Conformational Analysis. XVII. 2-Alkoxy- and 2-Alkylthiotetrahydropyrans and 2-Alkoxy-1,3-dioxanes. The Anomeric Effect[1]

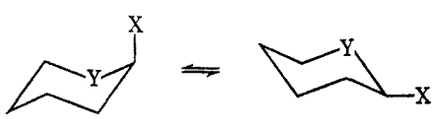
ERNEST L. ELIEL AND CHESTER A. GIZA

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received March 12, 1968

The position of the *cis–trans* equilibrium has been determined for six 2-alkoxy-6-methyloxanes (methoxy, ethoxy, isopropoxy, *t*-butoxy, 2,2,2-trifluoroethoxy, and dimethylethylcarbinyl), two 2-alkylthio-6-methyloxanes (methylthio and *t*-butylthio), two 2-alkoxy-4-methyloxanes (methoxy and ethoxy), 2,6-diethoxyoxane, and two 2-alkoxy-1,3-dioxanes (methoxy and ethoxy) in various solvents. In carbon tetrachloride the axial (*trans*) isomer always predominates at equilibrium; in the more polar solvent acetonitrile it is less favored. The results are explained in terms of the solvent-dependent "anomeric effect" superimposed on which appear to be less important steric effects. Possible explanations of the anomeric effect in terms of dipole repulsion, electron-pair repulsion, or double bond–no bond resonance are discussed.

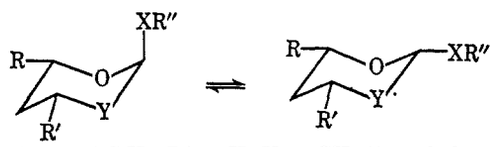
Recent publications from other groups[2-7] prompt us to report our own experimental findings with regard to the anomeric effect,[8-10] by which term is meant[9] the greater preference of an electron-withdrawing group (X, eq 1) for the axial position when it is located adjacent to a heteroatom (Y, eq 1) in a ring than when



(1)

it is located elsewhere. The effect was originally found in anomeric equilibria of α- and β-glycosides, hence its name. Usually the group X has been alkoxyl[2,4,8-11] or halogen,[3,5,7] the ring has been six membered,[12] and the ring heteroatom has been oxygen[2-4,6-8] or sulfur.[5] Quantitatively, the anomeric effect has been expressed[2,9] as the difference in conformational free energy $(\Delta G^\circ_X)_Y$ for the process shown in eq 1 (Y = heteroatom) and the corresponding process in cyclohexane (Y = CH_2) (ΔG°_X); *i.e.*, anomeric effect = $(\Delta G^\circ_X)_Y - \Delta G^\circ_X$ kcal/mol. Because of the favoring of the axial position in the heterosystem, $(\Delta G^\circ_X)_Y$ will be more positive (or less negative) than ΔG°_X and the value for the anomeric effect thus expressed will therefore be a positive number.

We have studied the acid-catalyzed equilibrium of a number of 2-alkoxy- and 2-alkylthio-6-methyltetrahydropyrans ("oxanes") (eq 2) synthesized[13] by addition of alcohols and mercaptans to 6-methyl-2-oxene as well as corresponding equilibrations of two 2-alkoxy-4-methyloxanes analogously synthesized, of 2,6-diethoxyoxane, and of two 2-alkoxy-4-methyl-1,3-dioxanes synthesized from the appropriate alkyl orthoformates and 1,3-butanediol. Diastereoisomers were separated by preparative gas chromatography. Equilibrium was established by allowing solutions of the appropriate substrates in acetonitrile, carbon tetrachloride, or the alcohol corresponding to the alkoxy substituent stand at room temperature in the presence of mineral acid[11] until the ratio of the two diastereoisomers (eq 2) became constant. Analysis was effected gas chromatographically after neutralizing the acid catalyst with sodium methoxide. Configuration of diastereoisomers was deduced from nmr spectra.[4] The axial isomers showed narrow signals (equatorial protons) at 4.53–5.42 ppm; the equatorial isomers showed broadly split signals (axial protons) at 4.15–4.72 ppm. The results of the equilibration are shown in Table I.



