687. *The Direct Phthalimidation of the Aromatic Nucleus*

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Substitution in the aromatic nucleus by the phthalimido-group, derived from *N*-chlorosulphonylphthalimide is described. It is suggested that this substitution proceeds by attack of the *N*-phthalimido-radical on the aromatic substrate. The substitution pattern in biphenyl shows the phthalimido-radical to be more electrophilic than the phenyl radical, and subject to steric hindrance in its approach to the *ortho*-position. In the reaction of 1,4-dibromobenzene with *N*-chlorosulphonylphthalimide, the formation of bromine and phthalimide is evidence for the presence of phthalimido-radicals. *N*-Chlorophthalimide as an intermediate is excluded.

It has been reported recently [1] that the aromatic nucleus may be arylated by aryl radicals generated from arylsulphonyl halides. We now report the phthalimidation of aromatic compounds by means of *N*-chlorosulphonylphthalimide. We suggest that this also is a free-radical reaction, in which phthalimido-radicals attack the aromatic substrate.

[1] Bain, Blackman, Cummings, Hughes, Lynch, McCall, and Roberts, *Proc. Chem. Soc.*, 1962, **186**; Neale, McCall, and Rawlings, *J.*, 1962, 5288.

Substitution of the aromatic nucleus by the phthalimido-group has not been previously reported, although direct substitution by the succinimido-radical has been reported in two instances, *i.e.*, side reactions in brominations with *N*-bromosuccinimide.[2] Sulphonamidation of aromatic compounds is known to occur by means of arylsulphonyl azides, which appear to react *via* an intermediate biradical, which has electrophilic properties.[2,3]

We now report that *N*-chlorosulphonylphthalimide in an excess of refluxing biphenyl, 1,4-dibromo-, 1,4-dichloro-, 1,3,5-trichloro-, or 1,2,4,5-tetrachloro-benzene, yields the *N*-arylphthalimide, with evolution of sulphur dioxide and hydrogen chloride. With purified biphenyl, the rate of reaction was slower than when biphenyl of commercial quality was used, but the rate was increased by the addition of cuprous chloride to the reaction mixture. Copper naphthenate similarly increased the rate of reaction with 1,3,5-trichlorobenzene. Either of these accelerators was employed in the other substrates to ensure that satisfactory rates of reaction were obtained, although in 1,4-dichlorobenzene, where the boiling point was only 180°, the rate was still low.

Yields of *N*-arylphthalimide from the halogeno-substrates were from 4% for 1,4-dibromobenzene, to 30% for 1,2,4,5-tetrachlorobenzene. With 1,4-dibromobenzene, the major product was phthalimide (*ca.* 64% yield), and bromine was also liberated. With biphenyl as substrate, a mixture of *o*-, *m*-, and *p*-phthalimidobiphenyl was obtained in 70% yield. The *para*-isomer could be isolated by crystallisation from solvents, but, to show the presence of the *ortho*- and *meta*-isomers, the mixture was converted by hydrazinolysis into the corresponding mixture of aminobiphenyls. When analysed by gas chromatography, the mixture of amines afforded the *ortho* : *meta* : *para* ratio for substitution of the phthalimido-group into biphenyl. The average of five analyses from three experiments gave the distribution, *ortho*, 34·3; *meta*, 28·6; *para*, 36·4%. This distribution is different from that obtained in the phenylation of biphenyl with benzoyl peroxide [4] at 80° (*ortho*, 48·5; *meta*, 23·0; *para*, 28·5%), or with benzenesulphonyl chloride [5] at 256° (*ortho*, 47·0; *meta*, 28·5; *para*, 24·5%). A by-product of the phthalimidation of biphenyl was phthalimide, and while an exact weight balance was not obtained, the quantity of phthalimide roughly accounts for the discrepancy between the yields of sulphur dioxide and the phthalimidobiphenyl isomers.

