2-ALKOXY-3-HYDROXYTETRAHYDROPYRANS AND 2-ALKOXY-3-HYDROXYTETRAHYDROFURANS

I. PREPARATION, STRUCTURE, AND SOME DERIVATIVES[1]

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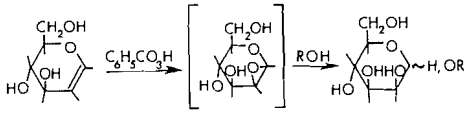
ABSTRACT

Oxidation of 2,3-dihydrofuran or 2,3-dihydropyran with peroxybenzoic acid or *m*-chloroperoxybenzoic acid in the presence of an alcohol has produced, respectively, *trans*-2-alkoxy-3-hydroxytetrahydrofurans in 59 to 64% yield and *trans*-2-alkoxy-3-hydroxytetrahydropyrans in 65 to 80% yield. In the presence of acids, these acetals isomerize readily to give an equilibrated mixture of *cis* and *trans* isomers.

INTRODUCTION

Simple models of pyranosides and furanosides which possessed, in addition to the anomeric hydroxyl or alkoxy group, only one hydroxyl group in the ring (and that specifically on C_2) were required for a study of the influence of substituents on the selective hydrogenolysis of acetals and ketals (1). The dihydroxylation of α,β-unsaturated ethers was considered to be a means to this end.

This approach has been used by several workers, but yields in general were not satisfactory. Glycals (2), which are α,β-unsaturated cyclic ethers, have in a number of cases been oxidized by peroxybenzoic acid to give, first, what is believed to be an intermediate epoxide. Under the reaction conditions this was rapidly converted into either a reducing sugar or a glycoside in the presence of water or an alcohol or a carboxylic acid (2–4) (Reaction Scheme 1).



R = H, alkyl, or benzoyl

REACTION SCHEME 1.

In a similar reaction, Bergmann *et al.* (5) showed that oxidation of 2-methyl-5,6-dihydropyran with peroxybenzoic acid provided the diol 2-methyl-2,3-dihydroxytetrahydropyran, isolated by these authors as the acyclic compound 4-hydroxy-4-aceto-1-butanol. Methanolysis of a dimer of this compound, obtained if the above product was isolated by distillation at 60° rather than 30°, gave 2-methyl-2,3-dimethoxytetrahydropyran.

Barker *et al.* (6) oxidized 5,6-dihydropyran with peroxybenzoic acid and obtained 2-benzoyloxy-3-hydroxytetrahydropyran, to which they tentatively assigned the *trans* configuration.

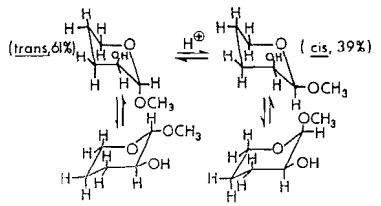
Recently (7), a mixture of hydrogen peroxide and a nitrile has been used to convert *n*-butyl vinyl ether in methanol into *n*-butyl β-hydroxy-α-methoxyethyl ether in 33% yield. Here also, the intermediate was considered to be an epoxide.

[1]*From the work of F. Sweet to be submitted to the Department of Chemistry, University of Alberta, Edmonton, as part of the requirements for the degree of Doctor of Philosophy.*

RESULTS AND DISCUSSION

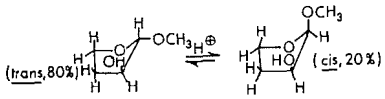
With the work mentioned above as a basis, we have obtained a simple and more productive route to 2-alkoxy-3-hydroxytetrahydropyrans and 2-alkoxy-3-hydroxytetrahydrofurans, using either peroxybenzoic acid or *m*-chloroperoxybenzoic acid to oxidize dihydropyran or dihydrofuran dissolved in the appropriate alcohol. The results of these experiments are shown in Tables I and II. In all cases the nuclear magnetic resonance (n.m.r.) spectra of the compounds were consistent with the structures designated. Oxidation of *n*-butyl vinyl ether by this modified method gave a 92% yield of pure *n*-butyl β-hydroxy-α-methoxyethyl ether.