(2)

R = CH_3 or OC_2H_5; R′ = H; Y = CH_2 (6-methyl series, 6-ethoxyl series)
R = H; R′ = CH_3; Y = CH_2 (4-methyl series)
R = CH_3; R′ = H; Y = O (1,3-dioxane series)

The method chosen here for establishing conformational equilibria has been explained and justified elsewhere.[2] In several respects our results confirm and somewhat amplify those obtained by other investigators. Thus we find that, except for the cases of 2-*t*-butoxy- and 2-alkylthiooxanes in a high dielectric solvent (acetonitrile), the axial conformation of –XR (X = O or S) in the 2 position of the oxane is preferred by 0.2–0.8 kcal/mol owing to the anomeric effect. The effect is clearly of polar origin, for it is uniformly greater in a low dielectric solvent such as carbon tetrachloride (ϵ = 2.24 D[14]) than in a high dielectric solvent such as acetonitrile (ϵ = 37.5 D[14]); in alcohol solvents (ϵ = 10.9 – 33.6 D[14]) the effect is intermediate. The effect decreases in the series methyl, ethyl, isopropyl, *t*-butyl and this factor, because of a satisfactory correlation with Taft σ^* parameters, has been ascribed to electrostatic effects also;[4] we would like to point out, however, that an alternative explanation in terms of a

(1) (a) From the Ph.D. Dissertation of C. A. Giza. We acknowledge support of this work by the National Institutes of Health (Grant GM 13,515). (b) Paper XVI: E. L. Eliel and M. Carmeline Knoeber, *J. Amer. Chem. Soc.* **90**, 3444 (1968).

(2) C. B. Anderson and D. T. Sepp, *Chem. Ind.* (London), 2054 (1964); *Tetrahedron*, **24**, 1707 (1968).

(3) G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, **31**, 544 (1966).

(4) G. O. Pierson and O. A. Runquist, *ibid.*, **33**, 2572 (1968).

(5) N. de Wolf, P. W. Henniger, and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **86**, 1227 (1967).

(6) G. Pfundt and S. Farid, *Tetrahedron*, **22**, 2237 (1966).

(7) L. D. Hall and J. F. Manville, *Carbohyd. Res.*, **4**, 512 (1967).

(8) R. U. Lemieux and N. J. Chü, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, p 31N.

(9) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1965, p 375.

(10) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).

(11) J. T. Edward, P. F. Morand, and I. Puskas, *Can. J. Chem.*, **39**, 2069 (1961); J. T. Edward and I. Puskas, *ibid.*, **40**, 711 (1962).

(12) See, however, M. C. Planje, L. H. Toneman, and G. Dallinga [*Rec. Trav. Chim. Pays-Bas*, **84**, 232 (1965)] for the analogous effect in an acyclic system.

(13) G. F. Woods and D. N. Kramer, *J. Amer. Chem. Soc.*, **69**, 2246 (1947).

(14) A. A. Maryott and E. R. Smith, Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514, U. S. Government Printing Office, Washington, D. C., 1951.

TABLE I

EQUILIBRIA IN 2-ALKOXY- AND 2-ALKYLTHIO-6-METHYLOXANES, 2-ALKOXY-4-METHYLOXANES, 2,6-DIETHOXYOXANE, AND 2-ALKOXY-4-METHYL-1,3-DIOXANES

2-Alkoxy or alkylthio group	Solvent: Carbon tetrachloride, % *cis*[i]	Carbon tetrachloride, $\Delta G°$, kcal/mol	Acetonitrile, % *cis*[i]	Acetonitrile, $\Delta G°$, kcal/mol	Alcohol[j], % *cis*[i]	Alcohol[j], $\Delta G°$, kcal/mol
6-Methyl series						
CH_3O[a]	22.7 ± 0.3	0.73 ± 0.01	35.7 ± 0.1	0.35 ± 0.01	37.5 ± 0.2	0.30 ± 0.01
C_2H_5O[b]	24.4 ± 0.3	0.67 ± 0.01	39.9 ± 0.2	0.24 ± 0.01	34.5 ± 0.4	0.38 ± 0.01
$(CH_3)_2CHO$[c]	25.3 ± 0.3	0.64 ± 0.01	42.0 ± 0.4	0.19 ± 0.01	30.3 ± 0.2	0.50 ± 0.01
$(CH_3)_3CO$[d]	30.2 ± 0.1	0.50 ± 0.01	53.2 ± 0.2	−0.08 ± 0.01	34.4 ± 0.3	0.38 ± 0.01
CF_3CH_2O[e]	19.7 ± 0.3	0.83 ± 0.01	43 ± 2	0.17 ± 0.05		
$HC{\equiv}C(CH_3)_2CO$	28.7 ± 0.1	0.54 ± 0.01	43.6 ± 0.4	0.15 ± 0.01		
CH_3S	35.7 ± 0.1	0.35 ± 0.01	53.2 ± 0.2	−0.08 ± 0.01		
$(CH_3)_3CS$	34.1 ± 0.4	0.37 ± 0.01	54.8 ± 0.1	−0.12 ± 0.01		
4-Methyl series						
CH_3O	19.8 ± 0.3	0.83 ± 0.01	33.0 ± 0.1[f]	0.42 ± 0.01	32.7 ± 0.3[g]	0.43 ± 0.01
C_2H_5O	22.1 ± 0.6	0.75 ± 0.02	37.7 ± 0.2	0.30 ± 0.01	32.1 ± 0.3	0.44 ± 0.01
6-Ethoxyl series						
C_2H_5O	12.2 ± 0.1	1.16 ± 0.01	21.7 ± 0.1	0.76 ± 0.01	18.1 ± 0.2	0.89 ± 0.01
1,3-Dioxane series[h]						
CH_3O	35.3 ± 0.2	0.35 ± 0.01				
C_2H_5O	35.4 ± 0.2	0.35 ± 0.01				

