Side-chain Halogenation of 2,3-Dimethylbenzofuran. Competition between Ionic and Free-radical Reactions

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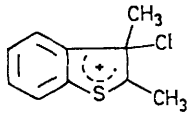
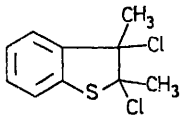
The chlorination and bromination of 2,3-dimethylbenzofuran lead predominantly to the formation of side-chain substituted products. The main product is 3-halogenomethyl-2-methylbenzofuran when the reaction occurs by a heterolytic mechanism and 2-halogenomethyl-3-methylbenzofuran when the reaction occurs by a free-radical mechanism. Competition between the two mechanisms is observed in conditions usually suitable for heterolytic halogenation. The formation of an addition product as a reaction intermediate in heterolytic halogenation can be excluded on the basis of the observed positional orientation. Probably, this reaction occurs by a mechanism similar to that postulated for electrophilic side-chain halogenation of polymethylbenzenes.

It has been shown [1] that 2,3-dimethylbenzothiophen is chlorinated in acetic acid, in the dark to give exclusively 2-chloromethyl-3-methylbenzothiophen by a heterolytic mechanism similar to that postulated for the side-chain



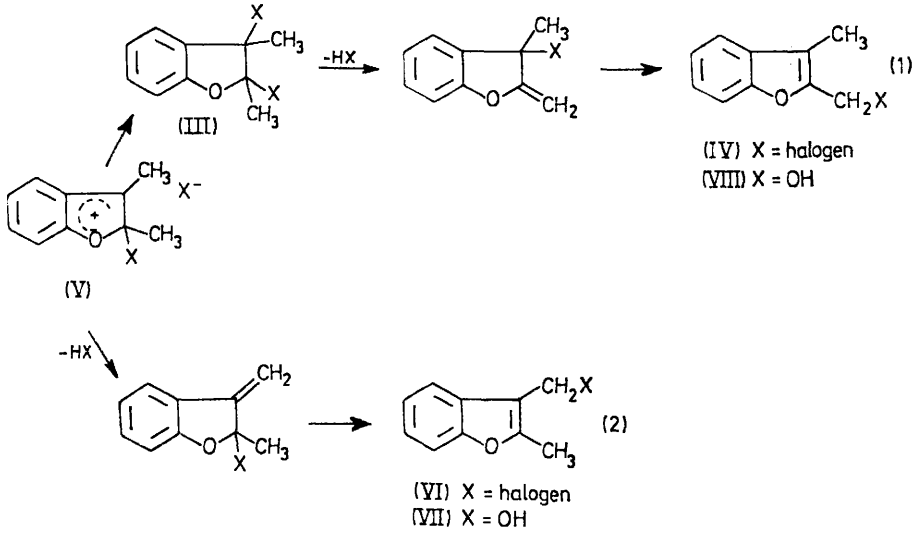
(I)



(II)

halogenation of polymethylbenzenes.[2] The kinetic behaviour of the chlorination suggests that the reaction occurs through the fast formation of a stable intermediate involving chlorine and substrate. Two possible reaction paths were envisaged. In the first the σ-complex (I) (chlorine attacks the 3-position which is the most reactive towards electrophiles) [1] is formed and 2-chloromethyl-3-methylbenzothiophen is obtained by loss of a proton from the 2-methyl group and subsequent rearrangement. Alternatively, compound (II) may be formed which could lose HCl and then rearrange to the chloromethyl derivative. However, in this case also, owing to the greater acidity of the methyl protons in the 2-position, formation of 2-chloromethyl-3-methylbenzothiophen may still be expected. Thus it is not possible to distinguish between the two reaction paths.

Some information on this problem can be obtained by a study of the halogenation of 2,3-dimethylbenzofuran. Benzofuran is much more likely than benzothiophen to give addition compounds with halogens; [3] moreover, since in benzofuran C-2 is the most reactive position towards electrophilic attack,[4] it would be possible to obtain evidence on the intervention of addition products on side-chain halogenation directly from a study of the reaction products. This follows from the fact that if (III; X = halogen) is an intermediate, (IV), formed by route (1), should be the principal product since for 2,3-dimethylbenzofuran the methyl protons in the 2-position exhibit greater acidity than those in the 3-position. If the side-chain substitution products are formed from (V) without the intervention of (III) compound (VI) would be expected [route (2)]



In this paper we report data on the chlorination and bromination of 2,3-dimethylbenzofuran under various experimental conditions.