N-Chlorophthalimide in an excess of boiling biphenyl, or of 1,2,4,5-tetrachlorobenzene, with or without a copper accelerator gave very low yields (*ca.* 1%) of the arylphthalimide. Chlorine was formed (less than 1% with biphenyl as substrate, but 14% with tetrachlorobenzene). From the amount of hydrogen chloride given off, much greater yields of the arylphthalimide could have been expected, but phthalimide was formed to an appreciable extent. Hence, *N*-chlorophthalimide is not an intermediate in phthalimidation with *N*-chlorosulphonylphthalimide.

It is known that *N*-chlorosulphonylphthalimide in the presence of benzoyl peroxide gives phthalimidosulphonyl radicals and chlorine atoms, which add to olefins [6] at 125—130°. At the higher temperatures of the aromatic substitutions described here (with no addition of peroxide), it appears that phthalimido-radicals and chlorine atoms are produced, with concomitant liberation of sulphur dioxide. The formation of bromine in the reaction of *N*-chlorosulphonylphthalimide with 1,4-dibromobenzene is in accord with the known displacement of nuclearly bound bromine by chlorine atoms.[7] The formation of phthalimide suggests that a phthalimido-radical abstracts hydrogen from the substrate or from an intermediate cyclohexadienyl radical. Such an intermediate, formed by the addition of the phthalimido-radical to the aromatic nucleus, should readily lose a hydrogen

[2] Williams, " Homolytic Aromatic Substitution," Pergamon Press, London, 1960, p. 122.
[3] Tilney-Bassett, *J.*, 1962, 2517; Heacock and Edmison, *J. Amer. Chem. Soc.*, 1960, **82**, 3460.
[4] Ref. 2, p. 68.
[5] Bain *et al.*, ref. 1.
[6] Kharasch and Moser, *J. Org. Chem.*, 1952, **17**, 453.
[7] Voegtli, Muhr, and Läuger, *Helv. Chim. Acta*, 1954, **37**, 1627; Miller and Walling, *J. Amer. Chem. Soc.*, 1957, **79**, 4187.

atom either to a chlorine atom or to a phthalimido-radical, leading to the formation of the arylphthalimide and hydrogen chloride or phthalimide. However, no evidence has been obtained on the mechanism of this reaction, other than that chlorine atoms appear to be involved and that therefore the phthalimido-radical must of necessity also be involved.

Further support for a free-radical reaction is given by the isomer ratios found in the phthalimidation of biphenyl. Whilst a high *meta*-substitution along with *ortho–para*-substitution may occasionally be found in heterolytic reactions, this is usually indicative of a free-radical substitution. However, a comparison of the isomer ratios for phthalimidation and phenylation of biphenyl suggests that the phthalimido-radical may be hindered in its approach to the *ortho*-position of biphenyl, the most reactive site.[8]

Comparison of the isomer ratios for phthalimidation and phenylation of biphenyl also shows that the phthalimido-radical must be electrophilic relative to the phenyl radical. If the radical were neutral, the lower degree of *ortho*-substitution would be expected to be reflected in increases in both *meta*- and *para*-substitution. In fact, the extent of *meta*-substitution is the same as for phenylation at 256°, indicating that *para*-substitution only has increased.

Experimental

Determination of Sulphur Dioxide and Hydrogen Chloride.—The reactions of *N*-chlorosulphonylphthalimide were carried out in an excess of the boiling substrate. A slow stream of dry nitrogen swept evolved gases, *via* an air condenser, to a trap containing 2N-sodium hydroxide (150 ml. for 1/15 mole of *N*-chlorosulphonylphthalimide). The solution in the trap was made up to 250 ml. and an aliquot part was added slowly to an excess of diluted 0·1N-iodine acidified with sulphuric acid, and the solution was back titrated with 0·1N-sodium thiosulphate to determine the amount of sulphur dioxide evolved. For the determination of the hydrogen chloride, an aliquot part of the solution, diluted and acidified with nitric acid, was briefly boiled to expel sulphur dioxide, cooled, neutralised with calcium carbonate, and titrated against 0·1N-silver nitrate with potassium chromate as indicator.