[a] Reference 4 reports 28% *cis* in the neat liquid (neat) in the 2-alkoxy compound by an nmr method; ref 2 reports 30% *cis* in solvent methanol. [b] Reference 4 reports 32% *cis* (neat). [c] Reference 4 reports 34% (neat). [d] Reference 4 reports 38% (neat). [e] Reference 4 reports 8% (neat). [f] Reference 2 reports 35%. [g] Reference 2 reports 31%. [h] Solvent ether. [i] Average deviation indicated. [j] Alcohol corresponding to the alkoxy group of oxane.

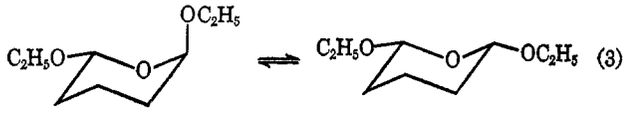
steric effect that increases in the series CH_3O, C_2H_5O, $(CH_3)_2CHO$, and $(CH_3)_3O$ and partly counterbalances the electrostatic anomeric effect is possible. Such an interpretation is made likely by the result for the dimethylethinylcarbinyl group, $HC{\equiv}C(CH_3)_2CO$, which fits in between isopropyl and *t*-butyl as predicted on steric grounds. A polar explanation would predict a greater percentage of axial character for this electron-withdrawing group; such an electrostatic effect is actually seen, as also indicated elsewhere,[4] for the trifluoroethoxy group, CF_3CH_2O.

The following findings of our investigation are novel.

(1) An axial RS group shows an anomeric effect similar to an RO group, though somewhat smaller.

(2) The monotonic decrease of $\Delta G°$ with size of the R in the RO series observed in solvents CCl_4 and CH_3CN is disturbed when the alcohol ROH is the solvent. Presumably this is because of a countertrend of the size of the R in RO on one hand and the dielectric constants[14] of the ROH solvents on the other (ϵ: CH_3OH, 33.6 D; C_2H_5OH, 25.1 D; $(CH_3)_2CHOH$, 18.3 D; $(CH_3)_3COH$, 10.9 D at 20°).

(3) The anomeric effects in the 4-methyltetrahydropyran and 6-methyltetrahydropyran series are slightly different. The difference is probably of the order of magnitude that one would expect from small polar and steric effects of alkyl substituents in different positions. On the other hand, the effect in 2,6-diethoxyoxane is very nearly the same as in 2-ethoxy-6-methyloxane after a correction has been made for the fact that the *trans* isomer on the left-hand side in eq 3



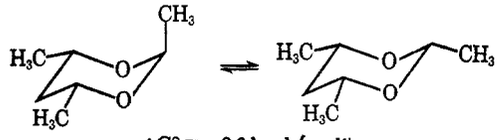
(3)

corresponds to a *dl* pair whereas the *cis* isomer on the right-hand side is a *meso* form. The *trans* isomer is therefore favored by an entropy of mixing of R ln 2. If this is allowed for, the observed $\Delta G°$ of 1.16 kcal/mol is decreased by RT ln 2 or 0.41 kcal/mol at 25°; the corrected value of 0.75 kcal/mol in CCl_4 is similar to the 0.67 kcal/mol observed for the 2-ethoxy-6-methyl homolog and the corrected values of 0.48 kcal/mol in ethanol and 0.35 kcal/mol in acetonitrile agree with the 0.38 kcal/mol and 0.24 kcal/mol values for the monoethoxy compound. (The comparison would be even better if it were made between the 2,6-diethoxy and 4-methyl-6-ethoxy series.)

