water, and 1 ml of 10% aqueous sodium hydroxide solution gave recovered **11a** (100%), mp 183–185°.

A 44.5-mg sample of epimer **11a'**, mp 115–120°, in 2.0 ml of absolute ethanol containing 10 mg of sodium methoxide was heated in a sealed glass tube at 150° for 3 hr. After removal of the ethanol the residue was extracted with hot hexane; the cooled extract deposited 4.4 mg of recovered **11a'**, mp 116–118°; no other crystalline product could be isolated. In a second experiment with 50 mg of **11a'** in 5 ml of 95% ethanol and 0.5 ml of 10% aqueous sodium hydroxide, the solution was allowed to stand at room temperature for 114 hr. From the reaction mixture there was obtained 26.4 mg of recovered **11a'**, mp 116–120°, as the only crystalline product.

Registry No.—**6a**, 16831-37-1; **6b**, 16831-33-7; **6d**, 16831-34-8; **6e**, 16831-35-9; **9**, 16859-74-8; **11a**, 16831-38-2; **11a'**, 16831-39-3; **11b**, 16831-36-0; **11c**, 16831-40-6; **11d**, 16831-41-7; **11e**, 16831-42-8; **11f**, 16831-43-9; **11g**, 16831-44-0; **12a**, 16831-45-1; 2,4-dinitrophenylhydrazone of **12a**, 16831-07-5; **12b**, 16830-99-2; 2,4-dinitrophenylhydrazone of **12b**, 16831-00-8; **13**, 16831-01-9; **14**, 16831-02-0; 4-diethylaminostyryl ethyl ketone, 16831-03-1; 1-(2-methoxyphenyl)-2-methyl-1-penten-3-one, 16831-04-2; 1-(2,4-dimethoxyphenyl)-1-buten-3-one, 16831-05-3; 1,5-bis-(2-methoxyphenyl)-2-methyl-1,4-pentadien-3-one, 14164-68-2.

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The Conformational "Size" of the Methyl Group in 4-, 5-, and 6-Methyl-2-carbomethoxytetrahydropyrans

C. B. ANDERSON AND D. T. SEPP

Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California

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The conformational preferences of the methyl group in 4-, 5-, and 6-methyl-2-carbomethoxytetrahydropyran were found to be 1.70, 1.27, and 1.70 kcal/mol, respectively. The value at the 5 position is smaller because of the smaller size of the oxygen with its unshared electron pairs compared to a methylene group. The conformational preference of the carbomethoxy group in 2-carbomethoxy-6-*t*-butyltetrahydropyran was found to be larger than in cyclohexane (1.6 *vs.* 1.1 kcal/mol). This effect is attributed to a dipole–dipole interaction.

Recently Eliel and Knoeber[1] have reported that a series of 2-alkyl-5-*t*-butyl-1,3-dioxanes, where alkyl is methyl, ethyl, isopropyl, and *t*-butyl, show the same equilibrium *cis/trans* ratio. In each case, the *cis* isomer was less stable than the *trans* isomer by 1.4–1.5 kcal/mol. It was concluded that in each *cis* isomer the various 2-alkyl groups must be in equatorial conformations; thus the 5-*t*-butyl group must be in an axial conformation. This is a unique situation for the bulky *t*-butyl group which prefers the equatorial conformation in cyclohexane systems by *ca.* 5.6 kcal/mol.[2] In fact the cyclohexane ring is forced into a skew boat conformation, which is unfavorable compared to the chair by 5.3 kcal/mol, rather than have the *t*-butyl axial in the chair conformation.[3]

The 1,3-dioxane chair form has been estimated as 2.2 kcal/mol[4] more stable than the skew boat form although more recently arguments have been advanced in favor of a larger estimate, greater than 3 kcal/mol.[5] Although a boat 1,3-dioxane (even at 3 kcal/mol) may seem to be an energetically feasible alternative explanation to an axial *t*-butyl group, Eliel and Knoeber[1] concluded from an interpretation of nmr coupling constants that the above substituted 1,3-dioxanes must be in chair conformations. The small value of the conformational preference of the 5-*t*-butyl group in the 1,3-dioxane system compared to that in cyclohexane was ascribed to the smaller steric bulk of the unshared electron pairs on the ring oxygens compared to the *syn, axial* hydrogens in cyclohexane. A 5-methyl group was observed to have a 0.80-kcal/mol preference for the equatorial conformation in the 1,3-dioxane system.

We have been investigating conformational effects in tetrahydropyran derivatives[6] and were also interested by the steric consequences of the ring oxygen. In order to assess the conformational preference of the methyl group in methyltetrahydropyrans, an epimerizable group is needed which is of steric size comparable to the methyl group. (Otherwise the data are inaccurate as can be shown in the calculation below.) The 2-carbomethoxy group can be epimerized conveniently with sodium methoxide in methanol.

