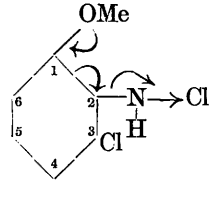
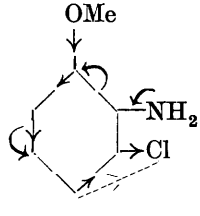
CCCXCIV.—*Halogenation of Anisole Derivatives.*

By Herbert Henry Hodgson and Arnold Kershaw.

When 3-chloro-2-nitroanisole is reduced with tin and hydrochloric acid, 3 : 5-dichloro-2-aminoanisole is obtained instead of the anticipated 3-chloro-2-aminoanisole, a result which, together with other cases subsequently cited, may be interpreted on current electronic theories (see especially Allan, Oxford, Robinson, and Smith, J., 1926, 401, and numerous papers by Robinson and by Ingold) as follows : The first stage of the reduction is probably the formation of 3 : *N*-dichloro-2-aminoanisole (I), in which, owing to the powerful electron-source effect of the methoxyl group, the *N*-chlorine is very labile, and is liberated as the free element in acid solution (compare Jones and Orton, J., 1909, **95**, 1056); this attacks the 5-position (II) owing to (i) the greater directive (alternating) influence of the amino- as compared with the methoxyl group, (ii)

(I.)





(II.)

the activation of carbon in the 5-position by a powerful inductive (suppressed alternating) effect of the methoxyl group (compare Hodgson and Jenkinson, this vol., p. 1640, who find exclusive substitution para to the hydroxyl group for the Reimer–Tiemann reaction with salicylic acid), and (iii) the assistance afforded by the chlorine in the 3-position owing to its relatively greater deactivation of the 4-position by the general (inductive) effect. Nitroanisoles are prone to give chlorinated products during this particular reduction process, for the competing pair of electron-source groups not only favour the chlorinating activity of the *N*-chloroamine (in acid solution) first formed, but also, by a combined alternating and direct effect, render exceedingly active the carbon in the position para to the stronger electron source.

In the case of 3-chloro-2-iodoanisole dichloride, which on keeping changes spontaneously into 3 : 4-dichloro-2-iodoanisole, the effective chlorinating agent is either the molecule itself or atomic or molecular chlorine. The intermediate product which is chlorinated is probably 3-chloro-2-iodoanisole, since the analogous intermolecular decomposition of iodobenzene dichloride produces 4-chloroiodobenzene,

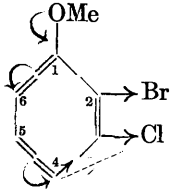
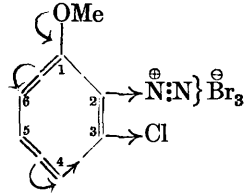
whereas, if the dichloride itself were chlorinated, the meta-directing influence of its dipole $-\overset{+}{\mathrm{I}}\begin{smallmatrix}\nearrow \mathrm{Cl}^{e/2} \\ \searrow \mathrm{Cl}^{e/2}\end{smallmatrix}$ (compare Ingold, *Ann. Reports*, 1926), would entail the formation of 3-chloroiodobenzene dichloride and hence of 3-chloroiodobenzene (or more highly chlorinated derivatives).

The 4-position in 3-chloro-2-iodoanisole is less deactivated by the halogens than in 3-chloro-2-bromoanisole (see below), whilst the kationoid reagent (probably nascent chlorine) is much stronger, so that exclusive chlorination of the 4-position is more probable than the exclusive bromination discussed in the next case (compare Lapworth and Robinson, *Mem. Manchester Phil. Soc.*, 1928, **72**, 43; also Ingold, Smith, and Vass, J., 1927, 1245, who found that *o*-iodoanisole dichloride was transformed into 4-chloro-2-iodoanisole). That 3 : 4-*dichloro*-2-*iodoanisole* is the sole product of reaction, has been established by its independent synthesis, and also by the preparation of 3 : 6-*dichloro*-2-*iodoanisole*, which has a different m. p.

