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CONFORMATION AND THE ANOMERIC EFFECT IN 2-OXY-SUBSTITUTED TETRAHYDROPYRANS

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Abstract—Conformational effects, especially the anomeric effect, were examined in 2-methoxy, -iosbutoxy, -acetoxy and -hydroxy-4-methyltetrahydropyrans as well as the corresponding derivatives of 6-methyl- and 6-oxymethyltetrahydropyran. Results are related to anomeric equilibria of xylose and glucose derivatives.

THE equilibrium between α-D-glucose and β-D-glucose in water favors the β-anomer, which has all substituents equatorial.[1] The β-anomer is more stable by 0·34 kcal/mole in free energy than the α-anomer, which differs in that the OH at the anomeric position (C-1) is in the axial conformation. This energy difference corresponds to a 64:36 preference for the β-anomer. Other pyranoses show similar behavior. Qualitatively this agrees with well known conformational relationships. The OH group of cyclohexanol, for example, is predominantly equatorial, preferring the equatorial conformation by 0·4 to 1·25 kcal/mole (the *A* value), depending rather strongly upon the solvent.[2]

In striking contrast to glucose itself, the α-anomers of methyl glucoside and penta-O-acetyl-D-glucose, as well as glucosyl halides,[3] are lower in conformational energy than the corresponding β-anomers, where all the substituents are equatorial. This preference of electronegative substituents at C-1 of the pyranose ring for the axial conformation has been called the anomeric effect[4] (earlier, the Hassel–Ottar effect), and was attributed by Edward[5] to electrostatic repulsive forces between the C-1 substituent and the atomic dipole moment due to the unshared electron pairs of the pyranose ring oxygen.

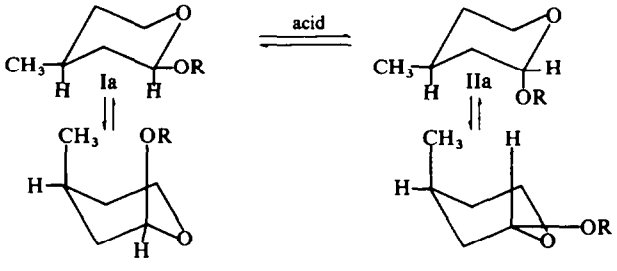
Lemieux[6] was able to correlate free energy differences between anomers of various pyranose acetates with an empirical equation of five terms. The equation, which fits the data well, gives a value of 0·18 kcal/mole for the interaction energy of an axial acetoxyl with one axial hydrogen. This value differs drastically from those for acetoxy and other substituents in cyclohexane and from the interaction energy found by Angyal in cyclitols.[7] Kabayama and Patterson,[8] from the heat of mutarotation of glucose, found an interaction energy of 0·17 kcal/mole for an axial OH at the anomeric position with one axial hydrogen, and suggested that the anomeric effect was the cause of this very low value.

The anomeric effect was evaluated by Bishop and Cooper[3b] at about 1·2 kcal/mole for four anomeric pairs of methyl pentopyranosides. It should be noted that the anomeric effect is in favor of the axial conformation in opposition to the steric effect which normally leads to a preference for the equatorial conformation. Thus for example in the case of methyl xylopyranoside, the difference between the free energy difference

between anomers (−0·48 kcal/mole) and twice the $O_a:H_a$ interaction energy of Angyal[7] (0·40 kcal/mole) is 1·28 kcal/mole. Because the only difference between anomers is the relative orientations of the C-5 to ring-oxygen bond dipole and the C-1 to substituent dipole, the anomeric effect was regarded as the result of the interaction of these two dipoles.