The 2-carbomethoxy-5-methyl- and 2-carbomethoxy-6-methyl-tetrahydropyrans could be obtained in poor yield (2–5%) from the Diels–Alder reaction[7] of methacrolein or methyl vinyl ketone and methyl acrylate. None of the desired 4-methyl product could be obtained from crotonaldehyde and methyl acrylate. A better preparative procedure was found to be the treatment of the alkyldihydropyran with amylsodium followed by treatment with carbon dioxide[8] which yielded, after acidification, hydrogenation, and esterification, the appropriate 2-carbomethoxyalkyltetrahydropyran. The alkyldihydropyrans were obtained by distillation of the corresponding 2-isobutoxymethyltetrahydropyran[6,9] in the presence of toluenesulfonic acid. The respective 2-isobutoxyalkyltetrahydropyrans were obtained by Diels–Alder reaction of isobutyl vinyl ether with crotonaldehyde, methacrolein, or methyl vinyl

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ketone.[10] In all cases elementary analysis was on the mixture of isomers obtained from the preparative procedure, which in some cases was purely one isomer. The other isomer was obtained by equilibration. Subsequently the *cis* and *trans* isomers were separated preparatively by gas chromatography.

The respective *cis* and *trans* isomers were identified by their nmr spectra which are partially listed in Table I. Axial 2 protons are found at higher field than the equatorial 2 protons.[11] Some of the isomers are not conformationally fixed, and consequently the chemical shift and multiplicity are time averages. The resonances for axial protons are quartets and those for equatorial protons are unresolved multiplets of smaller width.

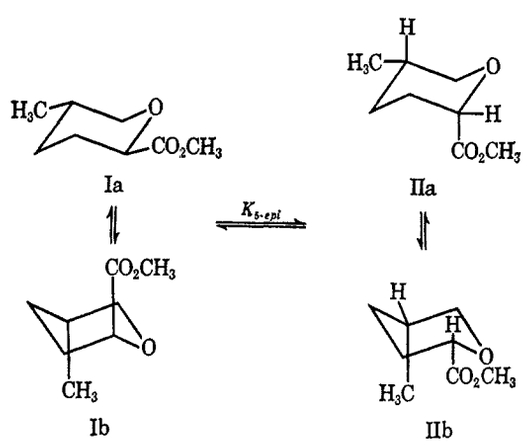
TABLE I

NMR SPECTRA[a] OF ALKYL-SUBSTITUTED 2-CARBOMETHOXYTETRAHYDROPYRANS[b]

2-Carbomethoxytetrahydropyran derivative	Isomer	Conformation	H_2 (τ)	J_{ae}, cps	J_{aa}, cps	CO_2CH_3, τ
6-*t*-Butyl	*cis*	e,e	6.17	2.5	10.5	6.34
6-*t*-Butyl	*trans*	e,a	5.55			6.26
6-Methyl	*cis*	e,e	6.18	2.4	10.4	6.34
6-Methyl	*trans*	e,a $\rightleftarrows$ a,e	5.70			6.32
5-Methyl	*cis*	e,a $\rightleftarrows$ a,e	5.88			6.31
5-Methyl	*trans*	e,e	6.27	2.3	10.8	6.34
4-Methyl	*cis*	e,e	6.23	2.2	11.2	6.35
4-Methyl	*trans*	e,a $\rightleftarrows$ a,e	5.73			6.32

[a] All spectra were taken of solutions 10 mol % of solute in carbon tetrachloride. Spectra were taken on both a Varian A-60 and HA-100 nmr spectrometers using tetramethylsilane as an internal reference. [b] The registry numbers are given in consecutive order: 16831-08-6, 16831-09-7, 16831-10-0, 16831-11-1, 16831-12-2, 16831-13-3, 16831-14-4, 16831-15-5.

Four chair conformers of 2-carbomethoxy-5-methyltetrahydropyran are possible (Ia and b and IIa and b) at equilibrium.



