# Preparation of 2-Methoxytetrahydropyran-3-one from Halogenated Dihydro- and Tetrahydropyran Precursors

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The reaction of 5-halo-3,4-dihydro-2*H*-pyran with halogen and sodium methoxide gives in good yield the corresponding 3,3-dihalo-2-methoxytetrahydropyran. The latter, upon treatment with aqueous sodium hydroxide or sodium methoxide in methanol failed to provide 2-methoxytetrahydropyran-3-one but instead gave the 3-halo-2-methoxy-5,6-dihydro-2*H*-pyran. The ketone, 2-methoxytetrahydropyran-3-one was obtained by the treatment of 5-chloro-3,4-dihydro-2*H*-pyran with *m*-chloroperoxybenzoic acid followed by the addition of sodium methoxide.

Attempts to prepare the 3,3-dibromo-2-methoxytetrahydropyran by the reaction of 3-bromo-2-methoxytetrahydropyran with bromine were unsuccessful, but gave the ring cleavage product, methyl 2,5dibromopentanoate.

La réaction d'un halo-5 dihydro-3,4-2*H*-pyrane sur un halogène et du méthoxyde de sodium conduit au dihalo-3,3 méthoxy-2 tétrahydropyrane avec un bon rendement. Ce dernier, après traitement avec de la soude aqueuse ou du méthoxyde de sodium dans le méthanol, conduit au halo-3 méthoxy-2 dihydro-5,6-2*H*-pyrane au lieu du méthoxy-2 tétrahydropyranone-3. La cétone méthoxy-2 tétrahydropyranone-3 a été obtenue par traitement du chloro-5 dihydro-3,4-2*H* pyrane à l'acide *m*-chloroperoxybenzoique suivi d'une addition de méthoxyde de sodium. Des tentatives de préparation du dibromo-3,3 méthoxy-2 tétrahydropyrane par réaction du bromo-3 méthoxy-2 tétrahydropyrane sur le brome ont échoué et ont conduit au dibromo-2,5 pentanoate de méthyle, produit de rupture de cycle.

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As part of a program exploring avenues leading to the total synthesis of monosaccharides, the preparation of 2-methoxytetrahydropyran-3-one from halogenated dihydroand tetrahydropyran precursors was undertaken, since the ketone might be a useful intermediate for some monosaccharide syntheses. This note describes the results obtained.

The reaction of 5-chloro-3,4-dihydro-2*H*pyran (1, X = Cl (1)) or its bromo analog, (1, X = Br (2)) with chlorine in the presence of methyl alcohol and sodium methoxide gave 3,3 - dichloro - 2 - methoxytetrahydropyran, (2, X = Y = Cl) and 3-bromo-3-chloro-2-methoxytetrahydropyran, (2, X = Cl, Y = Br) respectively, in very good yield (Scheme 1). Similarly, 2, X = Y = Br, was obtained by bromination of 1, X = Br. Attempts to prepare 2, X = Y = Br, by direct bromination of the acetal 3-bromo-2-methoxytetrahydropyran failed, but instead provided the acyclic compound methyl 2,5dibromopentanoate.

Base catalyzed hydrolysis of 2, X = Y = CI

or Br, or X = Cl, Y = Br, failed to produce the desired ketone 4 but instead gave 3 in 2% yield along with 90% of unchanged 2 when X = Y = Cl in 2, in 74% yield when X = Y = Br in 2, and in 95% yield when X = Cl, Y = Br in 2. Similarly, the reaction of 2, X = Cl, Y = Br, with sodium methoxide in methanol gave 3, X = Cl, in excellent yield while 3, Y = Br, was obtained in 62% yield by the same reaction with 2, X = Y = Br. In contrast, the methanolic sodium methoxide reaction with 2, X = Y = Cl, proved to be much more difficult, as with the hydrolysis reaction above, and provided 3, Y = Cl, in 5% yield along with 90% of unchanged 2, X = Y = Cl.

The ketone 4 was made available by the reaction of 1, X = Cl, with *m*-chloroperoxybenzoic acid in methylene chloride followed by addition of sodium methoxide (as shown in Scheme 2). There was obtained a mixture of six compounds (as shown by g.l.c.) in which 4 predominated in the relative proportion of 70% accompanied by unchanged 1, X = Cl (8%), 3-chloro-2-methoxytetrahydropyran (10%), 3,3-dichloro-2methoxytetrahydropyran (~1%), and two unidentified substances (each about 5%). Identifi-

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$$(1) \xrightarrow{m-ClC_6H_4CO_3H} 4 + \text{five minor products}$$

SCHEME 2

cation was made by both isolation of small samples by g.l.c. and by comparison of g.l.c. retention times with those of known compounds. It was possible to isolate 4 by fractional distillation from the mixture but decomposition and polymerization reduced the isolated yield to 20-25%.