Inevitably in quantitative conformational studies of carbohydrates and other polyols, the multiplicity of substituents leads to uncertainty as to what the causes of the measured effect are, and how much is due to which cause. In an effort to simplify the considerations with respect to dipolar, steric, solvent and hydrogen bonding effects, we have prepared some simple substituted tetrahydropyrans[9] which might also be considered deoxypyranoses. The tetrahydropyrans chosen have a methyl group in a 1,3-relation to the anomeric oxy-substituent. This methyl in a 1,3 relationship is sufficient to guarantee satisfactory conformational homogeneity of both *cis* and *trans* isomers. A similar investigation[10] of the anomeric effect in a tetrahydropyran system employed derivatives of 4-oxa-5α-cholestan-3α-ol where the fused ring system maintained conformational homogeneity. The results are in agreement with those reported here.

An *a priori* conformational consideration of the *cis*-2-oxy-4-methyltetrahydropyran indicates that the diequatorial conformer (Ia) should be considerably more stable than the diaxial conformer (Ib) by half the *A* value of methyl (1·7 kcal/mole),[11] half the *A* value of the oxy-substituent (ca. 0·7 kcal/mole)[11] and the 1,3-*syn*-diaxial interaction (ca. 2·4 kcal/mole)[11] but less stable by the anomeric effect (ca. 1·3 kcal/mole[3b,4,9]). The total difference of ca. 2·3 kcal/mole indicates that the conformational equilibrium Ia ⇄ Ib must be overwhelmingly in favor of Ia (ca. 98:2).



Ib IIb

The *trans*-2-oxy-4-methyltetrahydropyran is more stable with the oxy-substituent axial (IIa) rather than equatorial (IIb) by the *A* value of methyl (1·7 kcal/mole) and the anomeric effect of the oxy-substituent (ca. 1·3 kcal/mole)[3b,4,9] less the *A* value of the oxy-substituent (ca. 0·7 kcal/mole). This difference in free energy of ca. 2·3 kcal/mole is sufficient to ensure that the trans isomer is 98% the 2-axial-4-equatorial conformer (IIa). The situation with the 2-oxy-6-methyltetrahydropyrans is analogous.

The oxy-substituents examined were isobutoxy, methoxy, acetoxy and hydroxy. In general, the compounds were prepared from either 2-isobutoxy-4-methyltetrahydropyran or the 6-methyl isomer which could be easily obtained by Diels–Alder reaction of isobutyl vinyl ether with crotonaldehyde or methyl vinyl ketone.[12]

Exchange of the butoxy group in methanol or acetic acid under acid catalysis afforded the methoxy and acetoxy derivatives. The isobutoxytetrahydropyran could be converted to the dihydropyran by distillation from toluenesulfonic acid in high yield.[13] Methanol, acetic acid and water could be added to the dihydropyrans yielding the same compounds.

The cis and trans isomers of all compounds except the hemiacetals could be separated preparatively (and analytically) by VPC although the 2-acetoxy-6-acetoxymethyltetrahydropyrans suffered some elimination. These *cis* and *trans* isomers could be distinguished by their NMR spectra (Table 1). The isomer which displays the signal for the anomeric proton at higher field was identified as that with the axial proton,[14] that is, the *cis* isomer, Ia. The other isomer is then the *trans* isomer, IIa, with the anomeric proton equatorial. The observed multiplicities of these anomeric signals are also those expected, a quartet for the axial anomeric proton and an unresolved multiplet of smaller coupling constant for the equatorial anomeric proton. Although the hemiacetals, the 2-hydroxytetrahydropyrans, could not be analyzed by VPC, the signals of each isomer could be observed in the NMR spectrum.

When either the pure *cis* or the pure *trans* isomer was dissolved in a solvent at a concentration of ca. 0·1M with ca. 0·001M toluenesulfonic acid, the isomers were equilibrated to mixtures of the same composition. The mixtures were analyzed by VPC on a Carbowax 4000 column without prior work-up. A slight difference in thermal response for the *cis* and *trans* isomers was taken into account. The *cis*:*trans*

