Metal Ions and Complexes in Organic Reactions. Part X.[1] Effect of Methoxy-substituents on Copper-catalysed Nucleophilic and Reductive Replacement of Halogen in Reactions between Sodium Methoxide and Bromo- or Iodo-benzene Derivatives

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Seventeen bromo- and seventeen iodo-benzene derivatives, of general formula $C_6H_{5-n}(OMe)_nHal$, were subjected to reaction with sodium methoxide, catalysed by copper(I) iodide, in 2,4,6-collidine solution. Competition occurred between nucleophilic substitution, giving $C_6H_{5-n}(OMe)_{n+1}$, and reductive substitution, giving $C_6H_{6-n}(OMe)_n$. When neither position *ortho* to the halogen was occupied by a methoxy-group, reduction was negligible; when one *ortho*-position was thus occupied, the extent of competitive reduction increased as the number of methoxy-substituents increased; when both *ortho*-positions were thus occupied, reduction was the dominant reaction. In general, the iodides were more responsive to reduction than the bromides. The efficiency of formation of some polymethoxybenzenes gives the process practical value.

It has previously been reported that copper species catalyse reactions in organic solvents between sodium alkoxides and aryl bromides or iodides. Employment of a solution of copper(I) iodide [1] favoured nucleophilic substitution by methoxide (ArHal ⟶ ArOMe) whereas employment of a suspension of cuprous oxide [2] favoured reductive substitution by methoxide (ArHal ⟶ ArH). The copper(I) iodide-catalysed reaction proved to be widely applicable for conversions of the type $C_6H_4XBr \longrightarrow C_6H_4X\cdot OMe$ and gave highest yields when X was an alkyl, alkoxy-, or carboxy-group.[1] We have now tested a series of halides, $C_6H_{5-n}X_nHal$, with the object of discovering how their copper iodide-catalysed reactions with methoxide are affected by variations in the number and position of X, where $X = OCH_3$, Hal = Br, or I, and $n = 1$—5.

In a survey of this kind it is desirable to look for trends in a wide range of examples, since limited reproducibility is often a feature of copper-catalysed substitutions. In the case of bromides and iodides, there are 38 compounds of the general formula $C_6H_{5-n}(OMe)_nHal$. Most of these (17 bromo- and 17 iodo-compounds) were tested. The required methoxy-halides were synthesised by a variety of known methods, including (for bromination) use of *N*-bromosuccinimide in carbon tetrachloride,[3] and (for iodination) use of iodine–mercuric oxide,[4] iodine–silver trifluoroacetate,[5] and iodine–hydrogen peroxide–sulphuric acid.[6] All but four of the compounds were known. We failed to synthesise the unknown 1-bromo-(or 1-iodo-)2,3,5,6-tetramethoxybenzene; end-products of the bromination of 1,2,4,5-tetramethoxybenzene or 1,4-dihydroxy-2,5-dimethoxybenzene appeared to be quinones. This and other examples of quinone formation by reaction of halogens with methoxy-compounds have recently been studied by McOmie and his co-workers.[7]

Rates of reaction at *ca.* 110°, in systems of the type ArBr (or ArI)–NaOMe–MeOH–CuI–collidine, were briefly examined. Reaction was fast (complete in < 1 hr.) when Ar was 1-naphthyl; variable ease of conversion was observed in compounds of the type *o*-, *m*-, or *p*-C_6H_4XBr ($X = CO_2Me$, *ca.* 100% ArBr consumed in 1 hr.; OH or OMe, *ca.* 70%; Me, *ca.* 50%; Cl, *ca.* 20%). The members of the series of methoxy- and polymethoxy-

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[1] Part IX, R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc.* (*C*), 1969, 312.

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[3] R. A. B. Bannard and G. Latremouille, *Canad. J. Chem.*, 1953, **31**, 469.

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[5] D. E. Janssen, J. Van Allan, and C. V. Wilson, *J. Org. Chem.*, 1955, **20**, 1326.

[6] G. K. Hughes, K. G. Neill, and E. Ritchie, *Austral. J. Sci. Res.*, 1950, **3**, *A*, 497.

