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THE REMOTE EFFECT OF VICINAL LARGE GROUPS ON THE ANOMERIC EQUILIBRIUM: 2-METHOXY-*CIS*- AND -*TRANS*-5,6-DIMETHYLTETRAHYDROPYRANS

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Abstract—The anomeric equilibrium of 2-methoxy-*trans*-5,6-dimethyltetrahydropyran was found to have an enhanced fraction of axial methoxyl compared to 2-methoxy-4- or -6-methyltetrahydropyran. The 2-methoxy-*cis*-5,6-dimethyltetrahydropyran did not. The enhanced anomeric effect is attributed to a steric repulsion between the *trans* vicinal Me groups. A similar effect is postulated for methyl glucoside and glucose pentaacetate.

RECENTLY we showed[1] that simple 2-hydroxy-, 2-methoxy-, and 2-acetoxy-tetrahydropyran derivatives have about the same percentages of 2-axial isomers as do related pyranoses (Table 1) at equilibrium. The predominance of the α-isomer (axial C-1 substituent) over the β-isomer (equatorial C-1 substituent) for methyl pyranosides and pyranose acetates is called the anomeric effect. It has been shown that this effect is due to a dipole-dipole interaction between the ring C—O—C bond dipoles and the dipole of the electronegative substituent at the tetrahydropyran 2-position (or C-1 in pyranoses), the anomeric position.[2–4, 1]

The greater percent of axial anomer in methyl glucoside (77% α) over that found for methyl xyloside (68·6% α) and the 2-methoxytetrahydropyrans (ca. 69% axial) was considered anomalous. This anomaly is more pronounced if the glucose pentaacetate (88% α) is compared with xylose tetraacetate (78·5% α) and the 2-acetoxytetrahydropyrans (75% axial)· It has been suggested that the larger fraction of α-anomer in glucopyranose derivatives may be due to a polar effect of the 6-oxymethyl,[5] but this is not tenable because 6-deoxyglucose tetraacetate is the same (88·5% α) as glucose pentaacetate (88% α). Furthermore the percent of α-galactose pentaacetate is much less (79% α), the same as xylose tetraacetate (78·5% α). It was suggested that xylose tetraacetate has slightly more axial anomer than the 2-acetoxytetrahydropyrans because of a dipolar effect from the C-3 and C-4 acetoxyls.[1]

It was suspected that the larger degree of axial anomer for the glucose derivatives is due to the presence of a substituent (an oxy-group) at C-4 of the pyranose ring vicinal to a large substituent at C-5 (methyl or an oxymethyl). Two large vicinal groups may minimize steric repulsions by expanding the dihedral angle between them. Such a torsional effect between *trans*-5,6-substituents on a tetrahydropyran ring would tend to flatten the ring slightly and increase the distance between axial-2 and axial-6 substituents thus reducing the steric interaction for an axial group at the anomeric position. A similar torsion between *cis*-vicinal groups, moving them apart, tends to increase the puckering of the ring. Comparising these effects on Dreiding molecular models easily convinces one that the *cis*-vicinal groups cannot

TABLE 1. PER CENT 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 tetratetraacetate	78·5%[b]
D-Glucose pentaacetate	88%[b]
6-Deoxy-D-glucose tetraacetate	88·5%[b]
2-Deoxy-D-glucose tetraacetate	89%[b,c]
D-Galactose pentaacetate	79%[b]
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]
Methyl-D-galactoside	71%[i]
2-Hydroxy-4-methyltetrahydropyran	34%[g]
2-Hydroxy-4-hydroxymethyltetrahydropyran	37%[g]
D-Xylose	36%[h]
D-Glucose	36%[h]
D-Galactose	36%[h]

[a] Acetic acid solvent with ca. 0·001M HOTs.

[b] W. A. Bonner, *J. Am. Chem. Soc.* **81**, 1450 (1959); 50% AcOH Ac_2O with 0·5M H_2SO_4; analyzed by optical rotation.

[c] W. A. Bonner, *Ibid.* **83**, 962 (1961).

[d] MeOH solvent with ca. 0·001M HOTs.

[e] Ref. 3*b*; 0·5% HCl in MeOH. Analysis by a VPC at 35°.

[f] Ref. 2, p. 375; C. L. Jungius, *Z. physik. Chem.* **52**, 97 (1905).