TABLE 1. NMR SPECTRAL DATA OBTAINED IN CARBON TETRACHLORDE AT 40°C WITH A VARIAN A-60 NMR SPECTROMETER

Tetrahydropyran derivative	*cis*-isomer			*trans-isomer*	
	Chemical shift[a] of anomeric H, τ	$J_{1a,2a}$ c/s	$J_{1a,2e}$ c/s	Chemical shift[a] of anomeric H, τ	Half width c/s
2-Iso-butoxy-4-methyl	5·71	8·5[b]	2·0[b]	5·30	6·5
2-Methoxy-4-methyl	5·85	8·3	2·2	5·43	6·0
2-Acetoxy-4-methyl	4·51	9·0	2·5	3·97	6·0
2-Hydroxy-4-methyl	5·42	8·6	2·0	4·83	7·0
2-Isobutoxy-6-methyl	5·69	8·1	2·6	5·12	5·0
2-Methoxy-6-methyl	5·61	8·7	2·4	5·23	5·1
2-Acetoxy-6-methyl	4·22	8·5	2·5	3·70	4·8
2-Methoxy-6-hydroxymethyl	5·74	8	2·4	5·33	4·0
2-Acetoxy-6-acetoxymethyl	4·37	8	—	3·92	4·0
2-Hydroxy-6-hydroxymethyl	5·22	*c*	*c*	4·65	6·7
2-Methoxy	5·55[d]				4·5
2-Acetoxy	4·12[d]				5·5
2-Hydroxy-25m%	5·12[d]				7·5

[a] Relative to tetramethyl silane as an internal reference
Concentration of samples was 10 volume per cent in CCl_4 unless otherwise noted
Error is ±0·01 τ

[b] Error is ±0·5 c/s

[c] Unresolved multiplet due to coupling with OH

[d] A time averaged chemical shift.

response ratio was determined by analyzing, under the same conditions, mixtures of composition similar to the equilibrium mixtures. In each case the peak having the shorter retention time (*trans*) was favored by 1 ± 1% in peak area. Some of the equilibrium mixtures were also analyzed by NMR spectroscopy where the integrated areas of the anomeric protons represent the ratio of *cis* and *trans* isomers. Because NMR methods were the only means of analysis possible for the 2-hydroxytetrahydropyrans, the equilibria were measured by integration of the anomeric signal areas and by the method of Eliel[15] ($\delta = N_1\delta_1 + N_2\delta_2$) in which the chemical shift of the mobile 2-hydroxytetrahydropyran (δ) is the weighted average (N is mole fraction) of the corresponding chemical shifts for the anomeric proton in the conformationally rigid *cis* and *trans* -2-hydroxy-4-methyltetrahydropyrans (δ_1 and δ_2).

The equilibrium compositions for various 2-oxy-substituted tetrahydropyrans in various solvents are listed in Table 2. It can be seen that for 2-alkoxy and 2-acetoxy-tetrahydropyrans, the axial conformation is preferred. Furthermore there is evident

TABLE 2. EQUILIBRATION DATA FOR VARIOUS TETRAHYDROPYRANS

Tetrahydropyran derivative	Solvent[a]	Per cent trans[b] isomer (IIa)	Method[c] of analysis
2-Isobutoxy-4-methyl	dioxan	79	VPC
	acetonitrile	70	VPC
	50 m% H_2O-acetone	69	VPC
2-Methoxy-4-methyl	dioxane	77	VPC
	methanol	69	VPC
	acetonitrile	65	VPC
	50 m% aqueous methanol	66	VPC
	30 m% aqueous methanol	64	VPC
2-Acetoxy-4-methyl	90 V% CCl_4	72	NMR-2
	1:1 Ac_2O–AcOH	72	NMR-1
	acetic acid	75	VPC, NMR-1
2-Hydroxy-4-methyl	neat	53	NMR-2
	25 m% CCl_4	50	NMR-1, 2
	95 m% CCl_4	58	NMR-2
	90 V% in D_2O	43	NMR-2
	5 V% in D_2O	34	NMR-2
2-Isobutoxy-6-methyl	dioxan	78	VPC
	acetonitrile	67	VPC
2-Methoxy-6-methyl	methanol	67	VPC
2-Acetoxy-6-methyl	acetic acid	75	VPC
2-Methoxy-6-hydroxymethyl	methanol	70	NMR-1
2-Acetoxy-6-acetoxymethyl	acetic acid	75	NMR-1
2-Hydroxy-6-hydroxymethyl	D_2O	37	NMR-1