(4) A substantial anomeric effect persists in 2-alkoxy-1,3-dioxanes, the axial methoxy and ethoxy groups in that series being preferred by 0.35 kcal/mol despite the strong steric crowding of an axial 2 substituent in a 1,3-dioxane amounting to 3.6–4.1 kcal/mol for a methyl group.[1b,15]

On the basis of the present and preceding[1b] work, the following two observations may be added to what is already known about the anomeric effect.

(a) Although the effect is defined as the difference in $\Delta G°_X$ between a heterocycle and cyclohexane (see above), it must not be concluded that this difference as such represents the added electrostatic stabilization of the axial substituent in the heterocycle. Such a conclusion would presume that the steric interaction in a heterocycle is the same as that in the analogously substituted cyclohexane. In general, however, this is not true. For example in a 1,3-dioxane the steric interaction of an axial methyl substituent at C-2 (eq 4) is substantially larger than the corresponding



(4)

$\Delta G° = -3.6$ kcal/mol[1b]

$\Delta H° = -4.1$ kcal/mol[15]

interaction in cyclohexane (where $-\Delta G°_{Me} = 1.7$ kcal/mol). This is a result of the shortness of the C–O

(15) K. Pihlaja and J. Heikkilä, *Acta Chem. Scand.*, **21**, 2390, 2430 (1967).

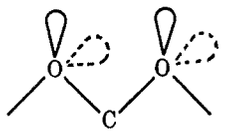
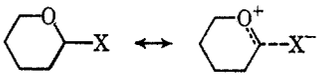


Figure 1.

distances in the ring, which in turn forces together the axial groups. A similar steric compression would be expected to exist in an axial 2-alkoxy-1,3-dioxane, and the fact that the alkoxy group in this type of compound nevertheless prefers the axial orientation must indicate the operation of an electrostatic factor whose magnitude is in excess of the calculated anomeric effect of 0.95 kcal/mol (using 0.6 kcal/mol for $-\Delta G_{OMe}$). In other types of rings it is conceivable that steric effects might be less than in cyclohexane, in which case the calculated anomeric effect would exaggerate the polar stabilization of the axial substituent.

(b) It is often assumed that the anomeric effect is a dipolar effect resulting from the interaction of the C–O–C bond dipoles of the ring with the dipoles of the equatorial and axial C–X bonds, favoring axial orientation of the latter.[9,10] Perhaps a more revealing way of looking at the dipoles when X = OR is to say that they are, in essence, engendered by the free pairs with the resultant dipole pointing along the bisectrix of the angle between the pairs. If the pairs are furthermore assumed to be oriented so as to occupy two corners of the tetrahedron around the oxygen,[1b] one may then obtain a qualitative picture of dipole interactions by saying that the most stable conformations will be those having the minimal number of *syn*-axial electron pairs. Inspection of models shows that an equatorial OR group will necessarily have either one or two of its electron pairs *syn* axial with the pairs around the oxygens of the ring (see Figure 1). An axial OR group, on the other hand, will have only one *syn*-axial pair in one of its sterically favored rotamers and none in the other. (The third rotamer in which the R group points into the ring may be disregarded for steric reasons.) One can thus clearly see that axial OR should be preferred over equatorial.[16] An alternative cause of the anomeric effect has been proposed[17] for chloro- and bromo-1,4-dioxanes on the basis of X-ray data which show that, in the axial isomers, the C–O bond is unusually short and the C–X bond is unusually long. This has been rationalized on the basis of an overlap of the antibonding lobe of the C–X σ bond with an axial p-electron pair of the ring oxygen; an equivalent valence-bond picture (double bond–no bond resonance) is shown in eq 5. The necessary overlap of orbitals is possible only if X is axial. It appears to us that, since the canonic form



(5)

shown in eq 5 is a polar one, the axial isomer should be stabilized by solvents of high dielectric constant more than the equatorial one; the contrary, however, is found in the present investigation. It is questionable, however, whether the overlap explanation can be applied when X is OR rather than halogen; it would thus be of interest to examine solvent effects for the case where X is halogen in order to see whether dipole effects or double bond–no bond resonance effects are dominating.