[g] D_2O solvent with or without 0·001M HOTs.

[h] Ref. 2, p. 408 in water. Analysis by rotation.

[i] Calculated from Ref. 11. This number is probably not accurate, but is the best available.

move away from each other while the *trans*-vicinal groups can more easily. An analogous effect has been used to explain the relative ease of forming ketals from *cis*-1,2-cyclohexanediols, compared to the *trans*-1,2-diols.[6] In this case torsion which moves *cis*-vicinal oxy-groups together aids formation of the ketal while torsion which moves *trans*-vicinal oxy-groups together is prohibitive in ring strain. In order to test this hypothesis, we proposed to study the anomeric equilibrium in the 2-methoxy-*cis*- and *trans*-5,6-dimethyltetrahydropyrans.

The compounds could be synthesized from 2-isobutoxy-5-methyl-3,4-dihydro-2*H*-pyran which could be obtained by Diels–Alder reaction of methacrolein and isobutyl vinyl ether. Addition of hydrogen chloride to this dihydropyran derivative followed by treatment with methyl magnesium iodide yielded a mixture of isomers of 2-isobutoxy-5,6-dimethyltetrahydropyran as well as several other products. Treatment of the isobutoxy compound in HCl–methanol yielded a mixture of 2-methoxy-5,6-dimethyltetrahydropyrans. A better method for the preparation of the methoxytetrahydropyrans is *via* the acid catalyzed elimination of isobutanol from the 2-isobutoxy compound giving a mixture of *cis* and *trans*-2,3-dimethyl-3,4-

dihydro-2*H*-pyrans. The separated pure *cis*-isomer and the pure *trans*-isomer were treated separately with acidic methanol giving the respective anomeric mixtures of 2-methoxy-*cis*-5,6-dimethyltetrahydropyrans and 2-methoxy-*trans*-5,6-dimethyltetrahydropyrans. Elemental analysis and NMR spectral analysis of the 2,3-dimethyl-3,4-dihydro-2*H*-pyrans and the 2-methoxy-5,6-dimethyltetrahydropyrans was sufficient to identify the isomeric compounds.

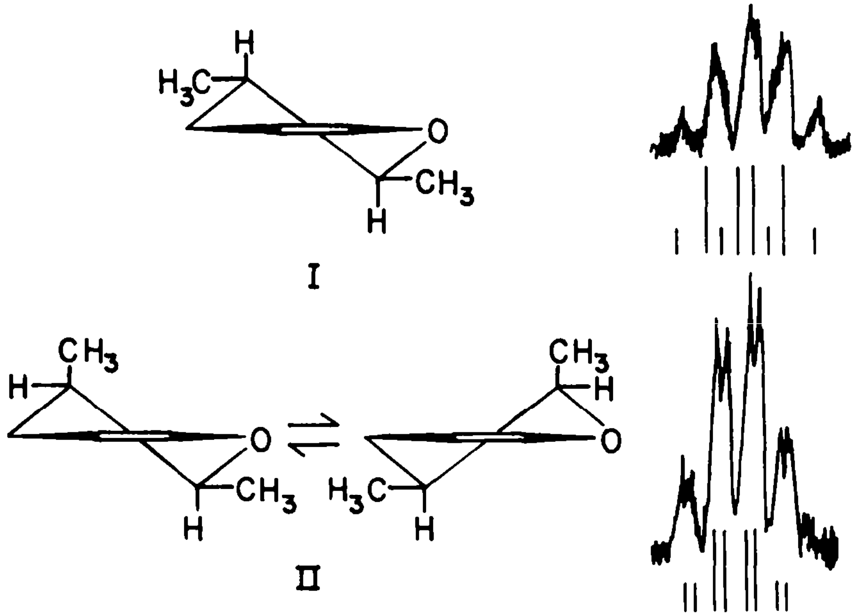


FIG. 1

The NMR spectrum of the *trans*-2,3-dimethyl-3,4-dihydro-2*H*-pyran, I, shows H_2 as a "quintet" (Fig. 1) at a chemical shift of 3·5 ppm downfield from TMS (J = 6, 9 c/s). The NMR spectrum of the *cis*-isomer, II, has a quartet of doublets at lower field δ = 3·9 ppm (J = 6, 2 c/s) which is consistent with a time averaged signal. The signal at higher field is identified as that with the axial proton.[7] Fig. 1 shows that first order analysis of coupling constants fits the observed multiplets.