[7] J. F. W. McOmie *et al.*, forthcoming publication; *cf.* reaction of 1,2,4,5-tetramethoxybenzene with iodine [D. W. Lawson, J. F. W. McOmie, and D. E. West, *J. Chem. Soc.* (*C*), 1968, 2414] and reaction of 2,3-dimethoxybiphenylene with bromine (J. M. Blatchly, D. V. Gardner, J. F. W. McOmie, and M. L. Watts, *ibid.*, 1968, 1545).

bromides and iodides were treated for much longer periods (15—20 hr.), under conditions summarised in the Table.

The conversion of *p*-bromoanisole into *p*-dimethoxybenzene had previously been achieved under similar conditions in almost quantitative yield.[1] When the copper iodide-catalysed reaction with other methoxyhalides follows the same course, *i.e.*, is entirely or largely the nucleophilic substitution [reaction (1)], the process is useful for the synthesis of polymethoxybenzenes, and hence of polyhydric phenols which may be obtainable from them. However, as the Table shows, reductive substitution [reaction (2)] was competitive or dominant in the case of many members of the series.

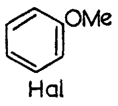
$$\begin{tikzcd} & C_6H_{5-n}(OMe)_{n+1} + Hal^- \quad (1) \\ C_6H_{5-n}Hal(OMe)_n + MeO^- \arrow[ur, "(CuI)"] \arrow[dr] & \\ & C_6H_{6-n}(OMe)_n + Hal^- + CH_2O \quad (2) \end{tikzcd}$$

The Table shows that yields of products from reaction (1), or from (1) plus (2), were in the range *ca.* 70—100%. Values quoted for yields are average figures from two or more runs. Deviation from the quoted mean averaged ±4% in nucleophilic substitutions (1) and ±2% in reductive substitutions (2). In some cases the deviation was zero, but it was occasionally about ±10%. Poor reproducibility could be attributed to variations in relative rates of reactions (1) and (2), or to imperfect chromatographic separation of the two types of product.

TABLE

Reaction between $C_6H_{5-n}Hal(OMe)_n$ (0·01 mole; $n = 1$—5), NaOMe (0·03 mole; in MeOH), and CuI (0·005 mole), in refluxing 2,4,6-collidine, for 15—20 hr., under N_2, giving $C_6H_{5-n}(OMe)_{n+1}$ and $C_6H_{6-n}(OMe)_n$; figures show, respectively, yield (%) of methoxy-substituted product; yield (%) of reduced product; and approximate ratio of methoxy-substituted to reduced product

A



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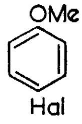
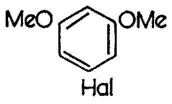
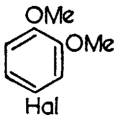
Hal = I: 91, 0, 1/0;



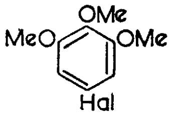
89, 0, 1/0;
95, 0, 1/0;



70, 0, 1/0;
75, 0, 1/0;

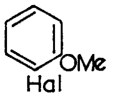


70, 3, 1/0·04;
70, 2, 1/0·03;



56, 0, 1/0
70, 0, 1/0

B



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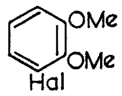
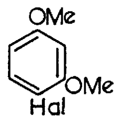
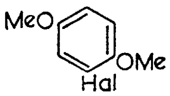
Hal = I: 68, 0, 1/0;



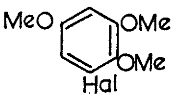
63, 9, 1/0·15;
57, 14, 1/0·25;



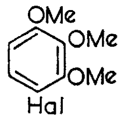
53, 27, 1/0·5;
43, 34, 1/0·8;



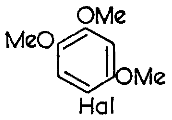
65, 8, 1/0·1;
62, 12, 1/0·2;



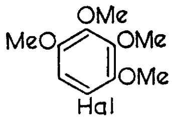
66, 14, 1/0·2;



50, 39, 1/0·8;
49, 37, 1/0·8;

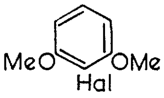


60, 18, 1/0·3;
45, 28, 1/0·6;



63, 22, 1/0·35
32, 55, 1/1·7

C



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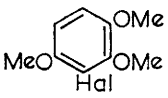
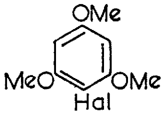
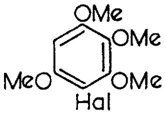
Hal = I: 13, 58, 1/4·5;



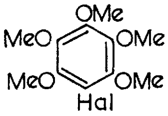
48, 50, 1/1·0;
24, 53, 1/2·2;



23, 64, 1/2·8;
12, 82, 1/6·8;



26, 50, 1/1·9;
24, 56, 1/2·3;



23, 77, 1/3·3

A pattern of reactivity is evident when the results are arranged in three series, as shown in the Table.