[a] Concentration of samples 10 volume per cent unless otherwise noted.
[b] Errors: VPC ±2%, NMR −1 ±2%, NMR −2 ±2–3%.
[c] VPC reaction temperature was 25°, concentration of sample was 0·1M.
NMR-1 is analysis by integration of anomeric protons, reaction temperature 40°, 10 V%.
NMR-2 is analysis by chemical shift method (Ref.15), temp 40°, 10 V%.

a rather small dependence on the solvent in that there is less *trans* isomer, IIa, in polar solvents like methanol and acetonitrile compared to the less polar dioxan. Comparison of equilibrations of 2-methoxy-4-methyl-tetrahydropyran in methanol, acetonitrile, and in 50 mole per cent aqueous methanol, which have dielectric constants of 33, 38 and 50 respectively,[16] does not show an increased proportion of equatorial isomer in the hydrogen bonding solvents over that in acetonitrile.

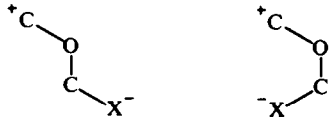
As stated earlier, the anomeric effect may be calculated as the sum of the free energy difference between *cis* and *trans* isomers and the *A* value for the oxy-substituent. For 2-methoxy-4-methyltetrahydropyran in dioxan, the anomeric effect is 0·71 + 0·6 or 1·3 kcal/mole, however in aqueous methanol, the anomeric effect is as low as 0·34 + 0·6 or 0·9 kcal/mole. The conformational effects for the isobutoxy group are the same as for methoxy probably because the additional three carbons are remote from the substituent oxygen atom. For the 2-acetoxy-4-methyltetrahydropyran in acetic acid, the anomeric effect is 0·65 + 0·7 or 1·35 kcal/mole.

The situation in the case of the 2-hydroxytetrahydropyrans is also consistent with these values of the anomeric effect and the *A* value of the hydroxyl group although this is not very obvious from Table 2. If the anomeric effect for the OH group in water is similar to that of methoxy in aqueous methanol, which was 0·9 kcal/mole, and if the *A* value of hydroxyl in water is taken as 1·25 kcal/mole,[17] then the equilibrium should favor the equatorial conformation by ca. 0·35 kcal/mole, in good agreement with the observed free energy of 0·41 kcal/mole (66% equatorial, Table 2). In carbon tetrachloride the position of the equilibrium for the 2-hydroxytetrahydropyran is shifted toward the axial side to the extent of 60% axial probably because of a decrease in the *A* value of hydroxy as well as because of the lower dielectric constant of the solvent which would increase the anomeric effect. In 95% carbon tetrachloride, the IR spectrum shows that the OH group is still strongly hydrogen bonded. Therefore one might expect that if it were possible to make measurements at greater dilution, the percentage of axial isomer would approach that of the methoxy and acetoxy compounds.

Calculation of the energy difference in dipole–dipole interaction between the two conformers can be made by simple application of Coulomb's Law ($U = e_1e_2/\varepsilon r$ where U is potential energy; e, the charge; r, the distance between charges; and ε, the dielectric constant) and the definition of dipole moment ($\mu = ed$, where μ is the bond moment; e, the charge separation; and d, the bond length). If in the case of the 2-methoxytetrahydropyran the O—Me bond dipole is temporarily neglected, the only difference between the axial and equatorial anomers is the distances between position 6 of the tetrahydropyran ring and the oxygen of the anomeric OMe. The situation is analogous for the 2-chloro- and 2-bromotetrahydropyrans which will be considered for comparison.[18] The difference between the potential energies at the distances r_{ax} and r_{eq} can be written:[18] $\Delta U = e_1e_2[1/\varepsilon_{ax}r_{ax} - 1/\varepsilon_{eq}r_{eq}]$. The distances ($r_{ax}$ and r_{eq}) may be measured from Dreiding molecular models with sufficient accuracy for this calculation. The charges at position 6 of the tetrahydropyran ring and that at the anomeric substituent, e_1 or e_2, are μ_{CX}/d_{CX} but that for oxygen is $2\mu_{CO}/d_{CO}$.