N-*Chlorosulphonylphthalimide.*—Potassium phthalimide and sulphuryl chloride in benzene gave *N*-chlorosulphonylphthalimide, m. p. 153—157°, by the method of Kharasch and Moser.[6] The product did not require recrystallisation from acetic acid, provided that the treatment of the benzene solution with hydrogen chloride was carried out with efficient stirring in order to decompose the *N*-chlorophthalimide formed as a by-product.

Phthalimidation of Biphenyl.—The commercial biphenyl used in all the experiments contained traces of metallic, and possibly organic, mpurities, which were shown to increase the rate of reaction in comparison with an experiment (not recorded here) where purified biphenyl was used. In the latter experiment, the yield was also lower, and less sulphur dioxide and hydrogen chloride were evolved than in the experiments described here. In the phthalimidations described under (*b*)—(*d*) below, a copper accelerator was added to ensure a satisfactory practical rate of reaction, independent of the amounts of trace impurities.

(*a*) Biphenyl (154 g.) and *N*-chlorosulphonylphthalimide (16·3 g.) were boiled under reflux, with a slow stream of dry nitrogen bubbling through the mixture to carry the evolved gases into a trap for determination as described above. After 1 hr., the evolution of sulphur dioxide was 79% and of hydrogen chloride 75%.

The mixture was fractionally crystallised from benzene to yield crude material (8·9 g.) which, crystallised from glacial acetic acid, gave 4-phthalimidobiphenyl, m. p. 296°. A mixed m. p. with the pure compound (prepared by heating 4-aminobiphenyl and phthalic anhydride at 160° for 3 hr.), was not depressed. The crude material (2·0 g.), in dioxan (25 ml.) containing hydrazine hydrate (1·0 ml.), was boiled for 15 min. to give a mixture, which was evaporated to dryness; and was partitioned between ether and dilute sodium hydroxide. The ethereal phase was evaporated to dryness to afford 4-aminobiphenyl, m. p. 51·5—52° on crystallisation from light petroleum. A mixture of this compound with a commercial sample of 4-aminobiphenyl showed no depression of m. p. (N.B. 4-Aminobiphenyl is a carcinogen).

(*b*) The phthalimidation was carried out as described under (*a*), but with the addition of cuprous chloride (100 mg.) and with the reaction time extended to 3 hr. Evolution of sulphur dioxide was 87% and hydrogen chloride 79%. The excess of biphenyl was distilled

[8] Brown, *J. Amer. Chem. Soc.*, 1953, **75**, 4077.

off at 126°/14 mm. from a bath at 160°, and the residue was set aside in petroleum (b. p. 40—60°) for 30 min. with occasional stirring to dissolve remaining traces of biphenyl. Decantation of the petroleum solution gave a mixture of phthalimidobiphenyls (13·5 g.). The isomeric mixture (10 g.) in 2-ethoxyethanol (500 ml.) was stirred with hydrazine hydrate (4·0 ml.) at the boiling point for 1 hr., and the mixture was distilled to dryness with stirring to avoid bumping. The residue was partitioned between dilute sodium hydroxide and ether, and the ethereal phase was washed with water and dried ($MgSO_4$). The ether was distilled off to yield a brown oil (6·0 g.) consisting of aminobiphenyl isomers (*o*-, 35·0; *m*-, 28·0; *p*-, 36·2%), determined as described under (*e*) below.

(*c*) In an experiment similar to that described under (*b*), the sulphur dioxide evolved was 87% and the hydrogen chloride was 81%. Excess of biphenyl was distilled off *in vacuo*, and traces of biphenyl were removed by steam-distillation. The mixture of phthalimidobiphenyl isomers (13 g.) was collected by filtration of the still contents, and the filtrates yielded crude phthalimide (2·3 g.) on evaporation to dryness. Treatment of the phthalimidobiphenyl mixture with hydrazine as above gave the mixture of aminobiphenyl isomers (*o*- 34·4, 35·6; *m*-, 28·0, 28·0; *p*-, 36·8, 35·8%) analysed as described under (*e*).