Experimental Section

6-Methyl-2-oxene was prepared as previously described,[18] from commercially available 6-hydroxymethyl-2-oxene by $LiAlH_4$ reduction of the tosylate, but with improvement of the yield to 80–84% in the first step and 62–74% in the second: bp 99.5–100.0° (745 mm); $n^{20}D$ 1.4351 [lit. bp 76–89° (737 mm); $n^{25}D$ 1.4314].[18]

2-Methoxy-6-methyloxane.[19]—A Pyrex glass ampoule containing 10.2 g (0.103 mol) of 6-methyl-2-oxene was cooled in a Dry Ice–acetone bath and a solution of 50 mg of *p*-toluenesulfonic acid in 6.4 g (0.20 mol) methanol was added; the ampoule was sealed, allowed to warm to room temperature, and then heated in a water bath at 65–70° for 18 hr. The ampoule was opened, the acid was neutralized with a slight excess of methanolic sodium methoxide, and the material was distilled through a spinning-band column. After most of the methanol had distilled, the pressure was reduced and the product (9.9 g, 74%) was collected at 64–68° (74–77 mm), 35–36° (12 mm), or 136–137° (749 mm). The isomers were separated on a 20 ft × 3/8 in (o.d.) 25% Carbowax 20M (with 5% added KOH) on 45/60 firebrick column at 120°; the combined recovery was about 43%. The *cis* isomer (96.6% pure) had the following properties: $n^{20}D$ 1.4243; ir (neat), 1220, 1180, 1165, 1075, and 1035 cm^{-1}; nmr δ 4.15 ppm (multiplet). The *trans* isomer (99.8% pure) had the following properties: $n^{20}D$ 1.4196; ir (neat), 1200, 1125, 1060, 975, and 925 cm^{-1}; nmr, δ 4.54 ppm (narrow).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.39; H, 10.91 (*cis* isomer). Found: C, 64.56; H, 10.93 (*trans* isomer).

2-Ethoxy-6-methyloxane was similarly prepared in 41% yield, bp (mixed isomers) 143–146° (739 mm); the preparative gas chromatography column was similar to that for the lower homolog, but the support was 60/80 mesh Chromosorb P and the temperature was 145°. The *cis* isomer (98.9% pure) had the following properties: $n^{20}D$ 1.4258; ir (neat), 1215, 1165, 1135, 1075, 1035, 1000, 965, and 900 cm^{-1}; nmr, δ 4.24 ppm (multiplet). The *trans* isomer (99.9% pure) had the following properties: $n^{20}D$ 1.4204; ir (neat), 1215, 1190, 1125, 1055, 1040, 1000, and 980 cm^{-1}; nmr, δ 4.67 ppm (narrow).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.70; H, 11.18 (*cis* isomer). Found: C, 66.90; H, 11.23 (*trans* isomer).

2-Isopropoxy-6-methyloxane.[20]—This material was prepared in an open vessel but otherwise similarly to its lower homologs; the isopropyl alcohol solvent was boiled at reflux for 2 hr. The material boiling at 158.5–159° (745 mm) was only 76% pure (glpc) and represents a 65% yield (adjusted for purity). A slight improvement in yield (to 78%) resulted when the preparation was carried out in an ampoule. Separation by preparative glpc was similar to that for the ethyl compound; recoveries of 91% were achieved by using a U-shaped collector with Vigreux-type indentations cooled in a Dry Ice–acetone bath. The *cis* isomer (99.1% pure) had the following properties: $n^{20}D$ 1.4246; ir (neat), 1200, 1160, 1130, 1070, 995, 965, 940, and 895 cm^{-1}; nmr, δ 4.33 ppm (multiplet). The *trans* isomer (99.6% pure) had the following properties: $n^{20}D$ 1.4199; ir (neat), 1265, 1215, 1175, 1110, 1090, 1045, 1005, 980, 920, and 910 cm^{-1}; nmr, δ 4.77 ppm (narrow).

(16) Repulsion of parallel-oriented electron pairs in O–C–O segments may be responsible for the fact that polyformaldehyde, $(CH_2O)_n$, has a helical conformation of the chain with *gauche* arrangement of the torsional angles, in contrast to polyethylene which has mainly *anti*-oriented torsional angles; *cf.* P. de Santis, E. Giglio, A. M. Liquori, and A. Ripamonti, *J. Polym. Sci., Part A-1*, **1**, 1383 (1963). Professor Dunitz (ETH, Zürich) and one of us (E. L. E.) have, at random, examined six X-ray structures of sugars, glycosides, and thioglycosides in the recent literature and have found that *in each case* the conformation in the crystal corresponds to that rotational conformation of the axial isomer in which there are *no* electron-pair eclipsings between oxygens. We hope to report on this point in more detail at a later time. See also R. U. Lemieux in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N.Y., 1964, pp 726, 739.