Correction.—In a previous paper (J., 1928, 191) the authors stated that 3-chloroanisole-2-diazoperbromide was converted by boiling glacial acetic acid into 3-chloro-2 : 6-dibromoanisole, the statement being based partly upon the reasonable assumption that sulphonation of *m*-chlorophenol at 100° occurred almost exclusively in the para-position. It is now established that the sulphonation takes place chiefly in the 6-position, since on dibromination and subsequent desulphonation, 3-chloro-2 : 4-dibromophenol was obtained, its constitution being established by its mononitration to 3-chloro-2 : 4-dibromo-6-nitrophenol, identical with the product of dibromination of 3-chloro-6-nitrophenol. It follows that the diazoperbromide had been converted into 3-chloro-2 : 4-dibromoanisole, the second bromine atom having entered the 4-position, apparently exclusively.

The reaction mechanism for this third case of intermolecular halogenation would appear to be an initial decomposition of 3-chloroanisole-2-diazoperbromide into 3-chloro-2-bromoanisole and molecular or atomic bromine (free bromine was found in the solution, and it is improbable that the negative perbromide ion would act as a brominating agent), followed by bromination in the 4-position; the great velocity of this reaction is evidence in favour of such initial decomposition. That the 4- and not the 6-position should be attacked by bromine is consistent with the general considerations advanced by Lapworth and Robinson (*loc. cit.*) for the ortho-para ratio in aromatic substitutions, *viz.*, that the methoxyl group activates the 6- and 4-positions by the alternating effect (III), the former more strongly and the latter more frequently; further,

that the halogens deactivate the whole molecule by the general effect (inductive and direct), the bromine in the activated phase

(III.)   (IV.)

(III) diverting part of the methoxyl-group effect, and the chlorine deactivating principally the 4-position. Thus, whilst the 4- and 6-positions suffer diminution of activity, the strong kationoid reagent (probably nascent bromine) takes advantage of the more frequent activations of the 4-position, which may perhaps be less affected by steric hindrance. If direct bromination of 3-chloroanisole-2-diazoperbromide occurred simultaneously, then the 6-position should undergo preferential attack, since the powerful positive pole (IV) will weaken the activation of the molecule by the methoxyl group far more than does the bromine in (III), so that if any bromination can occur at all, some must be at the 6-position. That bromination occurs only in the 4-position is evidence in support of 3-chloro-2-bromoanisole being the actual intermediate which is subsequently brominated.

Experimental.

Reduction of 3-Chloro-2-nitroanisole with Tin and Concentrated Hydrochloric Acid.—The usual procedure gave an amine volatile in steam, which appeared from analysis to be mainly a dichlorinated product. Replacement of the amino-group with chlorine by means of the Sandmeyer reaction gave a product which crystallised from alcohol in colourless needles, m. p. 84° (Found : Cl, 50·3. Calc. for $C_7H_5OCl_3$: Cl, 50·4%), identical with the 2 : 3 : 5-trichloroanisole prepared by direct synthesis.

Synthesis of 2:3:5-Trichloroanisole.—(1a) *Separation of 3-chloro-4- and -6-nitroanilines.* To an ice-cold solution of *m*-chloroacetanilide (62 g.) in glacial acetic acid (62 c.c.) and concentrated sulphuric acid (100 c.c.), nitric acid (20 c.c.; *d* 1·5) was added in such wise that the temperature did not exceed 15°. After being kept over-night, the mixture was poured on ice (1000 g.), the precipitated 3-chloro-4- and -6-nitroacetanilides were filtered off, heated for 30 minutes on the water-bath with concentrated hydrochloric acid (400 c.c.) and water (100 c.c.), and then neutralised by sodium hydroxide and steam distilled; the slowly volatile 3-chloro-6-nitroaniline was completely removed only after several litres of

distillate had been collected. The tarry non-volatile residue was extracted with boiling dilute hydrochloric acid (200 c.c. each of concentrated acid and water), the solution filtered, and the 3-chloro-4-nitroaniline (12 g.) precipitated from it by means of ammonia.