(*d*) In an experiment similar to that described under (*b*) the excess of biphenyl was distilled off *in vacuo* and needles of phthalimide (m. p. 231—235°) were collected from the lower part of the still head. The residue was treated with hydrazine in 2-ethoxyethanol, without removing the remaining traces of biphenyl, to give the mixture of aminobiphenyl isomers (*o*-, 33·3, 33·3; *m*-, 29·0, 29·8; *p*-, 37·0, 36·4%) analysed as described under (*e*).

(*e*) *Analysis of aminobiphenyl mixtures by gas chromatography.* The analysis was carried out in a Pye Argon Chromatograph on a stationary phase of 10% asphalt supported on Gas Crom P in a 4 ft. column of 4 mm. diameter, with an argon flow of 80 ml./min. at 160°. Calibration was carried out with known mixtures of the three isomers (the *ortho*- and *para*-isomers were commercial materials; the *meta*-isomer, m. p. 29—30°, was obtained by hydrogenation of 3-nitrobiphenyl, m. p. 59·5—60°, prepared by the procedure of Hwang Hsu [9]). The standard deviation of the method (*ca.* 2·5%) was determined with these mixtures. The average values for five analyses of the products of experiments (*b*)—(*d*) are given in the Discussion.

Reaction of N-*Chlorosulphonylphthalimide with* 1,4-*Dibromobenzene.*—*N*-Chlorosulphonylphthalimide (12·3 g.), copper naphthenate (0·6 ml. of a 6% solution in white spirit), and 1,4-dibromobenzene (119 g.) were boiled under reflux for 3 hr. with a slow stream of dry nitrogen passing through the mixture. The evolution of sulphur dioxide (85%) was complete after 1 hr., although during the remaining 2 hr. more hydrogen halide (*ca.* 6%) was liberated, bringing the total of hydrogen halide to *ca.* 70%. Bromine was also evolved, being carried over and condensing mainly in the gas line. Some bromine vapour reached the trap and complicated the determination of hydrogen chloride. Bromide ion (*ca.* 4% of the total halide ion) was found in the trap solution by the method of Summergill.[10]

The excess of dibromobenzene was distilled off at 110°/28 mm., from a bath at 150°, and traces of the substrate were removed by steam-distillation. The still contents were filtered hot, the filtrates yielding crystals of phthalimide (3·1 g.), m. p. 235—237°, on cooling. The dark solid (5·9 g.) was filtered off and extracted with benzene to yield crystals (2·1 g.), m. p. 190—200°, while further extraction with benzene gave phthalimide (0·85 g.) and an insoluble dark residue (0·74 g.). The crystals were crystallised twice from ethanol to yield N-(2,5-*dibromophenyl*)-*phthalimide* (0·7 g.), m. p. 221—221·5° (Found: C, 44·8; H, 1·9; Br, 41·5; N, 3·6. $C_{14}H_7Br_2NO_2$ requires C, 44·1; H, 1·9; Br, 41·9; N, 3·7%). The ethanolic mother-liquors yielded impure phthalimide (0·7 g.), and the benzene mother-liquors yielded impure dibromophenylphthalimide (0·4 g.), m. p. 215—217°.

Reaction of N-*Chlorosulphonylphthalimide with* 1,4-*Dichlorobenzene.*—*N*-Chlorosulphonylphthalimide (16·3 g.), 1,4-dichlorobenzene (100 g.), and copper naphthenate (0·6 ml. of a 6% solution in white spirit) were boiled under reflux (180°) intermittently during 4 days for a total of 25 hr. The sulphur dioxide and hydrogen chloride evolved were determined daily, and had fallen to a low level on the fourth day. The total sulphur dioxide trapped was 72%, and the hydrogen chloride 64%. The excess of dichlorobenzene was distilled off at 120° (bath)/45 mm., the dark residue was boiled with ethanol, and the mixture was cooled and filtered to separate any remaining dichlorobenzene. The crude brown product (17·2 g.) was crystallised from

[9] Hwang Hsu, *Acta Chim. Sinica*, 1959, **33**, 171—177; cf. Cadogan, *J.*, 1962, 4257.
[10] Summersgill, *Chem. and Ind.*, 1961, 783.