## Experimental

All melting points and boiling points are uncorrected. The elemental analyses were performed by Mrs. D. Mahlow of this Department. The p.m.r. spectra were obtained by Mr. R. N. Swindlehurst using a Varian Associates A60 spectrometer and by Mr. Glen Bigam using a Varian Associates HR100 spectrometer in this Department. Tetramethylsilane was used as reference. G.I.c. analyses were made with an F and M model 700 chromatograph using a column, 1/8 in.  $\times 12$  ft, containing 20% butanediol succinate on Gas-Chrom P (60– 80 mesh) with a helium flow-rate of 40 ml/min. The i.r. spectra were obtained with Perkin-Elmer instruments, models 21 and 421. Solvents were removed by rotary evaporator under reduced pressure unless otherwise stated.

#### Halogenation of 3,4-Dihydro-2H-pyrans

By use of the reported procedure (5) for the bromination of 2-methoxymethyl-3,4-dihydro-2*H*-pyran, the following compounds were obtained.

# 3,3-Dichloro-2-methoxytetrahydropyran

This was obtained from the addition of 0.5 mol of chlorine in 300 ml of carbon tetrachloride to 0.5 mol of 5-chloro-3,4-dihydro-2*H*-pyran (1) in 1 l of methanol containing 0.5 mol of sodium methoxide. Yield 83%; b.p. 54° at 1.6 mm;  $n_{\rm D}^{25}$  1.4752 (lit. (3) b.p. 40-42° at 2 mm).

#### 3-Bromo-3-chloro-2-methoxytetrahydropyran

This was obtained from the addition of 0.5 mol of bromine in carbon tetrachloride to 0.5 mol of 5-chloro-

3,4-dihydro-2*H*-pyran (1) in methanol (1 l) containing sodium methoxide (0.5 mol). Yield 78%; b.p. 56° at 0.9 mm;  $n_D^{25}$  1.5027.

Anal. Calcd. for  $C_6H_{10}BrClO_2$ : C, 31.39; H, 4.39; halogen determined as chloride, 30.90. Found : C, 31.29; H, 4.14; halogen (as chloride) 30.88.

Both the p.m.r. and i.r. spectra agreed with the structure proposed.

In addition there was obtained an 8% yield of *cistrans*-3-chloro-2-methoxytetrahydropyran, b.p. 60° at 8 mm,  $n_D^{23}$  1.4583 (lit. (1) b.p. 74° at 18 mm,  $n_D^{12}$  1.4646).

3,3-Dibromo-2-methoxytetrahydropyran

The addition of bromine to 5-bromo-3,4-dihydro-2*H*pyran (2) in methanolic sodium methoxide as described above gave 3,3-dibromo-2-methoxytetrahydropyran in 91% yield: b.p. 63° at 0.6 mm;  $n_D^{25}$  1.5305.

91% yield: b.p. 63° at 0.6 mm;  $n_D^{25}$  1.5305. Anal. Calcd. for C<sub>6</sub>H<sub>10</sub>Br<sub>2</sub>O: C, 26.29; H, 3.68; Br, 58.33. Found: C, 26.47; H, 3.91; Br, 58.49.

Both the p.m.r. and i.r. spectra agreed with the structure proposed.

## 3-Chloro-2-methoxy-5,6-dihydro-2H-pyran

(a) From 3-bromo-3-chloro-2-methoxytetrahydropyran The dehydrohalogenation procedure reported for the preparation of *trans*-2-methoxy-6-methoxymethyl-5,6dihydro-2*H*-pyran (5) was followed. From 22.9 g (0.1 mol) of the bromo-chloro compound there was obtained, by distillation under reduced pressure, 14.1 g (95%) of 3-chloro-2-methoxy-5,6-dihydro-2*H*-pyran; b.p. 64° at 12 mm;  $n_{\rm D}^{25}$  1.4706.

Anal. Calcd. for  $C_6H_9ClO_2$ : C, 48.49; H, 6.10; Cl, 23.85. Found: C, 48.39; H, 6.09; Cl, 23.80.

The p.m.r. spectrum obtained in CDCl<sub>3</sub> agreed with the structure and showed a quartet centered at 6.05 p.p.m. (1H)  $J \sim 3$  and 6 Hz; a singlet at 4.68,  $w_{1/2} \sim 2.5$  Hz; a multiplet at 4.20-3.65 (2H); a singlet at 3.42 (3H); a multiplet at 2.80-1.50 (2H). The i.r. spectrum (neat) showed weak absorption at 1660 cm<sup>-1</sup> (C=C).

The reaction of 3-bromo-3-chloro-2-methoxytetrahydropyran with aqueous sodium hydroxide gave a 93% yield of 3-chloro-2-methoxy-5,6-dihydro-2*H*-pyran.

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## (b) From 3,3-dichloro-2-methoxytetrahydropyran

The reaction of 18.5 g (0.1 mol) of 3,3-dichloro-2methoxytetrahydropyran with 0.2 mol of sodium methoxide in methanol, following the procedure used in (*a*) above gave 0.7 g (5%) of 3-chloro-2-methoxy-5,6-dihydro-2H-pyran and 16.6 g (90%) of unchanged 3,3-dichloro-2methoxytetrahydropyran.

A similar reaction, using aqueous sodium hydroxide gave a 2% yield of the olefin and 90% recovered unchanged dichloro compound.