The diaxial *trans* isomer (Ib) can be excluded on the basis of an *a priori* conformational analysis in which the energy difference between Ia and Ib is estimated as half the A value of methyl (1.7/2 kcal/mol[2]) and the A value of carbomethoxy (1.1 kcal/mol[2]) or 1.95 kcal/mol which means there should be 96.5% of Ia and 3.5% of Ib. (Actually if the correct conformational preference of the 2-carbomethoxy group in tetrahydropyran (*vide infra*) is used, the free energy difference becomes 2.65 kcal/mol.) Therefore only Ia, IIa, and IIb need be considered in the epimerization equilibrium as shown in eq 1. The ratio [IIa]/[Ia] is the conformational

$$K_{5\text{-}epi} = \frac{[\text{IIa}] + [\text{IIb}]}{[\text{Ia}]} = \frac{[\text{IIa}]}{[\text{Ia}]} + \frac{[\text{IIb}]}{[\text{Ia}]} \quad (1)$$

preference of the 2-carbomethoxy group ($K_{2\text{-COOMe}}$). The ratio [IIb]/[Ia] is the conformational preference of the methyl group which is drawn in the 5 position ($K_{5\text{-Me}}$) (eq 2a and b). Therefore, the relationships for

$$K_{5\text{-}epi} = K_{2\text{-COOMe}} + K_{5\text{-Me}} \quad (2a)$$

$$K_{5\text{-Me}} = K_{5\text{-}epi} - K_{2\text{-COOMe}} \quad (2b)$$

the 2-carbomethoxy-4-methyltetrahydropyran and 6-methyltetrahydropyran are exactly analogous.

The compositions of the equilibrium mixtures of the various compounds studied are listed in Table II. In each case equilibrium was approached from the side of *cis* as well as from the side of the *trans* isomer at 25°. In the solution, substrate concentration was 1.1 M and the sodium methoxide catalyst concentration was 0.6 M. Mixtures were analyzed by gas chromatography directly after neutralization of the base. The mixtures were also "worked-up" by neutralization of the base with hydrochloric acid followed by extraction with ether–water. Analysis of such "worked-up" solutions gave nearly the same results as the first procedure. Direct injection of the basic methanol solution into the gas chromatograph gave substantial isomerization (or possibly preferential hydrolysis) in the chromatograph. Response ratios for the isomers were determined with mixtures of composition similar to the equilibrium mixtures.

In order to obtain the conformational preference of the 2-carbomethoxy group, 2-carbomethoxy-6-*t*-butyltetrahydropyran was prepared *via* the *t*-butyl dihydropyran as outlined above. The compound, *ca.* 1 M, was equilibrated in dried methanol with *ca.* 0.6 M sodium methoxide at 25° under the same conditions as the other esters. The equilibrium constant for epimerization of the 2-carbomethoxy-6-*t*-butyltetrahydropyran was found to be 0.064. Using the values in Table II, the constant for the equilibrium between an equatorial and axial methyl group in the 5 position may be calculated: $K_{5\text{-Me}} = 0.179 - 0.064 = 0.115$. This corresponds to a free energy difference of −1.27 kcal/mol. Analogous calculations for both the 4 and 6 positions give K_{Me} as 0.056 and the free energy differences as −1.7 kcal/mol.

It is a little surprising that methyl groups at the 4 and 6 positions have the same conformational preference, and also that they have the same conformational preference as methyl on cyclohexane (−1.7 kcal/mol)[2] although the range of values reported is 1.5–2.1 kcal/mol. This suggests that the geometry of the tetrahydropyran ring is practically identical with that of cyclohexane. If a Dreiding molecular model of tetrahydropyran is examined, it is evident that this cannot be the case. Because of the shorter C–O bonds, the 2–6 distance (2.34 Å) is shorter than the 2–4 or 4–6 distances (2.54 Å), and so an axial methyl group at position 6 would be expected to have a larger steric interaction with a *syn*, axial hydrogen than would a methyl group at position 4. However it should be also noted that there is considerable torsional strain in the

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TABLE II

EQUILIBRATIONS OF 2-CARBOMETHOXY ALKYLTETRAHYDROPYRANS AT 25° IN METHANOL

Tetrahydropyran	e,a isomers, %	K^c	K_{Me}	$-\Delta G_{Me}$, kcal/mol
2-Carbomethoxy-4-methyl	10.7 ± 0.4[a] (12)[d]	0.120 ± 0.005[b]	0.056 ± 0.010[b]	−1.70 ± 0.10
2-Carbomethoxy-5-methyl	15.2 ± 0.4 (16)	0.179 ± 0.006	0.115 ± 0.011	−1.27 ± 0.05
2-Carbomethoxy-6-methyl	10.7 ± 0.4 (11)	0.120 ± 0.005	0.056 ± 0.010	−1.70 ± 0.10
2-Carbomethoxy-6-*t*-butyl	6.0 ± 0.4 (8)	0.064 ± 0.005		

[a] Errors are average deviations of several measurements. [b] Error is maximum error calculated from error in per cent e,a isomer. [c] K is defined as e,a isomers/e,e isomer. [d] Value in parentheses is the equilibration value obtained by ether extraction work-up. The better value is without work-up.