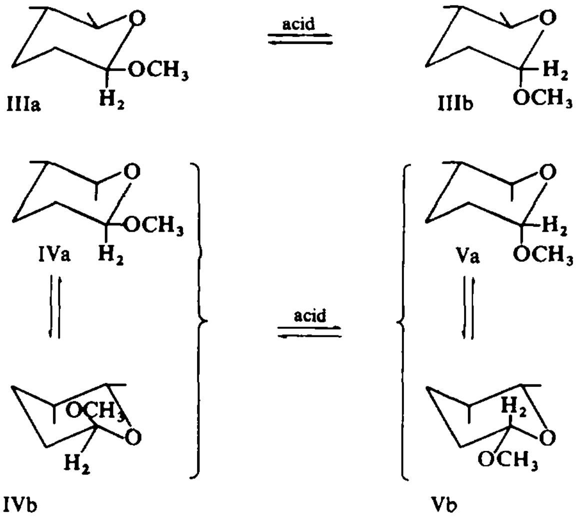
Each pure isomer of the 2,3-dimethyl-3,4-dihydro-2*H*-pyran was treated with acidic methanol to form an anomeric pair of isomers which, after separating them by preparative GC, could be distinguished by their NMR spectra (Table 2). The NMR spectra of the two anomers formed from the *trans*-dimethyldihydropyran shows signals for the anomeric protons, H_2, at 4·16 ppm (quartet, J = 2,2 8·5 c/s; $w_{\frac{1}{2}}$ = 11·94 c/s) and at 4·54 ppm (unresolved multiplet, $w_{\frac{1}{2}}$ = 5·04 c/s). The anomer IIIa with the anomeric proton at the higher chemical shift is then identified as that with H_2 axial[7] and the OMe group equatorial. The multiplicities observed are in agreement with the assignment. The signal for the proton H_6 in both cases is similar to that observed for the *trans*-dimethyldihydropyran in shape (Fig. 1) and chemical shift. The *cis*-dimethyldihydropyran derivative, II, when treated with acidic methanol also gave an anomeric mixture, IV and V, each anomer of which must be an equilibrium mixture of two conformers (IVa $\rightleftarrows$ IVb and Va $\rightleftarrows$ Vb). After separating the

TABLE 2. NMR SPECTRAL MEASUREMENTS OF DIMETHYLPYRAN AT 40° IN CARBON TETRACHLORIDE

Structure number	Anomeric Proton			C—C$\underline{H}$(Me)O		Gas chromatography retention Time, min
	δ ppm	J c/s	$w_{\frac{1}{2}}$ c/s	δ ppm	J c/s	
I	—	—	—	3·48	6, 9	—
II	—	—	—	3·95	2, 6	—
IIIa	4·16	2·2, 8·6	11·94 ± 0·08[a]	3·03	6·2, 8·4	21·9
IIIb	4·54	—	5·04 ± 0·16[a]	3·36	6·4, 8·5	13·5
IVa, b	4·53	—	6·38 ± 0·06[a]	3·97	2·5, 6·5	17·0
Va, b	4·19	—	11·72 ± 0·08[a]	3·58	2·5, 6·5	24·3

[a] Measured using the Varian HA-100 NMR spectrometer, probe at 30°.

two anomers by GC, the NMR spectra were compared. The NMR spectrum of the anomer with the shorter retention time in GC shows a quarter of doublets for H_6 at 3·97 ppm (J = 2·5, 6·5) and H_2 at 4·53 ppm ($w_{\frac{1}{2}}$ = 6·38 ± 0·06 c/s). The NMR spectrum of the other anomer shows a quartet of doublets at 3·58 ppm for H_6 (J = 2·5, 6·5 c/s) and an unresolved multiplet at 4·19 ($w_{\frac{1}{2}}$ = 11·72 ± 0·08 c/s).