2-ethoxyethanol to give crystals (5·8 g.), m. p. 206—207°. Recrystallisation of a sample to constant m. p. gave *N*-(2,5-dichlorophenyl)phthalimide, m. p. 208—209° (Found: C, 57·6; H, 2·6; Cl, 24·3; N, 4·7. Calc. for $C_{14}H_7Cl_2NO_2$: C, 57·6; H, 2·4; Cl, 24·3; N, 4·8%). The m. p. 185—190°, recorded by Evans and Dehn,[11] appears to be erroneous.

Hydrazinolysis in boiling 2-ethoxyethanol yielded 2,5-dichloroaniline, m. p. 49·5—50° (lit.,[12] m. p. 50°), as needles from aqueous ethanol.

Reaction of N-*Chlorosulphonylphthalimide with* 1,3,5-*Trichlorobenzene.*—*N*-Chlorosulphonylphthalimide (10 g.) and trichlorobenzene (74 g.) were boiled under reflux (209°) for 5 hr. with the evolution of sulphur dioxide (1·2%) and hydrogen chloride (7·6%). After being kept at room temperature overnight, the mixture was treated with copper naphthenate (0·3 ml. of a 6% solution in white spirit) and was boiled under reflux for 5·5 hr., with a markedly increased rate of gas evolution, so that the total gases evolved over 10·5 hr. were, sulphur dioxide (79%) and hydrogen chloride (87%). The excess of trichlorobenzene was distilled off at 128°/75 mm., and the residue was triturated with carbon tetrachloride, leaving an insoluble solid (2·6 g.). The carbon tetrachloride solution was evaporated to dryness and the residue was recrystallised from methanol to yield *N*-(2,4,6-trichlorophenyl)phthalimide (2·5 g.), m. p. 179—180°. The arylphthalimide, m. p. 179—180° (from ethanol), was also obtained by heating trichloroaniline (1·0 g.) with phthalic anhydride (1·7 g.) at 170° (bath) for 3 hr. A mixed m. p. of the two products was undepressed.

The solid insoluble in carbon tetrachloride was extracted with ethanol in a Soxhlet apparatus, and the extract (1·5 g.), m. p. 207—214°, obtained by evaporation of the solvent, was recrystallised from ethanol to yield phthalimide, m. p. 234—236°. The insoluble residue from the Soxhlet extraction could not be crystallised.

Reaction of N-*Chlorosulphonylphthalimide with* 1,2,4,5-*Tetrachlorobenzene.*—*N*-Chlorosulphonylphthalimide (16·3 g.), 1,2,4,5-tetrachlorobenzene (144 g.), and cuprous chloride (70 mg.) were boiled under reflux (250°) for 9·5 hr. Sulphur dioxide (70%) and hydrogen chloride (57%) were evolved.

In an attempt to simplify isolation of the product, the reaction mixture was crystallised from benzene to yield a pale blue solid (83 g.) and a sample of this (10 g.) was steam-distilled to remove the residual substrate. The solid residue from the steam-distillation was collected by filtration, washed with water, dried, and washed with carbon tetrachloride to remove traces of substrate. The pale blue residue (0·5 g.), m. p. 285°, gave N-(2,3,5,6-*tetrachlorophenyl*)-*phthalimide* as needles (0·3 g.), m. p. 285—286°, from 2-ethoxyethanol (Found: C, 47·3; H, 1·5; Cl, 38·9; N, 3·6. $C_{14}H_5Cl_4NO_2$ requires C, 46·6; H, 1·4; Cl, 39·3; N, 3·9%).

To avoid the tedious steam-distillation, the above procedure was not used to obtain the remainder of the product. Only part (2·0 g.), m. p. 285—287°, could be obtained by fractional crystallisation of the remainder (73 g.) of the above mixture of substrate and product from carbon tetrachloride. Therefore, the benzene and the carbon tetrachloride mother-liquors were combined, and distilled to dryness, and the tetrachlorobenzene was distilled off at 174—184°/70 mm. The dark residue was treated with hot carbon tetrachloride to remove traces of tetrachlorobenzene (the gummy extract obtained by evaporation of the carbon tetrachloride solution yielded needles of phthalimide on extraction with water), and the residue (5·5 g.) gave the arylphthalimide (3·2 g.), m. p. 283—286°, by crystallisation from 2-ethoxyethanol.