[1] E. Baciocchi and L. Mandolini, *J. Chem. Soc.* (*B*), 1968, 397.
[2] (*a*) E. Baciocchi and G. Illuminati, *Progr. Phys. Org. Chem.*, 1967, **5**, 1; (*b*) G. Illuminati, L. Mandolini, A. Patara, and E. Baciocchi, *Tetrahedron Letters*, 1972, 4161 and references cited therein.
[3] L. A. Paquette 'Principle of Modern Heterocyclic Chemistry,' Benjamin, New York, 1968, p. 167.
[4] (*a*) S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc.* (*B*), 1971, 79; (*b*) ref. 3, p. 163.

RESULTS AND DISCUSSION

Both chlorination and bromination of 2,3-dimethylbenzofuran lead to the predominant formation of side-chain substituted products. However, since both the halogenomethyl derivatives of 2,3-dimethylbenzofuran are expected to be very unstable, we made no attempt to isolate these compounds but hydrolysed, in slightly basic, aqueous acetone, the crude products to convert the halogeno-derivatives into the corresponding alcohols, 2-methyl-3-hydroxymethyl- (VII) and 2-hydroxymethyl-3-methyl-benzofuran (VIII). These were analysed by g.l.c. by comparison with authentic specimens. The product ratio between the two isomeric alcohols, (VII) : (VIII) was taken to indicate the relative reactivities of the 3- and 2-methyl groups in halogenation. Results are reported in the Table.

Either bromination or chlorination, in dry acetic acid, in the dark, give a (VII) : (VIII) ratio of *ca.* 3. Hence

Distribution of isomeric alcohols [(VII) : (VIII) ratio] obtained in the side-chain reactions of 2,3-dimethylbenzofuran with bromine, chlorine, and *N*-bromosuccinimide

Reagent, conditions [a]	Reaction time (h)	Total yield of alcohols (%)	(VII) : (VIII)
Br_2, Anhydrous acetic acid 25°	3	74	3·2
Cl_2, Anhydrous acetic acid, 25°	2	75	2·7
Cl_2, 90% Acetic acid, 25°	2	74	25
Cl_2, Anhydrous acetic acid, oxygen, 25°	0·2	*b*	16
NBS, Carbon tetrachloride, benzoyl peroxide, 110°	2	43	0·14
NBS, Carbon tetrachloride, benzoyl peroxide, 25°	6	6	0·33
NBS, Anhydrous acetic acid 25°	6	19	7·5

[a] Solvent, catalyst or inhibitor, and temperature are reported in that order. [b] In this case the total yield in alcohols was not determined, since the chlorine concentration was unknown (see Experimental section). Moreover, several peaks other than those of the two alcohols and 2,3-dimethylbenzofuran were observed in the chromatogram. Probably in this case there is a reaction of oxygen with the methyl groups leading to different products.[6]

halogenation involves both the methyl groups of 2,3-dimethylbenzofuran, with attack at the 3-methyl group predominating. This excludes a major role for the addition product (III) in the mechanism. Even though route (2) is important, the formation of compound (VIII) suggests that some of the reaction might occur *via* intermediate (III). In other words the σ-complex (V) may partly decompose to the 3-halogenomethyl derivative (VI) [route (2)], and partly to (III), which then gives the 2-halogenomethyl derivative (IV) by route (1).

Alternatively, the results for the reaction in acetic acid could be explained by assuming a competition between ionic, leading to substitution at the 3-methyl group, and free-radical halogenation, leading to substitution at the 2-methyl group.[5] Chlorination in dry acetic acid in the presence of oxygen (conditions where the free-radical reaction is inhibited) [6] and in aqueous acetic acid (conditions where ionic chlorination is favoured) [7] lead to very high (VII) : (VIII) ratios. This provided good evidence that in dry acetic acid substitution at the 3-methyl group proceeds by an ionic mechanism and that substitution at the 2-methyl group proceeds by a free-radical mechanism.