#### 3-Bromo-2-methoxy-5,6-dihydro-2H-pyran

Following the above procedure to prepare 3-chloro-2-methoxy-5,6-dihydro-2*H*-pyran, 27.4 g (0.1 mol) of 3,3-dibromo-2-methoxytetrahydropyran heated with methanol and sodium methoxide, gave 4.4 g (16%) of unchanged dibromo compound and 12.0 g (62%) of 3-bromo-2-methoxy-5,6-dihydro-2*H*-pyran: b.p. 52° at 2.2 mm;  $n_{\rm D}^{25}$  1.4970 (lit. (4) b.p. 92–94° at 14 mm;  $n_{\rm D}^{27}$  1.4960).

The p.m.r. spectrum in CDCl<sub>3</sub> agreed with the structure and showed a quartet at 6.28 p.p.m.,  $J \sim 2.5$  and 5.5 Hz (1H); a singlet at 4.75,  $w_{1/2} \sim 2.5$  Hz (1H); a multiplet at 4.10–3.65 (2H); a singlet at 3.42 (3H); a multiplet at 2.90–1.65 (2H). The i.r. spectrum (film) showed a weak band at 1648 cm<sup>-1</sup> (C=C).

When heated with aqueous sodium hydroxide at  $65^{\circ}$  for 18 h, 3,3-dibromo-2-methoxytetrahydropyran gave 3-bromo-2-methoxy-5,6-dihydro-2*H*-pyran in 74% yield. Higher temperatures resulted in lower yields.

#### 3-Bromo-2-methoxytetrahydropyran

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The reaction of 3,4-dihydro-2*H*-pyran with bromine and methanol was carried out by the procedure reported for the preparation of 3-bromo-2-methoxy-6-methoxymethyltetrahydropyran (5).

From 84 g (1 mol) of the dihydropyran there was obtained 165 g (85%) of 3-bromo-2-methoxytetrahydropyran which from previous experience with the bromomethoxylation of similar compounds (5) is considered to be nearly completely the *trans* isomer. B.p.  $87^{\circ}$  at 12 mm (lit, (6) b.p. 88–89° at 18 mm).

## Methyl 2,5-Dibromopentanoate

To a well-stirred mixture of 3-bromo-2-methoxytetrahydropyran (9.75 g, 0.1 mol) and 15.9 g of anhydrous sodium carbonate in 150 ml of carbon tetrachloride, kept at 35°, was added dropwise a solution of bromine (16.0 g, 0.1 mol) in 50 ml of carbon tetrachloride. The mixture was then stirred overnight and allowed to reach room temperature. The solids were then removed and the solution was shaken several times with saturated aqueous sodium bicarbonate. The organic solution was dried (Na<sub>2</sub>SO<sub>4</sub>), freed from solvent and the residue was distilled under reduced pressure yielding 9.6 g (35%) of methyl 2,5-dibromopentanoate: b.p. 63° at 0.6 mm;  $n_D^{26.5}$  1.5090 (lit. (7) b.p. 93–95° at 1.5 mm;  $n_D^{25}$  (1.5099).

## 2-Methoxytetrahydropyran-3-one

To a stirred solution of 35.5 g (0.3 mol) of 5-chloro-3,4-dihydro-2H-pyran in 250 ml of dichloromethane kept between 0 and  $10^{\circ}$ , was added slowly a solution of 64.8 g (0.3 mol) of 80% m-chloroperoxybenzoic acid in dichloromethane. The mixture was then stirred overnight and allowed to reach room temperature. The precipitated m-chlorobenzoic acid was removed and to the residual solution, kept cool with an ice bath, was added 32.4 g (0.6 mol) of sodium methoxide. The mixture was then stirred overnight (room temperature), following which the solids were separated and the solvent removed under reduced pressure. The residual oil (24 g, ~60%) was found by g.l.c. to consist of 2-methoxytetrahydropyran-3-one (70%), unchanged 5-chloro-3,4-dihydro-2*H*-pyran (8%), 3-chloro-2-methoxytetrahydropyran (9%), 3,3dichloro-2-methoxytetrahydropyran (1-2%), and two unidentified substances (each about 5%).

The crude mixture, when subjected to fractional distillation under reduced pressure, decomposed with polymerization and provided only a relatively small amount (20–25%) of pure 2-methoxytetrahydropyran-3one: b.p. 44° at 2 mm;  $n_D^{26.5}$  1.4611.

Anal. Calcd. for C<sub>6</sub>H<sub>10</sub>O<sub>3</sub>: C, 55.37; H, 7.74. Found: C, 54.60; H, 7.72.

The p.m.r. spectrum in  $CDCl_3$  agreed with the structure proposed, showing a singlet at 4.54 mm (1H); broad multiplet, 4.4–3.7 (2H); singlet, 3.49 (3H); broad multiplet, 2.9–2.0 (4H). The i.r. spectrum (film) showed strong absorption at 1730 cm (C=O) and at 1100 cm<sup>-1</sup> (C=O-C).

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