The dielectric constants in the equation are not the bulk dielectric constant of the solvent but the effective microscopic dielectric constants between the charges. If the ends of the dipoles are imagined at the ends of ellipsoidal volumes through

which most of the lines of force are concentrated, it is seen that the C—O—C—X bonds fill the ellipsoid for the equatorial anomer, filling the space between the ends of the dipoles (Structure III), while in the axial anomer these parts of the molecule are peripheral to such an ellipsoid (Structure IV). The polarization of the bonds



III IV

within the ellipsoidal volume by the electrostatic field screens the charges from each other and constitutes an increased dielectric constant. One might expect ε_{eq} to be about 2 which is the macroscopic dielectric constant for compounds without permanent dipoles, and ε_{ax} to be close to 1 as in a vacuum. The dielectric constant ε_{eq} can be estimated from the index of refraction (n) using Maxwell's relation $\varepsilon = n^2$. Such a dielectric constant obtained from the index of refraction of visible light allows only for electronic polarization as is appropriate here. If the portion of the molecule (C—O—C—X) inside the ellipsoid is approximated by dimethoxymethane, chloromethyl ether or bromoethyl ether for the respective substituted tetrahydropyrans, the index of refraction for the ellipsoid in the direction along r_{eq} can be calculated from the longitudinal polarizabilities and bond refractions calculated by Denbigh,[19] using also the Lorenz–Lorentz equation, $[R] = M(n^2 - 1)/\rho(n^2 + 2)$ where M and ρ are the molecular weight and density respectively and $[R]$, the molar refraction. The dielectric constants (ε_{eq}) obtained for the methoxy, chloro, and bromo compounds were 1·9, 2·2 and 2·4 which is the order of bond polarizability:[19] C—O < C—Cl < C—Br. These values are average dielectric constants over the entire molecular volume and therefore since the electrostatic lines of force will be concentrated along the more dense part of the molecule, these values will probably be too small and too similar. The solvent has been disregarded entirely in estimating the dielectric constant because the solvent is peripheral to the ellipsoidal volume, it is simpler to do so, and the effect of solvent on the anomeric effect was not found to be large. Using these dielectric constants for ε_{eq}, unity for ε_{ax}, bond moments of C—O, C—Cl, and C—Br as 1·1, 2·0 and 2·0 D respectively (from alkyl ethers and halides other than methyl)[20] and bond lengths 1·43, 1·77 and 1·91 Å respectively,[21] differences in electrostatic energy between axial and equatorial anomers of 3·7, 2·8 and 2·6 kcal/mole were obtained for the 2-methoxy-, 2-chloro-, and 2-bromotetrahydropyrans respectively.

The calculation for methoxytetrahydropyran so far neglected the dipole of the OMe. Examination of molecular models leads to the conclusion that one rotamer of the axial anomer is considerably more favored than the others for steric and electrostatic reasons. The most favorable rotamer is that in which the O—Me bond bisects the ring-oxygen-C—H angle. For the equatorial anomer there are two rotamers of similar energy. These rotamers are those in which the O—Me bond bisects the ring-O—C—H angle and the ring-O—C—C angle. The other rotamer may be excluded because of less favorable electrostatic interactions. Using measurements from models, the electrostatic energy difference between the most stable rotamer of the axial and

equatorial anomers due to the OMe bond dipole can be calculated then as 1·9 kcal/mole in favor of the equatorial form (including an entropy contribution). If this value is subtracted from the 3·7 kcal/mole, calculated above neglecting the O—Me dipole, 1·8 kcal/mole is obtained for the calculated value of the anomeric effect for 2-methoxytetrahydropyran.