The identity of the product was confirmed by hydrazinolysis in 2-ethoxyethanol which gave 2,3,5,6-tetrachloroaniline as long silky needles (1·35 g.), m. p. 109°, from ethanol (Found: C, 31·3; H, 1·1; Cl, 61·4; N, 6·1. Calc. for $C_6H_3Cl_4N$: C, 31·2; H, 1·3; Cl, 61·4; N, 6·1%). Peters *et al.*[13] recorded m. p. 107—108°; Dyson *et al.*[14] give m. p. 90°, but this appears to be erroneous.

Reaction of N-*Chlorophthalimide with Biphenyl.*—*N*-Chlorophthalimide[15] (9·1 g.) and biphenyl (77 g.) were boiled under reflux for 6 hr. A slow stream of dry nitrogen was passed through the reaction mixture to carry the gases evolved into a trap containing water, in which hydrogen chloride (*ca.* 25%) and chlorine (*ca.* 1%) were collected. The excess of biphenyl was removed by steam-distillation, 2N-sodium hydroxide (50 ml.) was added to the still contents (*ca.* 300 ml.), and the mixture was boiled for 2 hr. The solution was filtered from a small

[11] Evans and Dehn, *J. Amer. Chem. Soc.*, 1929, **51**, 3652.
[12] Graebe and Gourevitz, *Ber.*, 1900, **33**, 2025.
[13] Peters, Rowe, and Stead, *J.*, 1943, 372.
[14] Dyson, George, and Hunter, *J.*, 1926, 3044.
[15] Friedlander, "Fortschrifter der Teerfarben Fabrikation," Vol. 6, 1302.

amount of gummy solid, treated with decolourising charcoal, and acidified with concentrated hydrochloric acid to yield a grey precipitate (0·2 g.). Drying the precipitate in the oven caused cyclisation of the hydrolysis product (the mixed phthalamic acids), yielding a mixture, m. p. 109—120°, no longer soluble in dilute sodium hydrogen carbonate. Recrystallisation from glacial acetic acid gave a small quantity of impure (m. p. 285—286°) 4-phthalimidobiphenyl.

When the above reaction was repeated in the presence of copper naphthenate the evolution of hydrogen chloride was 56%, with a negligible amount of chlorine. The biphenyl was removed by steam-distillation and the still contents were filtered hot. Phthalimide (24% of theoretical) separated as needles when the filtrates were cooled, whilst the collected solid was treated with sodium hydroxide, etc., as above, to yield crude phthalimidobiphenyl (0·25 g.), m. p. 250—255°. Crystallisation from glacial acetic acid gave the *p*-isomer, m. p. 283°. The m. p. was undepressed when this product was mixed with the pure isomer prepared as described above.

Reaction of N-*Chlorophthalimide with* 1,2,4,5-*Tetrachlorobenzene*.—*N*-Chlorophthalimide (6·0 g.), 1,2,4,5-tetrachlorobenzene (72 g.), and cuprous chloride (33 mg.) were boiled under reflux while a slow stream of dry nitrogen was passed through the mixture to drive evolved gases into a trap containing water. Hydrogen chloride (16%) and chlorine (14%) were evolved during 6 hr. The excess of tetrachlorobenzene was distilled off under reduced pressure from an oil-bath, and remaining traces were removed by trituration with carbon tetrachloride at room temperature. The residue was extracted with hot benzene to give a residue of phthalimide (0·6 g.), m. p. 232—235°, and the benzene solution gave, on evaporation, crude *N*-(2,3,5,6-tetrachlorophenyl)phthalimide. Trituration of this crude product in acetone gave purer material (80 mg.), m. p. 278—283°, the m. p. being undepressed when this product was mixed with the pure compound prepared as described above.

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