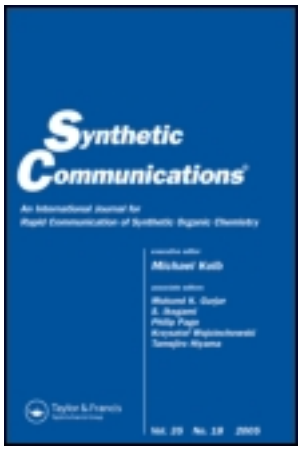

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A Simple Synthesis of Brominated Analogues of 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX)

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ABSTRACT

Three brominated analogues of the highly mutagenic drinking water micropollutant 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX) have been synthesized from MX by halogen exchange reaction.

Key Words: Brominated hydroxyfuranones; Disinfection by-products; Mutagenicity.

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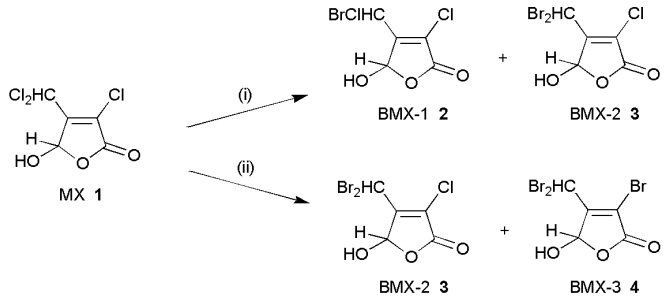
The chlorination of drinking water has virtually eliminated cholera, typhoid fever, and other waterborne diseases in developed nations. However, chlorinated compounds can be formed by the reaction of chlorine with small amounts of organic substances dissolved in the water and such disinfection by-products (DBPs) are now of concern because of their widespread consumption and the uncertainty regarding their health effects. There is some evidence from epidemiological studies of a causal role for chlorination DBPs in human cancer, particularly bladder cancer.[1]

3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX) **1** is a DBP which has been reported to make a substantial contribution to the mutagenic activity of chlorinated drinking water.[2,3] MX is one of the most potent known mutagens as determined by the Ames assay.[4] It has been shown to produce DNA damage in mammalian cells in vitro[5,6] and in vivo,[7,8] and to cause cancer in rats.[9] Several methods for the synthesis of MX have been reported.[10–13]

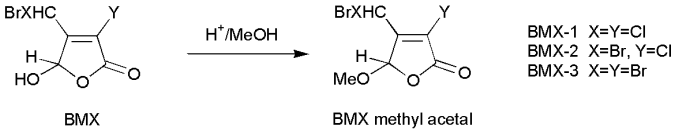
It is known that the chlorination of drinking water samples containing bromide ions often leads to the production of brominated trihalomethanes, and Fawell and Horth[14] proposed the similar formation of brominated analogues of MX (BMXs). Following our successful preparation of MX,[15] we were requested to synthesize three BMX compounds, 3-chloro-4-(bromochloromethyl)-5-hydroxy-2(5*H*)-furanone (BMX-1) **2**, 3-chloro-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (BMX-2) **3**, and 3-bromo-4-(dibromomethyl)-5-hydroxy-2(5*H*)-furanone (BMX-3) **4**, as standards for the analysis of drinking water and for the study of their mutagenicity.

Attempts to modify the route by Padmapriya et al.[10] for the preparation of MX to produce brominated analogues were unsuccessful.[15] We then investigated the synthesis of the BMX compounds directly from MX, which is commercially available,[16] by halogen exchange reaction. After trying a number of different reaction conditions we found that MX could be converted into BMX-1, BMX-2, and BMX-3 using conditions for the conversion of alkyl chlorides to alkyl bromides described by Willy et al.[17]

Reaction of MX with bromoethane and sodium bromide in 1-methyl-2-pyrrolidinone heated at reflux for 28 h gave a mixture of BMX-1 and BMX-2 (1:1).[18] When the reaction mixture was heated to a higher temperature (100°) in a sealed tube for 24 h a mixture of BMX-2 and BMX-3 (1:5.5) was obtained (Sch. 1). The individual compounds were then isolated in >98% purity[19] by preparative reverse phase HPLC and their identities were established by mass spectrometry following derivatization of the compounds as methyl acetals[20] (Sch. 2). The isotope patterns found in the mass spectra



Scheme 1. Reagents: (i) EtBr/NaBr/1-methyl-2-pyrrolidinone/75°/28 h, (ii) EtBr/NaBr/1-methyl-2-pyrrolidinone/100°/24 h.



Scheme 2. Formation of methyl acetal derivatives for analysis by mass spectrometry.

of the BMX acetals were diagnostic of the number of chlorine and bromine atoms present. The ^{1}H and ^{13}C NMR spectra of the BMX compounds were also recorded and are in accord with published spectral data.[21,22] The yields of BMX-1 and BMX-2, isolated from the lower temperature reaction, were 18% and 21%, and the yields of BMX-2 and BMX-3, isolated from the higher temperature reaction, were 6% and 32% respectively.

Using the BMX compounds supplied by Ultrafine,[23] Horth and co-workers tentatively identified their presence in a UK drinking water and found the BMXs to have similar mutagenic activity to that of MX in the Ames test.[14,24,25] We repeated our synthesis of BMX-1, BMX-2, and BMX-3 to supply material to Suzuki and Nakanishi[26] who found the compounds to be present in some samples of drinking water in Japan.