(1b) *Alternative separation.* The mixture of amines, after hydrolysis of the mixed acetanilides, was neutralised with ammonia and the solid precipitate dissolved in the minimal amount (about 350 c.c.) of boiling alcohol; on cooling, almost all the 3-chloro-4-nitroaniline (20 g.) separated from the solution in practically pure condition.

(2) 2 : 3 : 6-*Trichloro-4-nitroaniline.* 3-Chloro-4-nitroaniline (11 g.) was ground with pure concentrated hydrochloric acid (63 c.c.), the mixture heated to 50°, and finely powdered potassium chlorate (5·1 g.) added with vigorous stirring at a rate sufficient to maintain the temperature at 50°. After 2 hours' standing, the 2 : 3 : 6-*trichloro-4-nitroaniline* (14 g.) was filtered off and washed with water; it crystallised from glacial acetic acid in yellow needles, m. p. 143° (Found : Cl, 43·9. $C_6H_3O_2N_2Cl_3$ requires Cl, 44·1%).

(3a) 2 : 3 : 5-*Trichloronitrobenzene.* Sodium nitrite (7 g.) was added in small portions (after each effervescence had ceased) to a boiling solution of 2 : 3 : 6-trichloro-4-nitroaniline (11 g.) in alcohol (63 c.c.) and concentrated sulphuric acid (13 c.c.). The 2 : 3 : 5-*trichloronitrobenzene* (8 g.) was removed by steam distillation, and, after repeated crystallisation from 80% alcohol, was obtained in very pale yellow, flat needles, m. p. 45° (Found : Cl, 46·8. $C_6H_2O_2NCl_3$ requires Cl, 47·0%).

(3b) A much purer initial product was obtained by the following method. 2 : 4-Dichloroaniline (46 g.) was heated with acetic anhydride (29 c.c.) for 1 hour on the water-bath, the mixture poured into glacial acetic acid (40 c.c.) and cooled, concentrated sulphuric acid (90 c.c.) added, and nitration effected below 20° by addition of nitric acid (30 c.c.; *d* 1·5) during 1 hour. The fine crystals of 2 : 4-dichloroacetanilide dissolved during the nitration, and, after being kept over-night, the clear solution was poured on ice, giving a theoretical yield of 2 : 4-dichloro-6-nitroacetanilide, m. p. 188° (Witt, *Ber.*, 1874, **7**, 1603, gives m. p. 188°). This product was hydrolysed by 30 minutes' boiling with 50% sulphuric acid (300 g.), and the 2 : 4-dichloro-6-nitroaniline was precipitated by dilution with water and crystallised from alcohol (yield, 36 g.); m. p. 102° (Langer, *Annalen*, 1882, **215**, 111, gives m. p. 100°). 2 : 3 : 5-Trichloronitrobenzene was obtained by dissolving the foregoing nitroaniline (26 g.) in glacial acetic acid (20 c.c.), pouring the mixture into hot concentrated hydrochloric acid (100 c.c.), chilling it to 0°, diazotising it with sodium nitrite (10 g.), and following the usual

Sandmeyer procedure. The product (yield, 19 g.) formed almost colourless needles (from alcohol), m. p. 45°, unaltered on admixture with material obtained as in (3a).

(4) 2 : 3 : 5-*Trichloroaniline*. Iron filings (4 g.) were gradually added to a solution of 2 : 3 : 5-trichloronitrobenzene (7 g.) in glacial acetic acid (20 c.c.) and water (20 c.c.). After the vigorous reaction had abated, the mixture was heated on the water-bath, made slightly alkaline, and steam distilled; the 2 : 3 : 5-*trichloroaniline* (5 g.) that passed over crystallised from light petroleum in colourless needles, m. p. 73° (Found : Cl, 54·4. $C_6H_4NCl_3$ requires Cl, 54·2%).