When neither position *ortho* to the halogen atom was occupied (series A), nucleophilic substitution was virtually the sole reaction. The occupation of *meta*- and/or *para*-positions by methoxy-groups then had negligible effect in promoting reduction.

When only one *ortho*-methoxy-group was present (series B), no reduction was detected in the absence of other substituents, but reduction made a substantial contribution when the *ortho*-group was reinforced by methoxy-groups in *meta*- and/or *para*-positions. Broadly, the relative amount of reduction increased towards parity with nucleophilic substitution as the number of substituents was increased; there was some indication of *para*-substitution being particularly effective.

When both positions *ortho* to the halogen atom were occupied by methoxy-groups (series C), reduction was the dominant reaction, both in the presence and in the absence of *meta*- and/or *para*-methoxy-substituents.

In all three series, employment of an iodo-compound in place of the corresponding bromo-compound generally led to an increase in the amount of reduction relative to that of nucleophilic substitution. For the nine cases in which this effect was observed, the difference (ArI $\longrightarrow$ ArH compared with ArBr $\longrightarrow$ ArH) averaged 9%. An earlier observation of the same kind [1] was that a minor amount of reduction competed with substitution in the reaction system $1\text{-}C_{10}H_7I$–NaOMe–MeOH–CuX–collidine, but not in the corresponding system involving $1\text{-}C_{10}H_7Br$.

So far as the results in the Table are concerned, reactions leading to methyl ether formation might be regarded as copper-assisted nucleophilic displacements of halide by methoxide ion, whilst competing reductions might be regarded either as copper-assisted displacements of halide by hydride ion (donated by methoxide) or as homolytic processes involving an intermediate aryl radical and an oxidation–reduction cycle in the copper species.[2] The complex pattern of results emerging presumably reflects differences in response of the nucleophilic and reductive modes of reaction to steric and polar effects of nuclear methoxy-substituents. Further studies of substituent effects in copper-catalysed reactions are being undertaken.

EXPERIMENTAL

Methoxy-halides.—The bromo- and iodo-anisoles were commercial samples. Other methoxy-halides (listed in the order shown in the Table) were prepared as follows. M.p.s are recorded only in cases where an observed value (Kofler hot-stage) was higher than the recorded value.

(A) 1-Bromo-,[8] and 1-iodo-3,5-dimethoxybenzene: [9] *via* 3,5-dimethoxyaniline, which was synthesised from 3,5-dimethoxybenzoic acid.[8] 1-Bromo-,[3] and 1-iodo-3,4-dimethoxybenzene: [5] from 1,2-dimethoxybenzene by treatment in carbon tetrachloride, respectively, with *N*-bromosuccinimide or iodine–silver trifluoroacetate. 1-Bromo-3,4,5-trimethoxybenzene, m.p. 78·5—80·0° (lit.,[10] 78°; lit.,[11] 112°) and 1-iodo-3,4,5-trimethoxybenzene, m.p. 86—87° (lit.,[12] 82—83°): *via* 3,4,5-trimethoxyaniline, synthesised [12] from the trimethyl ether of gallic acid.