An *a priori* conformational analysis of the two isomers permits assigning the structures. In the following analysis, the appropriate conformational parameters from cyclohexane or cyclitol systems will be used as measures of the steric requirements of the substituents at the 2-, 4-, and 6-positions of the tetrahydropyran ring. It must be admitted that these values may be somewhat inaccurate here because the 2–6 distance in tetrahydropyrans (as a result of the shorter C—O bond lengths) may be shorter making axial conformations less stable, and because of the lack of vicinal hydrogens on the oxygen possibly increasing the stability of the equatorial conformation relative to cyclohexane. In spite of possible limitations, the cyclohexane values are the only estimates of steric size available. However, the conformational preference of the Me group in 4- or 6-methyl-2-carbomethoxytetrahydropyran was found to be experimentally the same as in cyclohexane.[8] In any case, for the purposes of the analysis below, only approximate values are required. Structure IVa has one axial Me group making that conformer +1·7 kcal/mole[9] in free energy (relative to a zero of all substituents equatorial). Structure IVb has one Me axial in the 5 position (+1·3 kcal/mole)[8] and an axial OMe (+0·6 kcal/mole)[9] less the anomeric effect (−1·3 kcal/mole)[1] which totals +0·6 kcal/mole. Therefore structure IVb should predominate (by about 87%). Structure Va has one *syn*-axial Me–H interaction (+1·7/2 kcal/mole)[9], a *syn*-axial OMe–H interaction (+0·6/2 kcal/mole),[9] a *syn*-axial Me–OMe interaction (ca. 2·0 kcal/mole)[9] but less the anomeric effect of the OMe (−1·3 kcal/mole)[1] which makes Va unstable by +1·85 kcal/mole. The other conformer Vb has an axial Me at the 5-position which then makes it relatively unstable by +1·3 kcal/mole.[8] Thus compound V should be somewhat more Vb than Va (about 72% Vb). Since IVb with the axial OMe (and equatorial H_2) and Vb with an equatorial OMe (and axial H_2) are the predominate conformers, the isomer with the narrower anomeric proton (H_2) NMR signal must be IV and the isomer with the wider anomeric signal must be V. Furthermore the isomer with the larger fraction of conformer with axial H_2 must be that with the anomeric signal at higher field, and so by this criterion also, structure IV is the isomer with the shorter GC retention time.

Equilibration of either pure anomer of 2-methoxy-*trans*-5,6-dimethyltetrahydropyran (IIIa and IIIb) in ca. 0·001M toluenesulfonic acid in methanol at 25° gave the same equilibrium mixture of anomers which was 77·3 ± 0·5% the axial-OMe anomer. This result significantly supports the hypothesis that 5,6-vicinal groups increase the percent of axial anomer. However, the coincidence of 77% axial which is exactly the same percentage as the methyl glucoside is probably partly fortuitous.

Equilibration of either pure isomer of 2-methoxy-*cis*-5,6-dimethyltetrahydropyran in methanol with ca. 0·001M toluenesulfonic acid at 25° gives a mixture of anomers which is 71·2 ± 0·5% the anomer of structure IV. Since the anomers IV and V are each an equilibrium mixture of two conformers, this equilibration value itself does not mean much. However the equilibrium between structure IVb and structure Vb is similar to the anomeric equilibrium of methyl galactoside (in which the C-4 OH is axial). In order to obtain the value for this equilibrium, the half-widths of the anomeric signals were carefully measured using benzene as a standard (Table 2). Half-widths were used as an approximation of the separation between the terminal lines of the X-resonance in these ABX systems because the multiplets were not all resolved.[10] If the observed half-width of a time averaged signal (w) is the weighted average of the axial signal half-width (w_{ax}) and the equatorial signal half-width (w_{eq}), the mole fraction of axial (N_{ax}) and equatorial conformer (N_{eq}) can be calculated: $w = N_{ax}w_{ax} + N_{eq}w_{eq}$. A similar relationship may be applied to the chemical shift, however the chemical shift is sufficiently sensitive to substitution elsewhere on the ring that it would be useless in this system. Coupling constants or half-widths are much less sensitive to substitution. The best model compounds available from which to obtain w_{ax} and w_{eq} were the anomers of 2-methoxy-*trans*-5,6-dimethyltetrahydropyran. Thus for IVa ⇄ IVb: $6{\cdot}38 = N_{ax}5{\cdot}04 + N_{eq}11{\cdot}94$, and the per cent of axial conformer