model especially between atoms 3–4 and 4–5. This might be alleviated by altering some of the interior ring angles. A crystallographic study of glucose[12] gave the C_5–O_5–C_1 angle at 113.1 ± 0.5°, the C_4–C_5–O_5 angle as 115.5 ± 0.6° and the others within one degree of tetrahedral. Bond lengths were C_5–O_5, 1.455 ± 0.009 Å, and O_5–C_1, 1.437 ± 0.009 Å; and the others were within experimental error of 1.54 Å except for C_3–C_4 which was 1.517 ± 0.010 Å. (One wonders whether the large angle at C-5 is due to the presence of the hydroxymethyl substituent.) In this structure the C_5–C_1 distance (corresponding to the 6–2 distance in tetrahydropyran) is 2.43 Å; the C_1–C_3 (2–4) distance is 2.49 Å; and the C_3–C_5 (4–6) distance is 2.50 Å. With these distances one would expect nearly the same steric interactions for large groups at tetrahydropyran positions 2, 4, and 6. Thus if individual tetrahydropyran derivatives have slightly different geometries in order to accommodate the shorter C–O bonds and to accommodate various substituents, it is not so surprising that a methyl group experimentally is found to have the same conformational preference whether at position 4 or 6. At the same time, this means that methyls may possibly have somewhat different conformational preferences in differently substituted tetrahydropyrans.

In contrast, the conformational preference of the 5-methyl is markedly smaller than that of the 4- or 6-methyl. As Eliel has suggested,[1] this decreased instability of the axial conformation may be due to the smaller "space requirements of the axial (?) electron pairs" on oxygen compared to the "larger space requirements of the axial hydrogens in cyclohexane." Presumably this results in a smaller van der Waals repulsion with the ring oxygen compared to a ring methylene. It is also possible that van der Waals attractive forces might be larger between the axial methyl group and a ring oxygen than between the axial methyl group and a ring methylene group because the unshared pairs of electrons are more polarizable than those shared in bonds.

If the interaction of the 5-methyl on the tetrahydropyran ring with one axial hydrogen is 0.85 kcal/mol, then the other interaction with the unshared electron pair must be 1.27 − 0.85 or 0.42 kcal/mol. Twice this interaction is 0.8 kcal/mol which is exactly that observed by Eliel for the 2-alkyl-5-methyl-1,3-dioxane (0.8 kcal/mol). It appears then that the 1,3 *syn*–axial methyl–hydrogen interaction and the 1,3-*axial* methyl–oxygen interactions are additive within the experimental errors. (The errors given in Table II are maximum errors, and thus are undoubtedly too large.) It is interesting to note that this effect in 5-methyltetrahydropyran is of nearly the same size as the 3-methyl ketone effect. For example, an axial 3-methyl group in a 3-methylcyclohexanone was found to be 0.6 kcal less unfavored than in cyclohexane.[13]

The conformational "size" of the unshared electron pair on nitrogen or oxygen has been the subject of considerable interest recently. Situations where the size of the unshared pair may be an important conformational factor are the conformational preference of the hydroxyl or amino groups on cyclohexane (A value), the conformational preference of the proton (or the unshared electron pair) on the nitrogen in piperidine, and the conformational preference of substituents in certain positions on nitrogen or oxygen heterocycles (*e.g.*, tetrahydropyrans, dioxanes as discussed above). The A values for the hydroxyl, amino, and methyl groups are 0.7, 1.2, and 1.7 kcal/mol,[2] respectively, in aprotic solvents. This is just the order of number of protons on the group, and thus the steric order suggests that hydrogens are larger in "size" than unshared electron pairs. Allinger and coworkers have concluded that in piperazines[14] the proton on nitrogen is predominately but not entirely equatorial from dipole moment measurements. However, from nmr studies, Lambert[15] has come to the opposite conclusion, that the N proton is almost entirely axial in piperidine. It has been suggested that two other effects may be operative besides steric size, namely, preferential solvation of the unshared electron pair and hyperconjugative effects on the equatorial unshared electron pair. Allinger[16] has very recently argued that the hydrogen on nitrogen should not necessarily prefer the equatorial conformation because van der Waals repulsive forces between *syn, axial* hydrogens should be negligible, and furthermore repulsive forces with the 2 and 6 hydrogens should favor the axial conformation.