(B) 1-Bromo-2,3-dimethoxybenzene, m.p. 25—275·° (lit.,[13] 22·7—23·2°) and 1-iodo-2,3-dimethoxybenzene: [14] *via* 2,3-dimethoxyaniline, which was synthesised from 2,3-dimethoxybenzoic acid.[14] 1-Bromo- [15] and 1-iodo-2,4-dimethoxybenzene: [16] from 1,3-dimethoxybenzene by respective treatment with *N*-bromosuccinimide in carbon tetrachloride,[3] or with iodine and mercuric oxide in benzene.[4] 1-Bromo- [17] and 1-iodo-2,5-dimethoxybenzene: [18] from 1,4-dimethoxybenzene by respective treatment with bromine in acetic acid, or with iodine and silver trifluoroacetate in carbon tetrachloride; [5] by-products were 1,4-dibromo-2,5-dimethoxybenzene, m.p. 147—148° (lit.,[19] 142°) and 1,4-di-iodo-2,5-dimethoxybenzene, m.p. 172—173° (lit.,[18] 171°). 1-Bromo-2,3,5-trimethoxybenzene: by modification of a method [6] involving oxidation of 5-bromovanillin, under nitrogen, in aqueous potassium hydroxide, with aqueous hydrogen peroxide, followed by reaction with dimethyl sulphate; corresponding treatment of 5-iodovanillin failed to give the analogous iodo-compound. 1-Bromo- [20] and 1-iodo-2,3,4-trimethoxybenzene: [20] by respective treatment of pyrogallol trimethyl ether with *N*-bromosuccinimide in carbon tetrachloride,[3] or, as a melt, with iodine and mercuric oxide.[20] 1-Bromo- [21] and 1-iodo-2,4,5-trimethoxybenzene: [6] by respective treatment of 1,2,4-trimethoxybenzene with bromine in acetic acid or with iodine and mercuric oxide in benzene. 1-*Bromo*-2,3,4,5-*tetramethoxybenzene*, m.p. 35—36° (from pentane) (Found: C, 43·5; H, 4·7; Br, 28·85. $C_{10}H_{13}BrO_4$ requires C, 43·3; H, 4·7; Br, 28·8%) was prepared (86%) by reaction of 1,2,3,4-tetramethoxybenzene with *N*-bromosuccinimide in refluxing carbon tetrachloride. The 1,2,3,4-tetramethoxybenzene [22] was obtained (45%; m.p. 88°) by a larger-scale repetition of the copper iodide-catalysed reaction shown for its preparation in the Table. Reaction with iodine, hydrogen peroxide, and sulphuric acid converted 1,2,3,4-tetramethoxybenzene into 1-iodo-2,3,4,5-tetramethoxybenzene.[6]

(C) 1-Bromo- [23] and 1-iodo-2,6-dimethoxybenzene: [24] *via* 2,6-dimethoxyaniline, which was synthesised from resorcinol.[24,25] 1-Iodo-2,3,6-trimethoxybenzene: by metalation of 1,2,4-trimethoxybenzene in ether solution with a solution of n-butyl-lithium in hexane and treatment of the product with iodine.[26] Similar reaction of the metalated compound was carried out with bromine in hexane; from the crude product resulting from this vigorous reaction 1-*bromo*-2,3,6-*trimethoxybenzene*, m.p. 77—78° (from pentane) (Found: C, 44·5; H, 4·5; Br, 31·9. $C_9H_{11}BrO_3$ requires C, 43·7; H, 4·5; Br, 32·3%) was isolated. Its i.r. spectrum was almost identical with that of the corresponding iodo-compound. The bromo-compound showed the following n.m.r. characteristics: a low-field AB quartet [τ_A 3·34 (1H), τ_B 3·56 (1H), J_{AB} 9·0 c./sec.] and a singlet at 6·24 (9H). It was necessary to isolate the bromo-compound (*ca.* 20%) by chromatography on a large column of silica gel, which also

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gave (in yields of *ca.* 20%) liquid 1,2,4-trimethoxybenzene, and the isomeric 1-bromo-2,4,5-trimethoxybenzene, m.p. 52—53°, the formation of which was attributed to direct bromination of the aromatic nucleus. 1-Bromo-[27] and 1-iodo-2,4,6-trimethoxybenzene, m.p. 122—123° (lit.,[28] 119—121°): by respective treatment of 1,3,5-trimethoxybenzene with bromine in chloroform, or with iodine and mercuric oxide in benzene. 1-Bromo-[29] and 1-iodo-2,3,4,6-tetramethoxybenzene, m.p. 55—56° (lit.,[30] 52—53°): from 1,2,3,5-tetramethoxybenzene,[31] by respective treatment with *N*-bromosuccinimide in carbon tetrachloride, or iodine and mercuric oxide in benzene. *Bromopentamethoxybenzene*, m.p. 46° (from light petroleum) (Found: C, 43·1; H, 4·7; Br, 26·2. $C_{11}H_{15}BrO_5$ requires C, 43·0; H, 4·9; Br, 26·0%) was prepared (95%) from pentamethoxybenzene[31] by treatment with *N*-bromosuccinimide in refluxing carbon tetrachloride. *Iodopentamethoxybenzene*, m.p. 50—51° (from light petroleum) (Found: C, 37·1; H, 4·4; I, 35·7. $C_{11}H_{15}IO_5$ requires C, 37·3; H, 4·3; I, 35·8%) was prepared from pentamethoxybenzene by the method used for 1-iodo-2,3,4,5-tetramethoxybenzene.