IVb is 80·5% of IV. Likewise for Va $\rightleftarrows$ Vb $11{\cdot}72 = N_{ax}\ 5{\cdot}04 + N_{eq}\ 11{\cdot}94$ which calculates for 96·8% of the equatorial conformer Vb in V. At equilibrium (IV $\rightleftarrows$ V) then, there is 13·9 ± 2·0% of IVa, 57·3 ± 1·9% of IVb, 0·9 ± 1·2% of Va, and 27·9 ± 1·1% of Vb. From these percentages composition the equilibrium IVb $\rightleftarrows$ Vb is thus 57·3 to 27·9 or 67·3 ± 2·8% in favor of the axial side (IVb). (The error given is the probable error in this number calculated from the average deviations in the values of the half-widths and the GC analysis). The percentage obtained for the methyl galactoside-like equilibrium (67·3 ± 2·8%) is then within the experimental error of that found for methyl galactopyranoside (71% axial anomeric OMe) and even more nearly the same as those for methyl xyloside (68·6% α) and the simple 2-methoxytetrahydropyrans (67, 69% axial). It can be concluded then that *cis*-5,6-*vicinal* Me groups do not affect the anomeric equilibrium IVb $\rightleftarrows$ Vb detectably. (It should be pointed out that the methyl galactoside value is probably not very accurate being calculated from literature data[11] on the composition of galactoside mixtures which include furanosides as well as pyranosides.)

The larger percentage of the axial anomer of methyl glucoside compared to that for the 2-methoxytetrahydropyrans, methyl xyloside, and methyl galactoside has been accounted for as the effect of a repulsion between *vicinal–trans* large groups at C-4 and C-5. The even larger percent axial anomer for glucose pentaacetate will now be accounted for. Examination of models suggests that the ring distortion caused by the vicinal Me groups in the tetrahydropyran ring does not change the distance between the 6-position and the anomeric substituent much, thus the dipole–dipole effect should be little changed. Flattening the ring at the 6-position does however increase the distance from the 6-axial substituent to the axial anomeric substituent considerably. If then it is assumed that the effect of the *trans*-5,6-Me is to reduce the steric interactions for the axial anomeric group, the magnitude of the reduced steric interactions can be calculated. Substraction of the anomeric effect for OMe in methanol, 1·02 kcal/mole (calculated from the value for 2-methoxy-6-methyltetrahydropyran, 67%)[1] from the free energy difference for the anomeric equilibrium of the 2-methoxy-*trans*-5,6-dimethyltetrahydropyran, 0·72 kcal/mole, gives the steric interaction of 0·30 kcal/mole for the axial anomeric OMe which is much smaller than the normal *A* value of 0·6 kcal/mole.[7] Now if this steric effect of 0·3 kcal/mole is assumed to be valid for a 2-acetoxy-*trans*-5,6-dimethyltetrahydropyran (OMe and acetoxyl are of similar size)[7] and using an anomeric effect of 1·35 kcal/mole for the acetoxy group in acetic acid (calculated from 2-acetoxy-4-methyltetrahydropyran)[1], the per cent axial anomer predicted is 85·5%, remarkably close to the 88% α of glucose pentaacetate. If one takes into account the slightly larger per cent α for xylose tetraacetate (78·5% presumably due to the C-3 and C-4 acetoxyls), the per cent axial anomer predicted for a glucose-like acetate would be 87·8% axial anomer which is identical to the observed value (88%). The preparation of the acetoxydimethyltetrahydropyrans was not attempted because of the anticipated problems of dealing with an acylal, especially the tendency to eliminate and polymerize.

Although the difference in anomeric equilibrium between methyl glucoside and glucose pentaacetate and the corresponding xylose and tetrahydropyran derivatives have now been quantitatively explained, as an effect of *trans–vicinal* large groups, it is not clear why this effect does not appear for the pyranoses themselves in water (Table 1). Glucose has the same equilibrium percent axial anomer as do xylose, galactose and the simple hydroxytetrahydropyrans, and consequently the vicinal group effect seems not to operate in the pyranoses in water. It was pointed out previously that the conformational preference of pyranoses (ca. 0·34 kcal/mole in favor of the β anomer) could be rationalized[1] by a reduced anomeric effect of ca. 0·9 kcal/mole (from a 2-methoxytetrahydropyran in aqueous MeOH) and the larger A value for OH in water, 1·25 kcal/mole, (determined in D_2O[9]). Perhaps the reason that there is no effect due to the 5,6-vicinal groups in the pyranoses, is that for glucose in water there are five large groups on the ring, the OH groups being somewhat smaller than hydroxymethyl (ca. 1·25 *vs.* ca. 1·7 kcal/mole[7]) but still considerably larger than in less polar solvents due to strong hydrogen bonding. Widening the angle between the C-4 substituent and the largest substituent at C-5 flattens the ring somewhat at C-5 ,increasing the interactions between other substituents which probably becomes less desirable the larger these substituents are.

