.), benzoic acid (3·75 g., 0·5 mol.), and copper (6 g.) were heated initially to 195°, whereupon an exothermic reaction raised the internal temperature to 235° for 20—30 min. After 1 hr. the mixture was cooled and treated as in the previous condensation, giving copper salts, etc. (15 g.), and a fraction (4·5 g.), b. p. 130—150°/0·5 mm., which solidified. Treatment of this material with warm methanol (50 ml.) left an insoluble residue of 4,4′-dimethoxybiphenyl (0·4 g.), and afforded, on concentration to half bulk and

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cooling, colourless feathery plates of *p*-methoxyphenyl benzoate (3·25 g.), m. p. 88—89° (Found: C, 73·9; H, 5·6. Calc. for $C_{14}H_{12}O_3$: C, 73·7; H, 5·3%).

Miscellaneous Reactions.—Cupric benzoate, etc., with iodobenzene. Cupric benzoate (19 g.) was heated with iodobenzene (25 g.) at 200° for 5 hr., then cooled and extracted with dry ether. After filtration from unchanged cupric salt (17·6 g.) the ethereal extract was concentrated, then distilled *in vacuo*, giving iodobenzene (21·5 g.) and a mixed fraction (0·75 g.), b. p. 80—115°/0·6 mm., which solidified. Separation of the latter afforded benzoic acid (0·25 g.) and phenyl benzoate (0·3 g.).

Under identical conditions benzoic acid alone failed to react with copper.

Similar treatment of a mixture of copper salts, etc. (9 g.) (obtained from the Ullmann condensation of iodobenzene in a molar equivalent of benzoic acid as previously described), and iodobenzene gave phenyl benzoate (2·7 g.) and excess of iodobenzene (7 g.).

A comparable reaction with *p*-iodoanisole (10 g.) gave *p*-methoxyphenyl benzoate (2·5 g.).

Synthesis of 5,4′-*Methoxy*-2-*phenoxydiphenyl Ether* (VII).—4-*Methoxy*-2-*nitrodiphenyl ether.* 4-Bromo-3-nitroanisole (V) (21 g.), potassium phenoxide (13·2 g.), and copper (0·8 g.) were heated at 195° for 2·5 hr. The organic product was extracted with chloroform, and the extracts were washed with water, then fractionally distilled *in vacuo*, to give 4-*methoxy*-2-*nitrodiphenyl ether* (11·2 g.), b. p. 162—165°/0·5 mm. A sample crystallised from methanol (0·5 vol.) at 5° in yellow needles, m. p. 35° (Found: C, 63·6; H, 4·5; N, 5·4. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

2-*Amino*-4-*methoxydiphenyl ether.* The nitro-ether (10·5 g.), in boiling methanol–water (150 : 120 ml.) to which glacial acetic acid (25 ml.) had been added, was reduced by the portionwise addition of iron powder (15 g.) in 30 min. The solution was then refluxed for a further 2·5 hr. The colourless liquor was diluted with water (300 ml.) and extracted with benzene, and the whole filtered from suspended solid. The benzene layer was separated, washed with water, and concentrated. The residue crystallised from benzene–light petroleum in flesh-coloured plates of 2-*amino*-4-*methoxydiphenyl ether* (6·3 g.), m. p. 109—111° (Found: C, 72·7; H, 6·2; N, 6·4. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·0; N, 6·5%).

2-*Bromo*-4-*methoxydiphenyl ether* (VI). The primary amine (14·5 g.) was dissolved in hot hydrobromic acid solution (46—48% acid, 20 ml.; water, 50 ml.), then cooled to 5° with stirring to obtain a fine deposit of the base hydrobromide. The suspension was diazotised at 5° by sodium nitrite (4·7 g.) in 15% aqueous solution. Towards the end of the addition golden feathery plates were deposited. The whole was added to a solution of cuprous bromide (20 g.) in 46—48% hydrobromic acid (100 ml.). After the evolution of gas had subsided the dark liquors were extracted with chloroform (2 × 100 ml.), and the combined extracts washed with dilute sodium hydroxide solution and water. Distillation of the residue *in vacuo* after removal of solvent gave 2-*bromo*-4-*methoxydiphenyl ether* (VI) (4 g.), b. p. 138—142°/0·5 mm. Crystallisation from methanol gave colourless prisms (3·2 g.), m. p. 61—62° (Found: C, 56·3; H, 4·2; Br, 28·2. $C_{13}H_{11}O_2Br$ requires C, 55·9; H, 4·0; Br, 28·7%).

5,4′-*Dimethoxy*-2-*phenoxydiphenyl ether* (VII). The bromo-ether (VI) (2·5 g.), potassium *p*-methoxyphenoxide (1·62 g.), and copper (0·2 g.) were heated at 220—230° for 2 hr. Fractional distillation of chloroform extracts of the mixture gave the dehalogenation product, 4-methoxydiphenyl ether (1·5 g.), b. p. 118—125°/0·8 mm. (Found: OMe, 15·9%), and a crude viscous oil (0·7 g.), b. p. 160—200°/0·7 mm., which crystallised slowly from methanol at 5° to give the polyether (VII) in colourless prisms (0·35 g.), m. p. 66—67°, undepressed on admixture with a specimen obtained from the Ullmann condensation of iodobenzene in *p*-methoxyphenol (Found: C, 74·2; H, 5·5. Calc. for $C_{20}H_{18}O_4$: C, 74·5; H, 5·6%).

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