(17) C. Altona, Ph.D. Thesis, University of Leiden, Leiden, The Netherlands, 1964.

(18) R. Zelinski and H. J. Eichel, *J. Org. Chem.*, **23**, 462 (1958).

(19) *Cf.* B. Helferich and T. Malkomes, *Ber.*, **55B**, 702 (1922).

(20) *Cf.* E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.55; H, 11.53 (*cis* isomer). Found: C, 68.39; H, 11.49 (*trans* isomer).

2-*t*-Butoxy-6-methyloxane.—This compound was prepared in a sealed ampoule similarly to the ethyl compound but with a 3-hr heating period at 100°. The product boiling at 170–171° (745 mm) was about 96% pure and represents a 63% yield of mixed isomers, which were separated as in the earlier cases, except that the solid support was 60/80 mesh Chromosorb W and the column temperature was 150°. The *cis* isomer (98.3% pure) had the following properties: $n^{20}D$ 1.4263; ir (neat), 1195, 1160, 1130, 1070, 1030, 1025, and 995 cm^{-1}; nmr, δ 4.44 ppm (broad). The *trans* isomer (99.2% pure) had the following properties: $n^{20}D$ 1.4230; ir (neat), 1205, 1185, 1145, 1125, 1110, 1035, 1005, and 985 cm^{-1}; nmr, δ 4.98 ppm (narrow).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.86; H, 11.86 (*cis* isomer). Found: C, 69.86; H, 11.75 (*trans* isomer).

2-(2,2,2-Trifluoroethoxy)-6-methyloxane was prepared similarly to the isopropoxy compound in 59% yield, bp 144–146° (747 mm). The column was the same as for the ethoxy compound but operated at 120°. The *cis* isomer was 99.9% pure and had the following properties: $n^{20}D$ 1.3826; ir (neat), 1160 (broad), 1080, 1035, 995, and 960 cm^{-1}; nmr, δ 4.41 ppm (multiplet). The *trans* isomer was 99.6% pure and had the following properties: $n^{20}D$ 1.3781; ir (neat), 1155 (broad), 1090, 1040, 995, and 975 cm^{-1}; nmr, δ 4.78 ppm, (narrow).

Anal. Calcd for $C_8H_{13}F_3O$: C, 48.49; H, 6.61. Found: C, 48.62; H, 6.95 (*cis* isomer). Found: C, 48.50; N, 6.61 (*trans* isomer).

2-(2-Methyl-3-butyn-2-oxy)-6-methyloxane.—To 4.0 g (0.041 mol) of 6-methyl-2-oxene and 6.0 g (0.071 mol) of 2-methyl-3-butyn-2-ol in 5 ml of acetonitrile was added 50 mg of *p*-toluenesulfonic acid, and the solution was refluxed on a steam bath for 14 hr. The acid was then neutralized by adding a pellet of KOH and the solvent was distilled at atmospheric pressure (up to 104°). The residue was distilled at reduced pressure to give 2.0 g, bp 60–65° (1–2 mm), which was redistilled, bp 95–96° (28 mm). Separation on a 30 ft × 3/8 in. 33% Carbowax 20M and 60/80 mesh Chromosorb W preparative column at 135° led to separation of the two isomers. The *cis* isomer had ir peaks (neat) at 1235, 1205, 1180, 1155, 1125, 1090, 1070 (broad), 1035, 1010, 1000, 955, 920, 900, 870, and 850 cm^{-1}; the nmr spectrum had a signal at δ 4.72 ppm (broad). The *trans* isomer (neat) had ir absorptions at 1230, 1185, 1165, 1120, 1110, 1090, 1045, 1015, 995, 985, and 860 cm^{-1}; the nmr spectrum showed a signal at δ 5.25 ppm (narrow).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95. Found: C, 72.89; H, 9.97 (*cis* isomer). Found: C, 72.19; H, 9.90 (*trans* isomer).