An interesting result in Table II which has been neglected so far is the much larger preference of the 2-carbomethoxy group for the equatorial conformation (1.62 ± 0.05 kcal/mol) over what is "normal" in cyclohexane systems (1.1 kcal/mol).[2] The difference of 0.5 kcal/mol between them is probably to be attributed to a "reverse" anomeric effect (reverse because it favors the equatorial conformation). The anomeric effect, which is the preference of electronegative substituents α to the ring oxygen in pyranose derivatives for the axial conformation, has been shown to be the consequence of dipole–dipole interactions within the molecule.[6,17] Lemieux has noted a "reverse" anomeric effect in a

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(17) J. T. Edward, *Chem. Ind.* (London), 1102 (1955); see ref 2, p 376.

glucopyranosyl pyridinium salt.[18] The "reverse" anomeric effect in the 2-carbomethoxytetrahydropyran can be attributed perhaps then to the greater distance between positive ends of bond dipoles at the carboxyl carbon and the 6 position of the tetrahydropyran ring when the carbomethoxyl is equatorial.

Experimental Section

2-Carbomethoxy-4-methyltetrahydropyran.—Amylsodium (0.18 mol, 85% yield assumed) was prepared by the method of Paul and Tchelitcheff[8] using 9.5 g of sodium and 22.3 g of *n*-amyl chloride in a 500-ml, round bottom, three-necked creased flask fitted with a Cole-Parmer "Stir-O-Vac" model high speed stirrer. The flask was cooled in a carbon tetrachloride Dry Ice bath at −10°. A solution containing 15.6 g of 4-methyldihydropyran prepared by the method of Parham[9] in 50 ml of petroleum ether (bp 30–60°) was added dropwise over a 15-min period. After stirring at −10° for 1 hr, the reaction mixture was allowed to warm to room temperature and then poured over 50 g of Dry Ice. After the Dry Ice had evaporated, the resulting paste was dissolved in 100 ml of water. The aqueous layer was extracted three times with 100 ml of ether, acidified with 20 ml of concentrated hydrochloric acid, and extracted five times with 100 ml of ether. The ether extract was dried and evaporated leaving 5.6 g of a viscous sour-smelling liquid which when dissolved in 50 ml of ethyl acetate and hydrogenated for 2 days at atmospheric pressure over 3 g of 10% palladium on charcoal yielded 4.8 g of a bad-smelling yellowish viscous liquid. The acid was dissolved in 50 ml of methanol with a crystal of toluenesulfonic acid and refluxed for 18 hr. After the methanol was distilled off, 4.8 g (21%) of a sweet-smelling liquid remained. Vacuum distillation yielded a clear liquid which was found to be 100% pure by gas chromatographic analysis at 100° on a 2 m × 0.25 in. column of 30% 3-methyl-3-nitropimelonitrile on Chromosorb W nonacid washed (retention time 24 min). The esters hydrolyze very easily, but the acids do not come through the gas chromatograph except after very long times. The sample was further purified by gas chromatography at 100° on a 1 m × 0.5 in. column of 20% Carbowax 4000 (retention time 13.0 min) and then distilled, bp 99–100° (10 mm), $n^{25}D$ 1.4413.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.84; H, 8.87.

A solution of 1.28 g of the above *cis* isomer and 6.75 ml of 0.7 *M* sodium methoxide in dried methanol was sealed in an ampoule and heated at 100° for 4 days. The solution was acidified with concentrated hydrochloric acid and purified by gas chromatography at 100° (5 psi) on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W (retention times: *cis* 12.9 min, *trans* 8.1 min). The *trans* isomer was 100% pure by gc, $n^{25}D$ 1.4403.

2-Carbomethoxy-5-methyltetrahydropyran.—A mixture of 123.7 g of methacrolein and 239.6 g of methyl acrylate was heated in an autoclave for 2 hr at 190°. The resulting yellow liquid was distilled. At atmospheric pressure 206 g distilled below 80°. Under reduced pressure 58 g of 2,5-dimethyl-2H-3,4-dihydropyran-2-carboxaldehyde, bp 55° (5 mm), and an 18.6-g fraction, bp 61–86 (5 mm), were obtained. The last fraction was found by gas chromatography on a 0.5 m × 0.5 in. column of 10% Carbowax on Chromosorb W at 110° to be 36% the dimer of methacrolein and 64% the desired 2-carbomethoxy-5-methyl-2H-3,4-dihydropyran. This represents a 4% yield of ester and 52% of methacrolein dimer. This mixture was hydrogenated for 12 hr over a 10% palladium-on-carbon catalyst in 95% ethanol. After filtration and removal of solvent, the residual liquid was distilled yielding 6.5 g of liquid, bp 70.5–74° (5 mm), which gas chromatography indicated was *ca.* 95% the desired compound, 2-carbomethoxy-5-methyltetrahydropyran. The ester was purified by preparative gas chromatography and distilled: bp 70.5–71.0° (5 mm); $n^{25}D$ 1.4427. Nmr spectral analysis showed the product to be the pure *cis* isomer. No *trans* isomer was found.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.53; H, 9.21.