The results for the bromination of 2,3-dimethylbenzofuran with *N*-bromosuccinimide (NBS) agree with this conclusion. In CCl_4 at 110°, in the presence of benzoyl peroxide, conditions suitable for a free-radical reaction, the ratio (VII) : (VIII) is 0·14. This further confirms that in free-radical halogenation the 2-methyl group is attacked predominantly. At 25°, under these conditions, the (VII) : (VIII) ratio becomes 0·33. Evidently NBS is also an ionic reagent [8] and can attack the 3-methyl group. Ionic bromination by NBS is predominant in acetic acid, in the absence of an initiator, and the (VII) : (VIII) ratio is 7. In acetic acid the ionic reaction is more favoured with respect to the free-radical one with NBS than with bromine. Some evidence has been presented [9] that the reaction of SO_2Cl_2 with 2,3-dimethylbenzofuran in CCl_4 involves the 2-methyl group. Evidently, in these conditions SO_2Cl_2 behaves as a free-radical agent.

On the basis of these results it may be therefore concluded, that the heterolytic, side-chain halogenation of 2,3-dimethylbenzofuran occurs *via* route (2) without the intervention of an addition product such as (III).

This conclusion, of course, casts some doubt on the validity of the hypothesis that addition products are involved in the chlorination of 2,3-dimethylbenzothiophen, a system less likely than 2,3-dimethylbenzofuran to undergo addition reactions. Probably the side-chain chlorination of 2,3-dimethylbenzothiophen also proceeds by route (2). Competition between the ionic and free-radical mechanisms is unlikely in this case since some 2-methyl-3-chloromethylbenzothiophen should be formed * whereas the yield of 2-chloromethyl-3-methylbenzothiophen is nearly quantitative. Moreover, a free-radical mechanism is not consistent with the simple kinetic pattern observed.[1]

The lack of any evidence for the formation of addition products in the halogenation of 2,3-dimethylbenzofuran, whereas both Br_2 and Cl_2 form stable, isolable addition products with benzofuran,[3] suggests that there would be substantial eclipsing strain between the bromine atoms and the methyl groups in intermediate (III).

It may also be noted that free-radical halogenation of 2,3-dimethylbenzofuran appears to compete significantly

* In the benzothiophen system the relative reactivity of the 2- and 3-methyl groups towards free radicals is not large.[5]

[5] E. T. Strom, G. A. Russell, and J. H. Shoeb, *J. Amer. Chem. Soc.*, 1966, **88**, 2004.

[6] C. Walling, ' Free Radicals in Solution,' Wiley, New York, 1957, p. 352.

[7] L. M. Stock and A. Himoe, *J. Amer. Chem. Soc.*, 1961, **83**, 1937.

[8] S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Amer. Chem. Soc.*, 1958, **80**, 4327.

[9] E. Bisagni, J. P. Marquet, A. Chentin, and R. Royer, *Bull. Soc. chim. France*, 1965, 1446.

with ionic halogenation even under conditions where polyalkylbenzenes or 2,3-dimethylbenzothiophen [1,2] undergo only an ionic reaction. Clearly, the methyl derivatives of benzofuran are characterised by a reactivity towards free radicals much larger than that of methyl derivatives of benzene or benzothiophen relative to the reactivity towards ionic reagents. Also the selectivity of free-radical halogenation is quite large, as shown by the value of 0·14 for the (VII) : (VIII) ratio obtained with NBS in CCl_4 at 110° in the presence of benzoyl peroxide; in fact, this value is probably an upper limit, since some ionic reaction cannot be definitely excluded even under these conditions.

A final point of interest is the drastic difference in orientation of products following ionic and free-radical halogenation of 2,3-dimethylbenzofuran. This finding, which is in agreement with recent results for side-chain halogenation of isodurene,[2b] may be used in synthesis.