Alternative multi-step methods for the synthesis of the BMXs have been reported in recent years by 2 research groups. The synthesis of BMX-2 and BMX-3 has been reported by LaLonde et al.[21] and the synthesis of BMX-1, BMX-2, and BMX-3 by Lloveras and co-workers.[22] Both groups have reported mutagenicity studies on the BMX compounds.[21,27]

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EXPERIMENTAL

Caution. MX and the BMXs are highly mutagenic and suspected human carcinogens. Bromoethane is a carcinogen and 1-methyl-2-pyrrolidinone is also toxic. Suitable precautions must be taken to prevent exposure to these compounds.

NMR spectra were recorded on a Bruker AC-300E spectrometer in $CDCl_3$ solution (300 MHz for ^1H, 75 MHz for ^{13}C). Infrared spectra (liquid films) were recorded on a Perkin-Elmer 1310 spectrometer. Electron impact mass spectra were run by the Mass Spectrometry Service, Department of Chemistry, University of Manchester, UK. Ultra Violet spectra were recorded on a Perkin-Elmer 402 UV–VIS spectrometer in methanol solution.

For HPLC, Gilson equipment was used with UV detection at 225 nm and a 2 solvent system (where solvent A is methanol and solvent B is 0.1 M ammonium acetate solution containing 0.15% acetic acid). Analytical HPLC method: Spherisorb 5ODS2 column (4.6 × 150 mm); eluent 20% A/80% B; flow 1.0 mL/min; R_t 9.1 min (MX), 11.6 min (BMX-1), 14.7 min (BMX-2), 17.0 min (BMX-3). Preparative HPLC method: Rainin Dynamax Microsorb (C18, 5 μ) column (10.0 × 250 mm); eluent 1, for BMX-1 and BMX-2 mixture, 20% A/80% B; eluent 2, for BMX-2 and BMX-3 mixture, 25% A/75% B; flow 3.0 mL/min; R_t 26.7 min (BMX-1), 36.5 min (BMX-2) using eluent 1; and R_t 33.3 min (BMX-2), 36.3 min (BMX-3) using eluent 2.

Synthesis of BMX-1 2 and BMX-2 3

A stirred mixture of MX **1** (210 mg, 0.97 mmol), bromoethane (8.0 mL, 107 mmol) and sodium bromide (45 mg, 0.44 mmol) in anhydrous 1-methyl-2-pyrrolidinone (16.0 mL) was heated at reflux (oil bath at 75°) for 28 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (12 mL) and water (8 mL). The aqueous phase was re-extracted with ethyl acetate (12 mL) and the combined extract was dried ($MgSO_4$) and evaporated to afford the crude product mixture as a dark oil. The oil was dissolved in a mixture of HPLC eluent and methanol, and was then separated by preparative HPLC. The HPLC product fractions were extracted with ethyl acetate (3 extractions with volume equal to HPLC fraction) and the extracts were dried ($MgSO_4$) and evaporated to afford BMX-1 (45 mg, 18%) and BMX-2 (61 mg, 21%).

BMX-1 (2 diastereomers): ^{1}H NMR δ 6.65, 6.62 (s, 1H, H-6), 6.48, 6.40 (s, 1H, H-5), 4.85 (br, 1H, OH). ^{13}C NMR δ 164.26 (C-2), 151.25, 150.79 (C-3), 124.56, 124.14 (C-4), 97.10, 96.57 (C-5), 44.15, 43.68 (C-6). BMX-1 acetal: MS m/z 243, 245, 247, 249 $[M\text{-}OCH_3]^+$. BMX-2: ^{1}H NMR δ 6.45 (s, 1H, H-6), 6.42 (s, 1H, H-5), 4.9 (br, 1H, OH). ^{13}C NMR δ 164.52 (C-2), 151.58 (C-3), 123.73 (C-4), 97.54 (C-5), 24.86 (C-6). BMX-2 acetal: MS m/z 287, 289, 291, 293 $[M\text{-}OCH_3]^+$. The IR spectra of the BMX compounds were very similar, ν_{max} 3380, 1770, 1640 cm^{-1}, indicating the stretching frequencies of the hydroxyl group and the α,β-unsaturated lactone system.

Synthesis of BMX-2 3 and BMX-3 4

A stirred mixture of MX **1** (165 mg, 0.76 mmol), bromoethane (5.0 mL, 67 mmol) and sodium bromide (135 mg, 1.31 mmol) in anhydrous 1-methyl-2-pyrrolidinone (5.0 mL) in a sealed tube was heated at 100° (bath temp.) for 24 h. The products were then isolated in the manner described above for the mixture of BMX-1 and BMX-2. The yields of BMX-2 and BMX-3 were 14 mg (6%) and 85 mg (32%) respectively.

BMX-3: ^{1}H NMR δ 6.45 (s, 1H, H-6), 6.42 (s, 1H, H-5), 4.7 (br, 1H, OH). ^{13}C NMR δ 164.77 (C-2), 155.65 (C-3), 114.27 (C-4), 98.65 (C-5), 26.54 (C-6). BMX-3 acetal: MS m/z 331, 333, 335, 337 $[M\text{-}OCH_3]^+$.

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19. Purity determined by analytical HPLC.
20. A small amount of the BMX compound was dissolved in 2% H_2SO_4 in MeOH (1 mL) and the solution was heated at 70° (bath temp.) for 1 h. The methyl acetal was extracted into hexane (2×2 mL) and the solvent was evaporated.
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