A solution of 0.89 g of the above *cis* isomer and 4.0 ml of 0.7 *M* sodium methoxide in dried methanol was sealed in a flask with a serum cap and allowed to stand 3 weeks at 25°. The solution was acidified with 10 ml of 0.05 *M* hydrochloric acid and extracted with ether. Preparative gas chromatography at 96°, 10 psi on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W (retention times: *cis* 5.8 min, *trans* 8.3 min), yielded a fraction which was 94% *trans* and 6% *cis*, $n^{25}D$ 1.4438.

2-Carbomethoxy-6-methyltetrahydropyran.—A mixture of 86.6 g of methyl vinyl ketone and 159.1 g of methyl acrylate was heated in an autoclave for 2 hr at 180°. The resulting yellow liquid was distilled to obtain an 87-g fraction with bp 80–84° and a 32.7-g fraction with bp 65–90° (7.3 mm). The tarry residue was discarded. Gas chromatographic analysis at 100° on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W indicated a composition in the latter fraction of 62% 2-acetyl-6-methyl-2H-3, 4-dihydropyran (dimer of methyl vinyl ketone) and 30% of 2-carbomethoxy-6-methyl-2H-3,4-dihydropyran. The yield is then 6% of the desired ester and 27% in the ketone.

The fraction boiling at 65–90° was hydrogenated for 2 hr over 10% palladium-on-carbon in 75 ml of 95% ethanol. After filtering and removing the solvent, the residue was distilled yielding 14.3 g with bp 58–59° (5 mm) and 4.5 g with bp 79–81 (5 mm). The lower boiling fraction was shown to be 2-acetyl-6-methyltetrahydropyran by retention time in gas chromatography and the ir and nmr spectra of the collected peak. It was 97% pure by peak area. The higher boiling fraction was 96% pure 2-carbomethoxy-6-methyltetrahydropyran. Nmr spectral measurements indicated the compound was the *cis* isomer. The ester was purified by preparative gc on a 0.5 m × 0.5 in. column of 10% Carbowax 4000 on Chromosorb W at 116° (retention time 10.9 min), and then distilled: bp 63–64° (3.5 mm) (lit.[19] bp 205–210°); $n^{25}D$ 1.4432.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.61; H, 9.15.

The compound was also prepared by oxidation of the hydrogenated dimer of methyl vinyl ketone, 2-acetyl-6-methyltetrahydropyran, with bromine and aqueous sodium hydroxide as described by Alder and coworkers.[19] This product was found to be 99% *cis* and 1% *trans*.

A solution of 2.21 g of the pure *cis* isomer an 10 ml of 0.7 *M* sodium methoxide in dried methanol was sealed in a flask with a serum cap and let stand 3 weeks at 25°. The solution was acidified with 10 ml of 1 *M* hydrochloric acid and extracted with ether. The extract was purified by preparative gas chromatography at 100° and 10 psi on a l m × 0.375 in. column of 30% 3-methyl-3-nitropimelonitrile (retention times: *cis* 14.1 min, *trans* 7.9 min; $n^{25}D$ 1.4386).

6-*t*-Butyl-2-isobutoxy-2H-3,4-dihydropyran.—A mixture of 68.0 g of *t*-butyl vinyl ketone[20] and 91.0 g of isobutyl vinyl ether was heated in an autoclave for 2 hr at 185°. The resulting solution was distilled yielding 51.1 g (yield 40%) of colorless material, bp 77–82° (4 mm). Gas chromatographic analysis on a 3 m × 0.25 in. column of 20% Carbowax 4000 on Chromosorb W at 100° showed the product to be *ca.* 97% one component by peak area (retention time 21 min). A small portion was purified by preparative gas chromatography followed by distillation, bp 71–72° (3.5 mm), $n^{25}D$ 1.4424. Nmr spectral analysis confirmed the compound as 6-*t*-butyl-2-isobutoxy-2H-3,4-dihydropyran; these nmr values follow: a triplet at τ 5.09 with a coupling constant of 3.0 cps integrating for one proton, a quartet at 5.50 with coupling constants of 2.9 and 4.9 cps integrating for one proton, an octet at 6.64 integrating for two protons, a group of broad signals at *ca.* 8 integrating for five protons, a singlet at 8.95 integrating for nine protons, and a doublet at 9.10 with a coupling constant of 6.5 cps integrating for six protons.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.36; H, 11.16.