Other interesting correlations can be made from the equilibration data of the 2-methoxy-*cis*-5,6-dimethyltetrahydropyran isomers, IV and V. The equilibrium between IVa and Vb depends upon the difference between the conformational preference of the Me group in the 5- and 6-positions. This equilibrium is 13·9 to 27·9 giving a free energy difference of 0·42 kcal/mole which compares well with the difference between our earlier reported values of 1·70 for the 4- and 6-positions and 1·27 kcal/mole for the 5-position,[8] which is 0·43 kcal/mole. The Me group at the 5-position has a smaller preference for the equatorial conformation because when it is axial, it interacts with the ring oxygen and only one axial hydrogen.[8]

EXPERIMENTAL

2-Isobutoxy-5-methyl-3,4-dihydro-2H-pyran. A mixture of 164 g methacrolein and 246 g isobutyl vinyl ether was heated in an autoclvae for 1·5 hr at 200–220°. The mixture was distilled and the fraction b.p. 104–108° (50 mm), 308·2 g collected. Gas chromatographic analysis on a 1 m × ½ in column of 20% Carbowax 4000 on Chromosorb W (60/80 mesh) at 100° showed it to consist of 83% the desired compound and 17% methacrolein dimer. Redistillation gave 255 g (64% yield) of pure product, b.p. 97–97·5° (52 mm) [Lit.[12] 107° (50 mm)].

2-Methoxy-5,6-dimethyltetrahydropyran (mixture of isomers). A soln of 32·3 g anhyd HCl in 400 ml ether was added dropwise with stirring to a soln of 150 g 2-isobutoxy-5-methyl-3,4-dihydro-2H-pyran in 200 ml ether at 0°. This soln was immediately added dropwise to 1·0 mole of freshly prepared MeMgI as rapidly as the exothermic reaction would allow. Water was added to the reacton mixture and the aqueous phase was extracted with ether. After drying over $MgSO_4$ and the ether was removed, 110 g of a clear orange oil remained. Distillation gave a colorless fraction, b.p. 62–85° (7 mm). VPC analysis using a 2 m × ½ in column of 20% Carbowax 4000 on Chromosorb W (60/80 mesh) at 100° and 20 psi showed the presence of compounds with the following retention times: 3·5, 3·9, 4·4, 9·0, 11·3, 14·4, 16·3 and 20·6 min. The composition of the mixture was: 38% the first three peaks, 56% the next four, and 6% the last peak. The peak at 4·4 min was isobutanol. The two peaks at 3·5 and 3·9 min were subsequently identified (see below) as *trans* and *cis*-2,3-dimethyl-3,4-dihydro-2H-pyran. The four peaks, 9·0, 11·3, 14·4 and 16·3 min were the four isomers of 2-isobutoxy-5,6-dimethyltetrahydropyran. The last peak 20·6 min was not identified. Redistillation gave 11·8 g of a fraction b.p. 68–70° (7 mm) which by VPC analysis was 87% isobutoxy-5,6-dimethyltetrahydropyran (6% yield) 8% isobutanol and 5% unidentified compound.