The proposal of initial formation of an intermediate epoxide as in Reaction Scheme 1 (5) is supported by the fact that the reaction product is almost exclusively the *trans*-2-alkoxy-3-hydroxytetrahydropyran or *trans*-2-alkoxy-3-hydroxytetrahydrofuran. This is in agreement with the known preferred *trans* opening of the epoxide ring (8). Since we have not yet been able to isolate the proposed epoxide intermediate, it is not certain that it actually does occur in this reaction. However, to account for the *trans* product, either such an intermediate must be formed or, alternatively, an "epoxide-like" transition state must be involved. Evidence for the *trans* assignment is shown below and is supported by n.m.r. data. A detailed account of this and the conformational preference of the structures is given in part II in this series.[2]



REACTION SCHEME 2.

If the reaction mixture, obtained from the epoxidation and alcoholysis of the α,β-unsaturated cyclic ether, was worked up immediately after completion of the reaction (about 12 to 14 h), the *trans* isomer was obtained, as shown by gas–liquid chromatography, contaminated by less than 1% of the *cis* isomer. If the reaction mixture stood for 2 days at room temperature before work-up, the amount of *cis* contaminant increased to about 5–10%, showing that isomerization had taken place, no doubt caused by the presence of the benzoic acid.[3] When pure *trans*-2-methoxy-3-hydroxytetrahydropyran, obtained by gas–liquid chromatography, was dissolved in the appropriate alcohol containing some *p*-toluenesulfonic acid, an equilibrium mixture (39:61) of *cis* and *trans* isomers was obtained. The same proportion of *cis* and *trans* isomers was found when pure *cis* isomer was equilibrated under the same conditions (Reaction Scheme 2). In a similar manner, the acid-catalyzed isomerization of *trans*-2-methoxy-3-hydroxytetrahydrofuran gave an equilibrium mixture of *cis* and *trans* isomers in the ratio of 20:80 (Reaction Scheme 3).



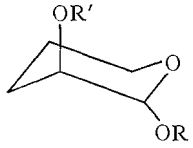
REACTION SCHEME 3.

[2]*F. Sweet and R. K. Brown, in preparation.*

[3]*These acetals are hydrolyzed and isomerized extremely easily, and can be preserved only in glassware carefully cleaned under alkaline conditions.*

TABLE I

trans-2-Alkoxy-3-hydroxytetrahydropyrans from the reaction of *m*-chloroperbenzoic or perbenzoic acid with 5,6-dihydropyran in alcohol (ROH)

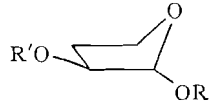


Substituent		Boiling point (melting point)	Refractive index, η_D (temperature)	% analysis						% yield
				Calcd.			Found			
R	R′			C	H	N	C	H	N	
CH_3	H	56° at 2 mm	1.4548 (23.5°)	54.53	9.15		54.58	9.18		76–82
CH_3	DNB*	(132–133°)		47.86	4.33	8.59	48.21	4.49	8.42	
CH_3	CH_3	110–111° at 110 mm	1.4318 (25°)	57.51	9.65		57.40	9.63		85
C_2H_5	H	63° at 2.5 mm	1.4506 (25°)	57.51	9.65		57.65	9.65		65
C_2H_5	DNB	(116–117°)		49.42	4.74	8.23	49.70	4.77	8.30	
C_2H_5	CH_3	46–47° at 5.2 mm	1.4322 (25°)	59.98	10.07		60.00	9.90		81
i-C_3H_7	H	63–64° at 2 mm	1.4467 (26.5°)	59.98	10.07		59.71	9.93		74
i-C_3H_7	DNB	(96–97°)		50.85	5.12	7.91	51.02	5.02	8.05	
i-C_3H_7	CH_3	92–93° at 30 mm, 56–57° at 7 mm	1.4299 (25°)	62.04	10.41		62.26	10.31		80
t-C_4H_9	H	62° at 1.5 mm	1.4487 (25°)	62.04	10.41		62.15	10.21		80
t-C_4H_9	DNB	(86–88°)		52.17	5.47	7.61	52.13	5.52	7.68	
t-C_4H_9	CH_3	61–62° at 7 mm	1.4322 (25°)	63.80	10.71		63.86	10.51		86
The *cis* isomer										
CH_3	H	62° at 2.2 mm‡	1.4517 (25°)	54.52	9.16		54.40	9.04		†
CH_3	DNB	(88°)		47.86	4.33	8.59	47.70	4.23	8.46	