The values calculated for the anomeric effect are then 1·8, 2·8 and 2·6 kcal/mole for the 2-methoxy-, 2-chloro-, and 2-bromotetrahydropyrans which approximate the respective experimental values of 1·3, 2·7 and greater than 3·2 kcal/mole.[18] The differences between experimental and calculated values might easily be attributed to the propagation of error in the calculation. However, besides the choice of dielectric constants, there are important approximations in the fundamental assumptions: that molecular dipoles can be regarded as resultants of bond dipoles with lengths equal to their bond lengths, and that bond dipoles are permanent dipoles whose magnitudes are unaffected by other dipoles in the molecule. Although such calculations are approximate, they may provide a convenient estimate of magnitudes when experimental values are not available.

The conformational equilibria for the simple 2-oxytetrahydropyrans are very similar in magnitude to the anomeric equilibria of xylose and glucose derivatives, as can be seen in Table 3. This supports the contention that the dipole–dipole interaction of the anomeric substituent with the carbon to ring oxygen bond is the

TABLE 3. PERCENT AXIAL ANOMERIC SUBSTITUENT AT EQUILIBRIUM AT 25°

2-Acetoxy-4-methyltetrahydropyran	75%[a]
2-Acetoxy-6-methyltetrahydropyran	75[a]
2-Acetoxy-6-acetoxymethyltetrahydropyran	75[a]
D-Xylose tetraacetate	78·5[b]
D-Glucose pentaacetate	88[b]
6-Deoxy-D-glucose tetraacetate	88·5[b]
2-Deoxy-D-glucose tetraacetate	89[b,c]
2-Methoxy-4-methyltetrahydropyran	69[d]
2-Methoxy-6-methyltetrahydropyran	67[d]
2-Methoxy-6-hydroxymethyltetrahydropyran	70[d]
Methyl-D-xyloside	68·6[e]
Methyl-D-glucoside	77[f]
2-Hydroxy-4-methyltetrahydropyran	34[g]
2-Hydroxy-4-hydroxymethyltetrahydropyran	37[g]
D-Xylose	36[h]
D-Glucose	36[h]

[a] Acetic acid solvent with ca. 0·001M HOTs.
[b] Ref. 3*a* 50% acetic acid–acetic anhydride with 0·5M H_2SO_4; analyzed by optical rotation
[c] W. A. Bonner, *J. Am. Chem. Soc.* **83**, 962 (1961).
[d] Methanol solvent with ca. 0·001M HOTs.
[e] Ref. 3*b* 0·5% HCl in methanol. Analysis by a VPC method at 35°.
[f] Ref. 1, p. 375; C. L. Jungius, *Z. Physik. Chem.* **52**, 97 (1905).
[g] Deuterium oxide solvent with or without 0·001M HOTs.
[h] Ref. 1. p. 408 in water. Analysis by rotation.

principal controlling factor in anomeric equilibria of pyranose derivatives, and that the other dipolar substituents of the pyranose ring have only minor effects. Minor differences between pyranose and tetrahydropyran derivatives will be noted however.

A very minor effect evident in Table 3 is the difference in percent axial anomer between the acetoxytetrahydropyrans and xylose tetraacetate (75 *vs* 78·5%). One might expect that the oxy-substituents at C-3 and C-4 of the pyranose acetate would have an electrostatic effect on the anomeric substituent. Calculation of such a dipole–dipole interaction gives an energy difference of about zero if distances are measured from molecular models and if dielectric constants are estimated. This result is in reasonable agreement with experiment, ca. 0·1 kcal/mole (75 *vs* 78·5%), considering that the calculation involves so many numbers that the propagation of errors makes the answer largely fortuitous. This effect should be sensitive to the polarity of the solvent and thus be negligible in water.