A soln of 5·3 g of this material and 31·5 ml of 0·001 M toluenesulfonic acid in abs MeOH was let stand 24 hr. VPC analysis as above showed the appearance of four new compounds with retention times 5·8, 7·1, 8·7 and 9·8 min besides the starting peaks of which 42% remained. The soln was neutralized with solid $NaHCO_3$ and the solvent removed. Distillation b.p. 44–47° (7 mm) gave 1·5 g of colorless liquid (36% yield) which by VPC analysis was 91% pure in the four new compounds. These four compounds were purified by preparative VPC collecting them all together. (Found: C, 66·47; H, 11·26. $C_8H_{16}O_2$

requires: C, 66·63; H, 11·18). The isomers were separated and purified from each other by preparative VPC using a 17 ft × $\frac{3}{8}$ in column of 20% Carbowax 4000 on Chromosorb W (60/80 mesh) at 100° and 30 psi, retention times: 13·5, 17·0, 21·9, and 24·3 min. Equilibration of each compound in 0·01M methanolic soln of *p*-toluenesulfonic acid established the compounds with retention time 13·5 and 21·9 min as epimers, and those with times of 17·0 and 24·3 min as epimers. NMR spectra for each pure isomer were obtained: Isomer of structure IIIb with retention time 13·5 min showed a doublet at 0·81 ppm from TMS (J = 6·0 c/s, integrating for 3 protons), a doublet at 1·08 ppm (J = 6·2 c/s, 3 protons), a broad unresolved signal at 1·4–1·8 ppm (5 protons), a singlet at 3·25 ppm (3 protons), a "quintet" at 3·36 ppm (J = 6·4, 8·5, 1 proton), and a multiplet at 4·54 ppm ($w_{\frac{1}{2}}$ = 5·04 c/s, 1 proton). Isomer of structure IV, a,b with retention time 17·0 min showed a doublet of 0·95 ppm (J = 6·6 c/s, 3 protons), a doublet at 1·01 ppm (J = 6·6 c/s, 3 protons), a broad unresolved absorption at 1·4–2·0 ppm (5 protons), a singlet at 3·26 ppm (3 protons), an octet at 3·97 ppm (J = 2·5, 6·5; 1 proton), and a multiplet at 4·53 ppm ($w_{\frac{1}{2}}$ = 6·36 c/s, 1 proton). Isomer of structure IIIa with retention time 21·9 min showed a doublet at 0·81 ppm (J = 5·6 c/s, 3 protons); a doublet at 1·17 ppm (J = 6·3 c/s, 3 protons), a broad unresolved absorption at 1·5–2·0 ppm (5 protons), a singlet at 3·34 ppm (3 protons), a "quintet" at 3·03 ppm (J = 6·2, 8·4; 1 proton), and a quartet at 4·16 ppm (J = 2·2, 8·6 c/s; 1 proton). Isomer of structure Vab with retention time 24·3 min showed a doublet at 0·93 ppm (J = 7·0 c/s, 3 protons), a doublet at 1·10 ppm (J = 6·3 c/s, 3 protons), broad unresolved signal at 1·5–1·8 ppm (5 protons), a singlet at 3·34 ppm (3 protons), an octet at 3·58 ppm (J = 6·5, 2·5; 1 proton), and a poorly resolved quartet at 4·19 ppm (1 proton).

cis *and* trans-*2,3-Dimethyl-3,4-dihydro-2*H*-pyran.* A soln of 5·9 g HCl in 90 ml ether was added dropwise with stirring at 0° to a soln of 26·9 g of 2-isobutoxy-5-methyl-3,4-dihydro-2*H*-pyran in 100 ml ether. This soln was added to 0·5 moles freshly prepared MeMgI as rapidly as the exothermic reaction would allow. Working up as above gave 18 g of light yellow oil. A crystal or two of *p*-toluenesulfonic acid was added to this oil which was placed in a 50 ml flask equipped for vacuum distillation and magnetic-stirring. The receiver was cooled in a dry-ice bath. The flask was heated at 90–110° with an oil bath and the vacuum maintained at 10 mm. The product was 5·8 g of an oil which when analyzed by VPC on a 17 ft × $\frac{3}{8}$ in column of 20% Carbowax 4000 on Chromosorb W (60/80 mesh) at 75° and 20 psi contained only four compounds with the following retention times: 23·8 (5%), 26·6 (13%), 28·8 (10%), and 33·7 min (72%). The 33·7 min peak was isobutanol. The other three components were separated from the butanol by preparative VPC on a 2 m × $\frac{1}{2}$ in column of 20% Carbowax 4000 at 75° and 20 psi (retention times: 5·1, 5·8, 6·4, and 7·9 min). The mixture of isomers was analyzed (Found: C, 74·62; H, 10·78. $C_7H_{12}O$ requires: C, 74·95; H, 10·78%). NMR spectra permitted their identification. The compound with retention time 23·8 min is *trans*-2,3-dimethyl-3,4-dihydro-2H-pyran, structure I: doublet at 0·93 ppm (J = 6·0 c/s, 3 protons), doublet at 1·38 ppm (J = 6·0 c/s, 3 protons), a broad signal at 2 ppm (3 protons), a "quintet" at 3·48 ppm (J = 6·0, 9·0 c/s; 1 proton), an unresolved multiplet at 4·48 ppm (1 proton), and a doublet with fine unresolved splitting at 6·18 ppm (1 proton). The compound with retention time 26·6 min is *cis*-2,3-dimethyl-3,4-dihydro-2*H*-pyran, structure II: doublet at 0·90 ppm (J = 6·0 c/s, 3 protons), doublet at 1·12 ppm (J = 6·0 c/s, 3 protons), a broad absorption at 2 ppm (3 protons), an octet at 3·95 ppm (J = 6·0, 2·0 c/s, 1 proton), an unresolved multiplet at 4·43 ppm (1 proton), and a doublet with fine unresolved splitting at 6·13 ppm (1 proton). The third compound with retention time 28·8 min is 2,5-dimethyl-3,4-dihydro-2*H*-pyran: a doublet at 1·18 (J = 6·0 c/s, 3 protons), a broad singlet at 1·50 ppm (3 protons), a broad unresolved absorption at 2 ppm (4 protons), an unresolved multiplet at 3·70 (1 proton), and a broad singlet at 6·02 ppm (1 proton).