*DNB = 3,5-dinitrobenzoyl.
†Obtained by separation of an equilibrated solution of *cis* and *trans* isomers.
‡Micro-determination.

TABLE II

trans-2-Alkoxy-3-hydroxytetrahydrofurans from the reaction of *m*-chloroperbenzoic acid or perbenzoic acid with 4,5-dihydrofuran in alcohol (ROH)



Substituent		Boiling point (melting point)	Refractive index, η_D^{25}	% analyses						% yield
				Calcd.			Found			
R	R′			C	H	N	C	H	N	
CH_3	H	68–70° at 7 mm	1.4421	50.84	8.53		50.72	8.68		59
CH_3	DNB*	(89–90°)		46.16	3.87	8.97	46.59	3.90	8.68	
CH_3	CH_3	57° at 21 mm	1.4201	54.53	9.15		54.87	8.92		93
C_2H_5	H	64–65° at 2.5 mm	1.4415	54.53	9.15		54.45	8.95		59
C_2H_5	DNB	(93–94°)		47.86	4.33	8.59	47.97	4.32	8.82	
C_2H_5	CH_3	71–72° at 26 mm	1.4214	57.51	9.65		57.83	9.58		86
i-C_3H_7	H	79–80° at 4 mm	1.4373	57.51	9.65		57.56	9.55		58
i-C_3H_7	DNB	(102–103°)		49.42	4.74	8.23	49.32	4.72	8.09	
i-C_3H_7	CH_3	52° at 10 mm	1.4196	59.98	10.07		60.05	9.98		92
t-C_4H_9	H	68° at 1.5 mm	1.4422	59.98	10.07		59.73	10.07		64
t-C_4H_9	DNB	(100°)		50.85	5.12	7.91	50.70	5.18	8.01	
t-C_4H_9	CH_3	46° at 6.5 mm	1.4242	62.04	10.41		61.77	10.21		88
The *cis* isomer										
CH_3	H	48° at 15 mm	1.4410	50.84	8.53		50.73	8.33		†
CH_3	DNB	(87°)		46.16	3.87	8.97	46.64	3.96	8.48	

*DNB = 3,5-dinitrobenzoyl.
†Obtained by separation of an equilibrated solution of *cis* and *trans* isomers.

The *trans* and *cis* assignments of the two isomeric 2-methoxy-3-hydroxytetrahydropyrans are supported by the n.m.r. signals for the respective anomeric protons. That for the *trans* isomer occurs as a doublet at τ 5.80 (J = 5.2 c.p.s.) whereas that for the *cis* isomer is a doublet centered at τ 5.43 (J = 3.2 c.p.s.). It is known that axial protons show signals at higher field than do those occupying an equatorial position (9). Furthermore, the coupling constant of 3.2 c.p.s. agrees with the axial–equatorial relation of the C_1 and C_2 protons found for *both* conformations of the *cis* isomer, and that of 5.2 c.p.s. is in agreement with an "average" signal obtained from two conformations of the *trans* isomer, one of which has a *trans* diaxial relation for the C_1C_2 protons, the other conformer having these two protons located diequatorially (9) (Reaction Scheme 2).

The *trans*-2-methoxy-3-hydroxytetrahydrofuran gave a singlet at τ 5.22 for the anomeric proton (unresolved even at high resolution). The signal for the anomeric proton of the *cis* isomer was a doublet centered at τ 5.05 (J = 6.3 c.p.s.). These figures support the *trans* and *cis* configurational assignments.

A more detailed discussion of the conformational arrangements will be given in part II in this series.[2]

EXPERIMENTAL

Melting points are uncorrected.