2-Methylthio-6-methyloxane was prepared in a sealed ampoule from 9.8 g (0.10 mol) of 6-methyl-2-oxene, 5.3 ml (0.10 mol) of liquefied methyl mercaptan, and 0.5 ml of acetyl chloride. After 45 hr at room temperature the ampoule was opened and the catalyst neutralized with methanolic sodium methoxide. Rapid distillation of the residue (after removal of solvent) gave a total of 8.3 g (57%) of product in three fractions. Analytical gas chromatography showed the presence of four components which were separated by preparative gas chromatography on a 20% Carbowax 20M on Chromosorb W column at 110°. The fractions whose nmr spectra corresponded to the desired products were obtained in 98.8% purity (*cis* isomer) and 99.5% purity (*trans* isomer). The *cis* isomer had the following properties: $n^{20}D$ 1.4907; ir (neat), 1245, 1200, 1180, 1145, 1075, 1035, 985, 955, and 930 cm^{-1}; nmr, δ 4.29 ppm (multiplet). The *trans* isomer had $n^{20}D$ 1.4799 and gave the following spectral properties: ir (neat), 1265, 1200, 1140, 1115, 1080, 1035, 965, and 790 cm^{-1}; nmr, δ 5.07 ppm (narrow). The *trans* isomer was not analytically pure.

Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.65. Found: C, 57.57; H, 9.60 (*cis* isomer).

The two other, apparently isomeric, components of the reaction mixture were tentatively identified as the 3-methylthio-6-methyloxanes but were not obtained in analytically pure form.

2-*t*-Butylthio-6-methyloxane.—When 100 mg of *p*-toluenesulfonic acid was added to a mixture of 9.0 g (0.092 mol) of 6-methyl-2-oxene and 8.0 g (0.089 mol) of *t*-butyl mercaptan placed in a 50-ml flask equipped with a condenser and stirrer, an exothermic reaction set in and the temperature rose to *ca.* 115°. After the mixture cooled, it was heated at 65–70° for 2 hr after which time the mercaptan odor had become faint. The acid was neutralized by addition of methanolic sodium methoxide and the residue after removal of methanol was distilled: bp 41–42° (0.7 mm); yield, 14.3 g (85%). Separation was effected on a 20 ft × 3/8 in. 20% tris-β-cyanoethoxypropane (TCEP) on Chromosorb P column at 125°. The *cis* isomer was 99.1% pure: $n^{20}D$ 1.4690; ir (neat), 1200, 1165, 1075, 1035, 990, 955, and 930 cm^{-1}; nmr, δ 4.57 ppm (multiplet). The *trans* isomer was 96.1% pure (the rest was mainly *cis*): $n^{20}D$ 1.4728; ir (neat), 1195, 1165, 1105, 1075, 1030. 965, 790, and 725 cm^{-1}; nmr, δ 5.42 ppm.

Anal. Calcd for $C_{10}H_{20}OS$: C, 63.78; H, 10.70. Found: C, 63.78; H, 10.60 (*cis* isomer). Found: C, 63.81; H, 10.69 (*trans* isomer).

2-Ethoxy-4-methyl-5-oxene was obtained from Aldrich Co. as a diastereoisomeric mixture, bp 51–52° (14 mm). Separation was effected by repeated passes through the preparative column used for the butynyl compounds (*vide supra*) at 125°. The *cis* isomer was 99.5% pure: $n^{20}D$ 1.4383; ir (neat), 1230, 1170 (broad), 1120, 1055 (shoulder), 1035, 1010, 910, 865, 835, 740 (broad); nmr, δ 4.82 ppm (double doublet). The *trans* isomer was 99.2% pure: $n^{20}D$ 1.4358; ir (neat), 1230, 1215, 1150, 1120, 1055, 1015, 975, 850, and 735 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.41; H, 9.96 (*cis* isomer). Found: C, 67.57; H, 10.04 (*trans* isomer).

2-Ethoxy-4-methyloxane.—The mixture of diastereoisomers was obtained by hydrogenating 14.8 g of the mixed oxene (above) in 100 ml of absolute ethanol over 100 mg of 10% palladium on charcoal in the presence of a few granules of sodium carbonate at 40 lb/in.^{2} for 6 hr. The catalyst was filtered and the product was distilled, bp 56–60° (20 mm), after prior removal of ethanol at atmospheric pressure. Separation was as in the case of the corresponding oxenes. The *cis* isomer was 99.9% pure: $n^{20}D$ 1.4265; ir (neat), 1235, 1145, 1130, 1070, 1020, 985, and 970 cm^{-1}; nmr, δ 4.23 ppm (double doublet). The *trans* isomer was 98.5% pure (impurity, oxene): $n^{20}D$ 1.4228; ir (neat), 1180, 1165, 1125, 1090, 1060, 1030, 985, and 850 cm^{-1}; nmr, δ 4.67 ppm (narrow).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.62; H, 11.18. Found: C, 66.47; H, 11.24 (*cis* isomer). Found: C, 66.71; H, 11.16 (*trans* isomer).