EXPERIMENTAL

Materials.—2,3-Dimethylbenzofuran was prepared by reaction of 3-bromobutan-2-one [10] with phenol, followed by cyclodehydration in H_2SO_4,[11] b.p. 103—105° at 17 mmHg, n_D^{24} 1·5538 (lit.,[11] b.p. 103—104° at 17 mmHg, n_D^{24} 1·5543). 2-Methylbenzofuran was prepared by metallation of benzofuran (Fluka; 22·6 g, 0·19 mol) in dry ether (170 ml) with a 20% solution of n-butyl-lithium in n-hexane (98·5 ml, 0·21 mol). Freshly distilled dimethyl sulphate (22 ml, 0·23 mol) in dry ether (22 ml) was added dropwise, and the mixture, after stirring for 3 h, was poured into water. The organic layer was separated, dried (Na_2SO_4), and distilled giving pure 2-methylbenzofuran (24·1 g, 97%), b.p. 188—190° (lit.,[12] 189—191°). 2-Hydroxymethyl-3-methylbenzofuran was prepared by reducing 2-ethoxycarbonyl-3-methylbenzofuran [13] (7 g, 0·034 mol) with $LiAlH_4$ (1·9 g, 0·05 mol) according to the procedure described for 3-methoxycarbonylbenzofuran.[14] The crude product (5·5 g, 81%) was crystallised from light petroleum (b.p. 40—60°), m.p. 83—84° (Found: C, 74·2; H, 6·0. Calc. for $C_{10}H_{10}O_2$: C, 74·05; H, 6·2%). 2-Methyl-3-hydroxymethylbenzofuran was prepared by reduction of 2-methyl-3-formylbenzofuran (2·8 g, 0·018 mol; from formylation of 2-methylbenzofuran [12]) with $LiAlH_4$ (1 g, 0·026 mol). A red oil was obtained, which after dissolution in hot light petroleum (b.p. 40—60°) gave, on cooling, a white solid (1 g, 34%), m.p. 92—93° (Found: C, 74·35; H, 6·25%). *N*-Bromosuccinimide (C. Erba) was used without further purification. Benzoyl peroxide (C. Erba) was recrystallised from chloroform and methanol. Acetic acid was purified as previously described.[1] Carbon tetrachloride (C. Erba) was refluxed over P_2O_5 for 18 h.

Halogenations.—The halogenations with both bromine and chlorine were carried out in the dark by adding dropwise, with stirring, solutions of the halogens (0·035—0·13M) in AcOH to a solution of the substrate (0·065—0·14M). After 2 h the mixtures were poured into a large excess of light petroleum (b.p. 40—60°) and washed with water to neutrality. The organic layer was evaporated at atmospheric pressure, the residue was hydrolysed by refluxing for 4 h with 2·5% NaOH in 50% aqueous acetone, and the mixture was treated with water, and extracted with ether. The organic layer was dried (Na_2SO_4), concentrated to 1—2 ml, and analysed by g.l.c.

Chlorination in the presence of molecular oxygen as an inhibitor was carried out in the dark, by bubbling chlorine and oxygen together into a solution of 2,3-dimethylbenzofuran in acetic acid for 10 min. The mixture was then worked up as before.

Reactions with NBS (*ca.* 0·075M) were carried out with an excess of substrate (*ca.* 0·2M) to minimise dibromination. At the end of the reaction succinimide was filtered off and the organic layer was worked up as described above.

G.l.c. analyses were performed on a GI Fractovap (C. Erba) using a 3 mm i.d. glass column (1·8 m) containing 0·1% FFAP on carbon-coated glass beads [15] with nitrogen as carrier gas. The column temperature was 130° for the separation and analysis of the hydroxymethyl derivatives and 90° for analysis of unchanged 2,3-dimethylbenzofuran. As internal standard, 2,4,6-trimethylbenzyl alcohol was introduced into the reaction mixtures immediately after the end of halogenation.

The total recovery of hydroxymethyl derivatives and unchanged starting material was >90% except for the chlorination in the presence of oxygen (see Table).

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[14] L. Capuano, *Chem. Ber.*, 1965, **98**, 3659.
[15] L. Zoccolillo and A. Liberti, *J. Chromatography*, 1973, **77**, 69.