6-*t*-Butyl-2-isobutoxytetrahydropyran.—A high pressure hydrogenation apparatus equipped for shaking was charged with 49.6 g of 6-*t*-butyl-2-isobutoxy-2H-3,4-dihydropyran, 250 ml of 95% ethanol, and 2 g of 10% palladium-on-charcoal. The hydrogenation was conducted over 5 days at a pressure of 900–1100 psi. Hydrogenation failed at lower pressures. After removal of the catalyst and solvent, the residue was distilled, bp 76–84° (3 mm), yielding 29.1 g (58% yield). Gas chromatographic analysis using a 2 m × 0.5 in. column of 20% Carbowax 4000 on Chromosorb W at 100° showed the product to be 12% *trans*- (retention time 11.8 min) and 86% *cis*-6-*t*-butyl-2-isobutoxytetrahydropyran

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(retention time 15.0 min.). The two isomers were separated by preparative-scale gas chromatography. The *cis* isomer was further purified by distillation: bp 82.5° (5 mm); $n^{25}D$ 1.4072.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.22. Found: C, 73.15; H, 12.36.

The nmr spectrum of the *cis* isomer showed a quartet for the anomeric proton at τ 5.58 (J = 2.3 and 7.8 cps). The *trans* isomer, $n^{25}D$ 1.4342, showed a broad unresolved signal for the anomeric proton at τ 5.31 with a half-width of 6 cps. As further evidence for the isomeric nature of these compounds, both isomers were equilibrated 0.1 M in acetonitrile with 0.001 M tosylic acid to the same mixture of isomers: 63.6% *trans* from pure *trans* isomer and 63.2% *trans* from pure *cis* isomer.

2-*t*-Butyl-2H-3,4-dihydropyran.—A catalytic amount of toluenesulfonic acid was added to 22.1 g of 6-*t*-butyl-2-isobutoxytetrahydropyran in a vacuum distillation apparatus connected to a receiver cooled in a Dry Ice–acetone bath. The liquid was heated with stirring at 3 mm of pressure for 5 hr using an oil bath at 65–75°. A yield of 19.8 g of colorless liquid was collected. Gas chromatographic analysis on a 3 m × 0.25 in. column of 20% Carbowax 4000 at 97° showed the distillate to be 46% isobutyl alcohol (retention time 5.3 min) and 54% 2-*t*-butyl-2H-3,4-dihydropyran (retention time 7.4 min) thus indicating a 97% yield. The isobutyl alcohol was separated by distillation. Redistillation gave pure material: bp 157.0–157.5°; $n^{25}D$ 1.4455. The nmr spectrum showed the following: a broad doublet at τ 3.72 (J = 6.0 cps, integrating for one proton), a broad signal at 5.48 (half-width 14 cps, one proton), a quartet at 6.69 (J = 2.5 and 10.0 cps, one proton), a broad group of signals at about 8 (four protons), and a singlet at 9.08 (nine protons).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.23; H, 11.69.

6-*t*-Butyl-4H-5,6-dihydropyran-2-carboxylic Acid.—Amylsodium (0.093 mol) was prepared by the method of Paul and Tchelitcheff[8] as above at −10° but using 6.3 g of sodium and 14.1 g of *n*-amyl chloride (70% yield). A solution of 50 ml of petroleum ether (30–60°) and 13.5 g of 2-*t*-butyl-2H-3,4-dihydropyran (containing 4% isobutyl alcohol as an impurity) was added dropwise over a 10-min period. The reaction solution was stirred for 1 hr, was allowed to warm, and was poured onto 75 g of Dry Ice. After warming to room temperature, the light gray slurry was poured into 100 ml of water, and the mixture was stirred until both layers became clear. The organic phase was separated, and the aqueous layer was extracted twice with 50-ml portions of ether, yielding 4.8 g of unreacted 2-*t*-butyl-2H-3,4-dihydropyran. To the remaining aqueous solution was added 20 ml of concentrated hydrochloric acid whereupon a white solid precipitated. The acidic aqueous solution was extracted five times with 100-ml portions of ether. After the solid in ether and the extracts were dried over magnesium sulfate, the ether was evaporated leaving 5.3 g (49% yield) of a white solid, mp 118–120°. Recrystallization from 20% benzene–cyclohexane gave pure products, mp 123–124°. Nmr spectral analysis showed a singlet resonance at τ −1.29 (integrating for one proton), a triplet at 3.84 (J = 3.2 cps, one proton), a quartet at 6.57 (J = 2.5 and 10.7 cps, one proton), a group of signals at 7.5–8.7 (four protons), and a sharp singlet at 9.00 (nine protons).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.46; H, 8.98.