*2-Methoxy-*cis- *and* trans-*5,6-dimethyltetrahydropyran.* Pure *cis*-2,3-dimethyl-3,4-dihydro-2*H*-pyran, 150 mg was dissolved in methanolic 0·01M toluenesulfonic acid soln making a 1M soln in the dihydropyran. The reaction was followed by VPC using a 17 ft × $\frac{3}{8}$ in column of 20% Carbowax 4000 on Chromosorb W (60/80 mesh) at 100° and 30 psi. Under these conditions the starting material has a retention time of 8 min and the two isomeric products 17, and 24 min. The reaction was complete after 3 hr. The reaction solution was neutralized with solid $NaHCO_3$, and the two products were collected by preparative VPC, obtaining 80 mg (42% yield). Comparison of VPC retention times, NMR and IR spectra showed these compounds to be identical to the isomers IV and V prepared above. The methoxy *trans* isomers were prepared from the pure *trans*-2,3-dimethyl-3,4-dihydro-2*H*-pyran in the same way. Comparison of VPC retention times (13·4 and 21·8 min) and NMR and IR spectra showed these compounds to be the same as IIIa and IIIb prepared above. The two isomers could be separated preparatively by VPC under the conditions stated.

Equilibration procedure. Equilibrations were performed in dried MeOH soln which was 1·0M in substrate and 0·01M in *p*-toluenesulfonic acid. The equilibrations were run at 25° and followed by VPC analysis using a 3 m × $\frac{1}{4}$ in column of 20% Carbowax 4000 on Chromosorb W (60/80 mesh) at 75° and 10 psi. The retention times of the four isomers of 2-methoxy-5,6-dimethyltetrahydropyran were: IIIb 33·4, IV 43·9, IIIa 53·8, and V 64·4 min. The equilibrations were followed until the ratio of isomers remained constant. Then 10 measurements were taken and averaged. Peak areas were weighed. All four pure isomers were separately equilibrated. The isomeric compounds were found to have thermal response ratios under the conditions of VPC used which were within experimental error of each other. For example a mixture of 0·0040 g IV and 0·0086 g V (68·3% V by weight) gave a peak area ratio of 67·6 ± 0·7%).

NMR measurements. NMR measurements were made on Varian A-60 and HA-100 spectrometers. Half-width measurements were made on a HA-100 instrument, (probe at 30°) using a sweep width of 100 c/s. The solutions analyzed were 10 mole per cent compound in CCl_4 and contained benzene as a standard, 1% by weight. In all measurements the anomeric signal and the benzene signal were recorded in one sweep. Each compound was analyzed 10 times and averaged (the error listed is the average deviation). The half-widths of the anomeric signals were adjusted for instrumental deviations by correcting all anomeric half widths arithmetically to the same benzene half-width. Data are listed in Table 2.

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