(5) 2 : 3 : 5-*Trichlorophenol*. 2 : 3 : 5-Trichloroaniline (10 g.) in glacial acetic acid (20 c.c.) was added to a mixture of sulphuric acid (40 g.) and water (40 c.c.), cooled to 0°, and diazotised by addition of a large excess of sodium nitrite (7 g.). The excess of nitrous acid was destroyed by means of urea, and the clear solution dropped gradually into boiling 70% sulphuric acid through which steam was passing. After nearly all the water had been removed, the 2 : 3 : 5-trichlorophenol came over as an oil which soon solidified; yield, 7 g.; m. p. 62° (Found : Cl, 53·7. Calc. : Cl, 53·9%). The product is peculiar in giving oils or gels when dissolved in hot solvents and allowed to cool, a very dilute hot aqueous solution setting when cold to an almost solid translucent gel (compare Holleman, *Rec. trav. chim.*, 1920, **39**, 736), partly fibrous and probably partly crystalline. When a solution of potassium dichromate is poured on such a gel containing silver nitrate, distinct but not well-defined Liesegang rings are produced in the gel.

(6) 2 : 3 : 5-*Trichloroanisole*. The foregoing phenol (1·5 g.), dissolved in 20% aqueous sodium hydroxide (20 c.c.), was shaken with methyl sulphate (5 g.) until the solid ether separated (1·5 g.); this crystallised from alcohol in colourless needles, m. p. 84° (Holleman, *loc. cit.*, gives m. p. 82°) (Found : Cl, 50·2. Calc. : Cl, 50·4%).

Intermolecular Halogenation in 3-*Chloro*-2-*iodoanisole Dichloride*.

3-*Chloro*-2-*iodoanisole dichloride* was prepared by passing chlorine into a solution of 3-chloro-2-iodoanisole (5 g.) in chloroform (15 c.c.) until absorption ceased; during the operation the product crystallised from the solution in minute bright yellow prisms, m. p. 72° (decomp.) (0·0987 G. gave 0·1941 g. of silver halides. Calc. : 0·1935 g.). When kept over-night, it was transformed into 3 : 4-dichloro-2-iodoanisole, which crystallised from alcohol in colourless needles, m. p. 84° (0·0886 G. gave 0·1540 g. of silver halides. Calc. : 0·1526 g.).

Synthesis of 3 : 4-*Dichloro*-2-*iodoanisole*.—(1) 1 : 2-Dichloro-4-

nitrobenzene was prepared by adding *o*-dichlorobenzene (57 g.) gradually (1 hour) with vigorous stirring to a cooled mixture of nitric acid (150 c.c.; *d* 1·5) and concentrated sulphuric acid (80 c.c.), the temperature being kept at or below 0°. After a further 6 hours' stirring, the reaction mixture was poured on ice, and the precipitated 1 : 2-dichloro-4-nitrobenzene removed and crystallised from the minimum amount of boiling alcohol (300 c.c.). Yield, 50 g.

(2) The above product (50 g.), dissolved in hot glacial acetic acid (90 c.c.) and water (90 c.c.), was reduced by the gradual addition of iron powder (32 g.); the mixture was heated on the water-bath for 1 hour after abatement of the reaction, then made alkaline with sodium hydroxide (60 g.), and the 3 : 4-dichloroaniline removed by steam distillation and converted into 3 : 4-dichlorophenol by our standard process (Hodgson, E.P. 200,714). Yield 32 g.; colourless needles from light petroleum, m. p. 65° (D.-R.P. 156333 gives m. p. 64—65°) (Found : Cl, 43·3. Calc. : Cl, 43·5%).

(3) 3 : 4-Dichlorophenol (17 g.) was heated with a solution of oleum (34 g.; 25% SO_3) and concentrated sulphuric acid (20 g.) on the water-bath until the mixture solidified. When cold, the product was ground with concentrated sulphuric acid (20 c.c.), and the paste treated gradually with a solution of nitric acid (5·1 c.c.; *d* 1·5) in oleum (21 c.c.; 25%). The solid passed into solution with rise of temperature, and the mixture was kept over-night, then diluted with water (30 c.c.) and hydrolysed during steam distillation; the 3 : 4-*dichloro*-2-*nitrophenol* (15 g.) which passed over crystallised from light petroleum in yellow needles, m. p. 76° (Found : Cl, 33·9. $C_6H_3O_3NCl_2$ requires Cl, 34·1%).