Attempted Preparation of 1-*Bromo- or* 1-*Iodo*-2,3,5,6-*tetramethoxybenzene*.—Treatment of 1,2,4,5-tetramethoxybenzene over long periods (*e.g.* 18 hr.) with bromine in chloroform, acetic acid, or methanol yielded insoluble yellow or brown solids, free of bromine and apparently quinonoid. Similar products were obtained by reaction of 1,4-dihydroxy-2,5-dimethoxybenzene with bromine or *N*-bromosuccinimide. Bromination of 1,2,4,5-tetramethoxybenzene for short periods (*e.g.* 45 min. in chloroform) led to precipitation of impure and unstable brown solid, m.p. *ca.* 145°, containing *ca.* 2 bromine atoms per molecule. In air it evolved acidic fumes and gave quinonoid material. It regenerated 1,2,4,5-tetramethoxybenzene if chromatographed on silica gel, or if recrystallisation was attempted in acetone, or if determination of the n.m.r. spectrum was attempted for solutions in hexadeuterioacetone or dimethyl sulphoxide.

1,2,4,5-Tetramethoxybenzene likewise yielded a brown quinonoid solid when treated with iodine and mercuric oxide in benzene. Metalation of the tetramethoxybenzene with n-butyl-lithium, followed by treatment with iodine, gave a mixture of two products.

Reaction of Methoxy-halides with Sodium Methoxide.—The following standardised procedure was used. The reaction flask was charged with magnesium-dried methanol (10—12 ml.). Reaction with freshly cut sodium (0·69 g., 0·03 mole) was allowed to proceed under dry nitrogen. The resulting sodium methoxide solution was diluted with 2,4,6-collidine (35 ml.), b.p. 170—172°, which had previously been purified by heating with barium oxide under reflux and distilling under nitrogen. Copper(I) iodide (commercial reagent, previously dried at 90°/0·5 mm. in the presence of silica gel) (0·95 g., 0·005 mole) and the methoxy-halide (0·01 mole) were added to the solution, which was then heated to boiling under a reflux condenser while a slow stream of dry nitrogen was passed through the apparatus. The temperature of the solution was generally 105—110° at this stage (if lower, it was raised by distilling off some of the methanol), but during the period of reaction (14—18 hr.) the nitrogen stream caused a slow displacement of methanol, and the temperature rose towards 170°. Initially the solution was generally light orange-brown in colour, but it progressively darkened as reaction proceeded, finally becoming transparent and practically colourless, while a red-brown inorganic crust was deposited.

The cooled, filtered mixture was acidified by addition to 5N-hydrochloric acid (150 ml.), the temperature being kept below 20°. The products were extracted with ether, and the residue from the dried and evaporated extract was subjected to careful chromatography on a column of silica gel (Whatman, type SG 31; *ca.* 50 g. per g. of product).

Elution was carried out with light petroleum, b.p. 40—60°, progressively reinforced, as necessary, with small amounts of ether (*e.g.* up to 5—10% for di- and tri-methoxybenzenes, and up to 10—20% for penta- and hexa-methoxybenzenes). This procedure normally resulted in effective separation of the two products, containing respectively *n* and *n* + 1 methoxy-groups, which resulted from many of the reactions. Exceptionally, mixtures of 1,2,3,5-tetramethoxybenzene and pentamethoxybenzene (from 1-halogeno-2,3,4,6-tetramethoxybenzenes) were not thus separable, and they were not clearly resolved on a g.l.c. column; the result of the reaction was accordingly determined in this case by quantitative i.r. analysis (by means of peaks at 10·50 and 11·40 μ), by use of carbon tetrachloride solutions of mixtures from which impurities had been removed by preliminary chromatography. Throughout the series of investigations, chromatographic fractions were compared [m.p., i.r., and g.l.c. characteristics (Perkin-Elmer F11 chromatograph)] with authentic samples of the various polymethoxybenzenes. G.l.c. analysis was used to demonstrate the absence of anisole in the crude products obtained from the various halogeno-anisoles, since the relative volatility of anisole (compared with polymethoxybenzenes) was found to prevent its quantitative recovery from a chromatographic column.

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