The glucose pentaacetate equilibrium is distinctly higher in axial anomer than are the 2-acetoxytetrahydropyrans (88 *vs* 75%). Similarly the methyl glucoside is 77% α while the 2-methoxytetrahydropyrans are about 69% axial. It is apparent (Table 3) that the larger amount of axial anomer for glucose pentaacetate is not caused by the polar effect of the 6-acetoxyl substituent, as has been suggested,[6] because 2-acetoxy-6-acetoxymethyl tetrahydropyran is 75% axial while 6-deoxy-D-glucose tetraacetate is nevertheless 88·5% axial. One might suspect that the larger degree of axial anomer is due to the presence of a substituent (an oxy group) at C-4 of the pyranose ring in addition to a large substituent at C-5 (methyl or oxymethyl). Conformational effects of steric interactions between vicinal large groups have recently been studied by Eliel and coworkers[22] in cyclohexane systems. In connection with this problem, 2-methoxy-*trans*-5,6-dimethyltetrahydropyran has been found to be 76% axial methoxy at equilibrium in methanol,[23] substantially more than the 2-methoxy-4- or -6-methyltetrahydropyrans (69%). There appears, however, to be more to this problem than steric effects because the discrepancy is largest for glucose pentaacetate in acetic acid (88 *vs* 75% for the 2-acetoxytetrahydropyrans), smaller for methyl glucoside (77 *vs* 69%), and zero for glucose in water which suggests a solvent effect, possibly the effect of dielectric constant on a dipolar interaction. Consequently the question of the minor difference between the percent of axial anomer in glucose pentaacetate and the 2-acetoxytetrahydropyrans must be left unanswered for the present.

EXPERIMENTAL

2-Isobutoxy-4-methyltetrahydropyran.[12,13] A mixture of freshly distilled crotonaldehyde (196 g) and isobutyl vinyl ether (306 g) was heated in a stainless steel autoclave at 190–200° for 1 hr. The resulting yellow liquid was distilled under reduced press, yielding 207 g (44% yield) of colorless 2-isobutoxy-4-methyl-2,3-dihydropyran, b.p. 75–77° (10 mm) [lit.[12] b.p. 122° (10 mm); b.p.[13] 75·5 (12 mm)]. A residue of presumably polymeric material remained. The product was hydrogenated at room temp in 95% EtOH over 10% Pd–C catalyst. After filtration, the soln was distilled yielding 156 g 2-isobutoxy-4-methyltetrahydropyran (75% yield), b.p. 86–90° (13 mm) [lit.[13] 91° (16 mm)].

2-Methoxy-4-methyltetrahydropyran. At room temp, 34 g 2-isobutoxy-4-methyltetrahydropyran were treated with 135 g of abs MeOH and 0·05 g *p*-toluene sulfonic acid. The disappearance of the isobutoxytetrahydropyran was followed by gas chromatography using a 1 meter column of 20% Carbowax 4000 on 60/80 mesh non-acid washed Chromosorb W. The soln was neutralized with $NaHCO_3$, the solvent

distilled off, and the residue distilled, b.p. 35–45° (10 mm). (Found: C, 64·30; H, 10·70. $C_7H_{14}O_2$ requires: C, 64·58; H, 10·84.) The liquid was fractionated on a spinning band column under reduced press giving an overall 20% yield of the two isomers of 2-methoxy-4-methyltetrahydropyran in two fractions: *trans* 30° (9 mm), and *cis* b.p. 40° (9 mm).

2-Acetoxy-4-methyltetrahydropyran. A soln of 75 g isobutoxy-4-methyltetrahydropyran, 47 g Ac_2O, 645 g of glacial HOAc and 0·1 g *p*-toluene sulfuric acid was stirred overnight at room temp. NaOAc was added to neutralize acid, and the soln was distilled to remove solvent. The dark concentrated soln was fractionated under reduced press yielding 8 g (10%) 2-acetoxy-4-methyltetrahydropyran, b.p. 70–71° (8 mm). (Found: C, 60·65; H, 8·93. $C_8H_{14}O_3$ requires: C, 60·74; H, 8·92.) A dark resin remained in the distillation flask. The *cis* and *trans* isomers were preparatively separated by GC using a 2 m × ½ in. column of 20% Carbowax 4000 on non-acid washed Chromosorb W.