(4) 3 : 4-Dichloro-2-nitrophenol (13 g.) was dissolved in xylene (30 c.c.), potassium carbonate (12 g.) added, and the mixture heated on the water-bath during the gradual addition of methyl sulphate (15 g.). After being refluxed for 6 hours, the mixture was made just alkaline and cooled, and the solid 3 : 4-dichloro-2-nitroanisole (6 g.) filtered off; it crystallised from alcohol in flat colourless needles, m. p. 126° (Found : Cl, 31·8. Calc. : Cl, 32·0%) (Meldola and Eyre, J., 1902, **81**, 997, give m. p. 128°).

(5) 3 : 4-Dichloro-2-aminoanisole was prepared from the above nitro-compound by reduction with iron and acetic acid. It was volatile in steam and was readily converted by the usual diazotisation-iodination method into 3 : 4-*dichloro*-2-*iodoanisole*, which crystallised from alcohol in colourless needles, m. p. 84° (0·1045 G. gave 0·1832 g. of silver halides. Calc. : 0·1800 g.), and was shown (mixed m. p. determination) to be identical with the product of transformation of 3-chloro-2-iodoanisole dichloride.

Synthesis of 3 : 6-*Dichloro*-2-*iodoanisole*.—2 : 5-Dichlorophenol

(16 g.), sulphuric acid (20 g.), and oleum (32 g.; 25% SO_3) were heated for 30 minutes on the water-bath. The partly solid mixture was cooled, and nitrated by gradual addition to it of a solution of nitric acid (2·4 c.c.; *d* 1·5) in oleum (10 c.c.; 25% SO_3), the temperature being allowed to rise until all the solid had dissolved. After standing over-night, the mixture was diluted with water (20 c.c.) and hydrolysed in a current of steam; 3 : 6-*dichloro*-2-*nitrophenol* (18 g.) passed over in a semi-liquid state, and was extracted by ether from the cooled distillate. It crystallised from light petroleum in yellow prisms, m. p. 70° (Found : Cl, 34·4. $C_6H_3O_3NCl_2$ requires Cl, 34·1%).

3 : 6-*Dichloro*-2-*nitroanisole* (9·5 g.) was obtained from the above phenol (14 g.) by the methylation procedure detailed on p. 2921. It is volatile in steam and crystallises from alcohol in colourless prisms, m. p. 70° (Found : Cl, 31·9. $C_7H_5O_3NCl_2$ requires Cl, 32·0%).

3 : 6-Dichloro-2-aminoanisole was obtained by reduction of this nitro-compound with iron filings and dilute acetic acid, removed as an oil by steam distillation, and converted into the *hydrochloride*, which crystallised from water in colourless needles (Found : Cl, 46·4. $C_7H_7ONCl_2,HCl$ requires Cl, 46·6%).

3 : 6-*Dichloro*-2-*iodoanisole*, prepared from the aminoanisole by the usual diazotisation-iodination procedure, crystallised from light petroleum (cooled by a freezing mixture) in needles, m. p. 21° (0·1122 G. gave 0·1953 g. mixed silver halides. Calc. : 0·1933 g.).

Monosulphonation of m-*Chlorophenol at* 100°. *Formation of* 3-*Chlorophenol*-6-*sulphonic Acid.*—*m*-Chlorophenol (6·5 g.) was heated for 8 hours at 100° with pure sulphuric acid (12 g.), the cooled mixture poured on ice (20 g.), and the solution diluted to 80 c.c. and treated with bromine (5 c.c.). The mixture was kept for 4 hours, the by-product, 3-chloro-2 : 4 : 6-tribromophenol (less than 1 g.), filtered off, sulphuric acid (30 c.c.) added, and the solution boiled during the passage of steam through it. The volatile product (9 g.) was identified as 3-chloro-2 : 4-dibromophenol by nitration to 3-chloro-2 : 4-dibromo-6-nitrophenol (8 g. of pure material), identical with the product produced by dibromination of 3-chloro-6-nitrophenol.

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