6-*t*-Butyltetrahydropyran-2-carboxylic Acid.—Unrecrystallized 6-*t*-butyltetrahydropyran-2-carboxylic acid (5.1 g) was hydrogenated for 3 days at atmospheric pressure in 50 ml of ethyl acetate with 3 g of 10% palladium-on-charcoal. After filtration and removal of the solvent, 4.1 g (80% yield) of a white solid remained, mp 56–62°. Ir and nmr analysis showed no evidence of unreacted starting material. The nmr spectrum showed the following signals: a singlet at τ −0.82, a quartet at 6.12 (J = 2 and 9 cps, one proton), a quartet at 7.01 (J = 2 and 10 cps, one proton), a broad set of signals at 7.8–8.7 (six protons), and a singlet at 9.08 (nine protons). The fact that no other signals were detected near that for the anomeric proton (τ 6.12) indicates that only one isomer is obtained, and that it must be the *cis* isomer because the signal is a quartet.

***cis*-6-*t*-Butyl-2-carbomethoxytetrahydropyran.**—A solution of 2.02 g of unrecrystallized 6-*t*-butyltetrahydropyran-2-carboxylic acid, 40 ml of absolute methanol, and three drops of concentrated hydrochloric acid was refluxed for 12 hr. The solution was neutralized and concentrated. The product *cis* ester was purified by preparative gas chromatography using a 1 m × 0.5 in. column of 20% Carbowax 4000 on Chromosorb W at 100° (retention time 12.9 min). The fruity smelling ester was distilled after collection yielding 1.42 g (68% yield): bp 85–86° (2.3 mm); $n^{25}D$ 1.4375. The nmr spectrum showed the following signals: a quartet at τ 6.17 (J = 2.5 and 10.5 cps, one proton), a singlet at 6.34 (three protons), a quartet at 7.10 (J = 1.8 and 10.7 cps, one proton), a group of signals between 7.8 and 8.7 (six protons), and a singlet at 9.10 (nine protons).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.12; H, 10.28.

Mixture of *cis*- and *trans*-6-*t*-Butyl-2-carbomethoxytetrahydropyran.—A solution of 844 mg of pure *cis*-6-*t*-butyl-2-carbomethoxytetrahydropyran and 3.5 ml of 0.6 M sodium methoxide in dried absolute methanol was sealed in a glass tube and heated for 3 days at 100°. The solution was neutralized with methanolic hydrogen chloride and concentrated. Gas chromatographic analysis on a 2 m × 0.25 in. column of 30% 3-nitro-3-methylpimelonitrile on Chromosorb W at 100° showed peak area percentages of 83.1% *cis* (retention time 18.2 min) and 16.9% *trans* (retention time 12.8 min). The product was put through a 0.5 m × 0.5 in. column of 10% Carbowax 4000 at 100° and the two esters were collected together. Then this mixture, 468 mg, having the same composition as before, was partially separated using a 1 m × 0.375 in. column of 30% 3-nitro-3-methylpimelonitrile on Chromosorb W at 100°. A mixture of isomers enriched in *trans* was obtained, $n^{25}D$ 1.4447, and found to be 64% *cis* and 36% *trans*. Nmr spectral analysis, using a time averaging computer to improve the spectrum, showed the following signals which were assigned to the *trans* isomer: an unresolved multiplet at τ 5.55 of half-width 4.1 cps, assigned to axial H_2; a singlet at 6.26, assigned to the methoxy group; a quartet at 6.72 (J = 2.5, 9.7 cps) assigned to axial H_6; and a singlet at 9.13 assigned to the equatorial *t*-butyl group. The signals at τ 5.55 and 6.72 integrated identically and roughly a third of that at 6.26.

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.03; H, 10.00.

Equilibration Method.—A 0.7 M solution of sodium methoxide in methanol was prepared from dried absolute methanol and sodium metal. The concentration was measured by titration. A typical reaction was 1.1 M ester substrate and 0.6 M sodium methoxide in dried methanol, prepared in a dried flask. The flask was closed with a serum cap and kept at 25°. Aliquots of this solution (50 μl) were removed with a syringe at various times over 2–3 weeks and quenched by adding methanolic hydrogen chloride to acidify the aliquot. This acidic solution was analyzed by gc. Basic solutions were found to isomerize upon gc analysis while acidic solutions did not. Response ratios were determined for *cis* and *trans* isomers and were found to be identical within experimental error. For example, 2-carbomethoxy-5-methyltetrahydropyran which was 75.7% *trans* by weight gave a peak area ratio of 75.9 ± 0.5% *trans*.

Registry No.—6-*t*-Butyl-2-isobutoxy-2H-3,4-dihydropyran, 16831-16-6; *cis*-6-*t*-butyl-2-isobutoxytetrahydropyran, 16822-20-1; *trans*-6-*t*-butyl-2-isobutoxytetrahydropyran, 16831-17-7; 2-*t*-butyl-2H-3,4-dihydropyran, 16765-52-9; 6-*t*-butyl-4H-5,6-dihydropyran-2-carboxylic acid, 16831-19-9; 6-*t*-butyltetrahydropyran-2-carboxylic acid, 16831-20-2.