2-Hydroxy-4-methyltetrahydropyran.[24] A soln of 173 g 2-isobutoxy-4-methyltetrahydropyran and 335 g 3% H_2SO_4 was heated on a steam bath for 1 hr and then steam distilled. The aqueous layer of the distillate was continuously extracted with ether for 3 days. The ether extract was combined with the organic layer of the steam distillate and dried. Evaporation of the ether followed by distillation yielded 12 g of 2-hydroxy-4-methyltetrahydropyran, b.p. 75–80° (5 mm) [lit.[24] b.p. 84–85° (15 mm)].

2-Isobutoxy-6-methyltetrahydropyran. A mixture of 141 g of methyl vinyl ketone and 212 g of isobutyl vinyl ether was heated in an autoclave for 2 hr at 180°. The product was distilled yielding 110 g (33% yield) 2-isobutoxy-6-methyl-2,3-dihydropyran, b.p. 79–82° (14 mm) [lit.[12] b.p. 117–119 (100 mm)]. The dihydropyran (110 g) was hydrogenated as above. The product was distilled after filtration and concentration yielding 82 g (80%) b.p. 49–51° (2 mm). (Found: C, 69·51; H, 11·63. $C_{10}H_{20}O_2$ requires: C, 69·72; H, 11·71.) The *cis* and *trans* isomers were then separated preparatively by GC using a 2 m × ½ inch column of 20% Carbowax 4000 on non-acid washed Chromosorb W.

2-Methoxy-4-methyltetrahydropyran.[25] A soln of 2-isobutoxy-6-methyltetrahydropyran and 89 g of abs MeOH with 0·03 g toluenesulfonic acid was stirred overnight at room temp. After neutralizing with $NaHCO_3$ and removing MeOH, the soln was distilled under reduced press, yielding 7 g (24% yield), b.p. 85–90° (20 mm) [lit.[25] b.p. 71·5–76 (11 mm)]. The pure *cis* and *trans* isomers were isolated by preparative gas chromatography on 1 m × ½ in Carbowax 4000 columns.

2-Acetoxy-6-acetoxymethyltetrahydropyran. The available 3,4-dihydro-2H-pyran-2-methanol (23 g) was heated in 18 g HOAc at 95–100° for 12 hr. A gram of anhyd NaOAc and 30 ml Ac_2O were added, and the soln was heated at 140° for 3 hr. The soln was extracted with ether and $NaHCO_3$ aq. The ether extract was dried, filtered and evaporated. The residue was distilled into fractions (1) b.p. 53–55° (0·3 mm), 49 g; (2) 55–105° (0·3 mm), 1·25 g and (3) 105–106° (0·3 mm), 16 g, n_D^{25} 1·4473. IR analysis showed fraction 2 to be the acetylated dihydropyran. Fraction 3 was an epimeric mixture of the desired compound. (Found: C, 55·34; H, 7·23. $C_{10}H_{16}O_5$ requires: C, 55·55; H, 7·46.)

2-Methoxy-6-hydroxymethyltetrahydropyran.[26] The available 3,4-dihydro-2H-pyran-2-methanol (47 g) was mixed with 136 g MeOH and 3 drops conc HCl, and the soln was allowed to stand for one day at room temp. The soln was neutralized with $NaHCO_3$ and the MeOH distilled off. The residue was distilled, b.p. 51–60° (0·3 mm) [lit.[26] b.p. 70–75° (1·8 mm)]. Analysis by VPC indicated the distillate was a mixture of *cis* and *trans* isomers. The isomers were separated preparatively on a 1 m × ½ in column of 20% Carbowax 4000 on non-acid washed Chromosorb W.

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