Analyses were carried out with a Burrell K-2 Kromo-Tog on a 2.5 m column packed with either 25% Carbowax 20 M on Gas Chrom P (60–80 mesh) or 20% butanediol succinate on Chromosorb B. Helium was used as the carrier gas at a flow rate of 60 ml/min, and the column temperature was 150°.

Separation of *cis* and *trans* isomers was accomplished with an Aerograph autoprep, model A-700, using a column packed with 25% Carbowax 20 M on Gas Chrom P (temperature 175°) and helium as the carrier gas at a flow rate of 110 ml/min. The equilibrium mixtures of *cis* and *trans* isomers were analyzed by gas–liquid chromatography on the butanediol succinate column by comparison of peak areas with those obtained from known and carefully weighed mixtures. These figures are consistent with those obtained by n.m.r. analyses.

Elemental analyses were carried out by Miss Darlene Roberts, Department of Chemistry, University of Alberta, Edmonton, and by Dr. C. Daessle, 5757 Decelles Avenue, Montreal.

Nuclear magnetic resonance spectra (in $CDCl_3$) were obtained with a Varian A-60 spectrometer. A Perkin–Elmer model 421 grating spectrophotometer was used to obtain infrared spectra of $CHCl_3$ solutions of the compounds.

4,5-Dihydrofuran was prepared, according to a modification (10) of published directions (11), by the base-catalyzed isomerization of commercially available 2,5-dihydrofuran. Fractional distillation in a spinning-band column gave an incomplete separation of the two isomers, as shown by gas–liquid chromatographic and n.m.r. spectroscopic analysis of each fraction. A 4 ft column packed with stainless-steel saddles gave an excellent separation. The 4,5-dihydrofuran boiled at 52.5° and 695 mm, η_D^{20} 1.4228, η_D^{25} 1.4204 (lit. b.p. 53–55° at 745, η_D^{20} 1.4200 (10); b.p. 54.3° at 760 mm, η_D^{20} 1.4282 (12)). The 2,5-dihydrofuran boiled at 63–65° and 700 mm, η_D^{25} 1.4292, η_D^{20} 1.4309.

General Procedure for the Preparation of 2-Alkoxy-3-hydroxytetrahydropyrans and 2-Alkoxy-3-hydroxytetrahydrofurans

To a cold (−10° to −5°) solution of 0.35 mole of commercial 5,6-dihydropyran or 4,5-dihydrofuran (10) in 350 ml of anhydrous alcohol[4] was added, over a period of 25 min with stirring, a suspension of 0.26 mole of peroxybenzoic acid (13) or *m*-chloroperoxybenzoic acid (FMC Corporation, 500 Roosevelt Avenue, Cartaret, New Jersey) in 150 ml of dry chloroform. The temperature during this addition was maintained at −10° to −5°. Stirring was continued at −5° for 15 min after complete addition of the oxidant. The cooling bath was then removed and the reaction mixture was stirred at room temperature overnight. The chloroform, alcohol, and excess dihydropyran (dihydrofuran) were removed under reduced pressure with a rotary evaporator and a water bath at 50°. The residue, consisting of a mixture of benzoic acid or *m*-chlorobenzoic acid and the 2-alkoxy-3-hydroxytetrahydropyran (2-alkoxy-3-hydroxytetrahydrofuran), was shaken vigorously with 400 ml of chloroform, and the mixture then cooled to 0° and filtered under suction. The benzoic acid residue in the funnel was washed twice with 25 ml portions of cold chloroform. The combined chloroform extracts and mother liquor were extracted with 10% aqueous sodium carbonate. Since these alcohols are water soluble, the aqueous sodium carbonate solution was saturated with sodium chloride and extracted in turn with chloroform to recover any of the alcohol. The combined chloroform extracts were dried (Na_2SO_4), filtered, and then freed from solvent (rotary evaporator). The colorless residue was

[4]*For the preparation of the t-butoxy analogue, the dihydropyran (dihydrofuran) was dissolved in a mixture of t-butyl alcohol (225 ml) diluted with chloroform (125 ml) to prevent solidification of the alcohol at these low temperatures.*

fractionally distilled under reduced pressure in a spinning-band column. The results are shown in Tables I and II.

The n.m.r. spectra (in deuteriochloroform) and the infrared spectra (in chloroform) of each product were consistent with the structures assigned.

The 3,5-dinitrobenzoates were prepared by the addition of 1.5 g of commercial 3,5-dinitrobenzoyl chloride to a solution of 500 mg of the alcohol in 5 ml of dry pyridine. The solution was heated in a water bath at 85° for 15 min and cooled, and then the bulk of the pyridine was removed by rotary evaporation. The residue, dissolved in diisopropyl ether or in chloroform, was washed successively with 5 ml quantities of water, 5% aqueous sodium carbonate, and water. The ether was removed, and the resultant glassy material was crystallized three times from aqueous methanol and simultaneously decolorized with charcoal. The solid was dried overnight in a vacuum desiccator at room temperature and 0.3 mm pressure.

2-Alkoxy-3-methoxytetrahydropyrans (2-Alkoxy-3-methoxytetrahydrofurans)

The alcohols were methylated by the silver oxide – methyl iodide procedure with dimethylformamide as solvent (14), or by the reaction of sodium hydride with a solution of the alcohol and methyl iodide in 1,2-dimethoxyethane. The latter method is similar to procedures which have appeared recently (15, 16). A typical experiment, with appropriate modifications, is described below for the methylation of 2-*t*-butoxy-3-hydroxytetrahydropyran. The pyran (16.0 g, 0.092 mole) was dissolved in 100 ml of 1,2-dimethoxyethane[5] containing 14.2 g (0.10 mole) of methyl iodide. The solution, in a 300 ml, three-necked flask equipped with a magnetic stirrer, an efficient condenser, and a thermometer, was cooled to 10° and four equal portions (total of 2.4 g, 0.10 mole) of sodium hydride[6] were added, with stirring, while the reaction mixture was kept at 5–10°. The mixture was then stirred for 2 h while it came to room temperature. The 1,2-dimethoxyethane was removed by distillation at atmospheric pressure until one-quarter of the volume of the mixture remained. The addition of 100 ml of dry diethyl ether precipitated the bulk of the sodium iodide. The filtered solution was freed from ether, and the residue was distilled in a spinning-band column to give 14.9 g (86%) of material boiling at 61–62° and 7 mm, n_D^{25} 1.4322.

The physical constants for the methylated compounds are shown in Tables I and II.

Isomerization of trans- and cis-2-Methoxy-3-hydroxytetrahydropyrans

A solution of pure *trans*-2-methoxy-3-hydroxytetrahydropyran in dry methanol containing a catalytic amount of concentrated hydrochloric acid was refluxed for 2 h. Analysis by gas–liquid chromatography indicated an equilibrium mixture of 61% *trans* and 39% *cis* isomers. Pure *cis*-2-methoxy-3-hydroxytetrahydropyran subjected to the same conditions gave the same proportion of *trans* and *cis* isomers.

The alcoholic solution of the equilibrated mixture was stirred with an excess of solid sodium carbonate as a suspension for half an hour until carbon dioxide evolution ceased. The solution was then filtered and freed from solvent on a rotary evaporator. The residue was dissolved in chloroform, washed with aqueous sodium carbonate (10%), dried (Na_2SO_4), filtered, and then freed from solvent. The isomers were separated with an Aerograph autoprep. It was more convenient to inject the mixture as a solution in an equal volume of solvent ($CHCl_3$), since the injector unit had a holdup of about 2–3 ml.

The *trans*- and *cis*-2-methoxy-3-hydroxytetrahydrofurans were isomerized in a similar manner.

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[5]*Ansul ether 121, treated with lithium aluminium hydride and subsequently distilled from the hydride.*

[6]*Sodium hydride (4.3 g of 56% suspension) from Metal Hydrides Corporation was washed with 1,2-dimethoxyethane to remove the mineral oil. This gave 2.4 g of sodium hydride.*