2-Methoxy-4-methyloxane.—A solution of 2.0 g (0.017 mol) of the above ethoxy compound, 4.0 g (0.13 mol) of methanol, and 50 mg of *p*-toluenesulfonic acid in 4.0 g of acetonitrile was kept at room temperature for 48 hr, cooled, and then neutralized with sodium methoxide. After removal of solvent, 1.8 g of a pleasant-smelling liquid remained and glpc analysis indicated that the alkoxy exchange had proceeded to the extent of 91.4%. A second, similar exchange was carried out for 24 hr and the recovered material (0.9 g) was distilled, bp 54–55° (28 mm); the extent of exchange was 98.9%. The isomers were separated on a 20 ft × 3/8 in. 6% TCEP on 40/60 mesh Chromosorb G preparative column at 70°; two passes through the column were necessary to obtain material of adequate purity. The *cis* isomer was 99.3% pure: ir (neat), 1210, 1185, 1170, 1145, 1125, 1075 (broad), 985, 915, 885, and 840 cm^{-1}. The *trans* isomer was 99.9% pure: ir (neat), 1200, 1180, 1165, 1120, 1055, 958, 955, 885, and 855 cm^{-1}.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.39; H, 10.80 (*cis* isomer). Found: C, 64.71; H, 10.80 (*trans* isomer).

2,6-Diethoxyoxane was obtained as an 88:12 *trans–cis* mixture from Aldrich Chemical Co.; the isomers were separated by four successive passes through a 30 ft × 3/8 in. 33% Carbowax 20M on 45/60 mesh Chromosorb W preparative glpc column at 145°. Even so, only a very small amount of 98.9% pure *cis* isomer was obtained for analysis. The following physical properties refer to a sample of 89.5% purity: $n^{20}D$ 1.4307; ir (neat), 1160, 1151 (broad), 1070, 1010, 970, and 950 cm^{-1}; nmr, δ 4.61 ppm (broad). The *trans* isomer was 99.6% pure: $n^{20}D$ 1.4287; ir (neat), 1165 (broad), 1115, 1020, and 970 (broad) cm^{-1}; nmr, δ 4.76 ppm (narrow).

2-Methoxy-1,3-dioxane.—A solution of 7.6 g (0.10 mol) of 1,3-propanediol and a trace of *p*-toluenesulfonic acid in 100 ml of benzene was brought to reflux in a 200-ml three-necked flask equipped with an addition funnel, stirrer, and condenser equipped with Dean–Stark trap. A solution of 10.6 g (0.10 mol) of trimethyl orthoformate in 50 ml of benzene was added dropwise and 80 ml of benzene–methanol azeotrope was collected in the

trap over a 1-hr period. The solution was cooled, extracted three times with 10% aqueous NaOH, dried, filtered, concentrated, and distilled to give 7.0 g (60%) of 2-methoxy-1,3-dioxane: bp 142–144° (745 mm); $n^{20}D$ 1.4250. The material was further purified by gas chromatography: ir (neat), 1240, 1205, 1135 (broad), 1095, 1075, 1035 (broad), 975, and 830 cm^{-1}.

Anal. Calcd for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 51.06; H, 8.62.

2-Methoxy-4-methyl-1,3-dioxane was prepared analogously from 1,3-butanediol in 56% yield, bp 130–143° (745 mm). The isomers were separated on a 10 ft × 3/8 in. 5% Carbowax 20M on Chromosorb G column at 120°. The *cis* isomer had the following properties: $n^{20}D$ 1.4250; ir (neat), ten strong peaks in the 8–10 μ region and peaks at 970 (double) and 920 and 895 cm^{-1}; nmr, δ 5.02 ppm for H_2. The *trans* isomer had the following properties: $n^{20}D$ 1.4178; ir (neat), eight peaks in the 8–10 μ region plus peaks at 995, 970, 950, 860, and 790 cm^{-1}; nmr, δ 5.14 ppm for H_2. The configurational assignment must be considered tentative in this case.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.43; H, 9.15 (*cis* isomer). Found: C, 54.81; H, 9.00 (*trans* isomer).

2-Ethoxy-4-methyl-1,3-dioxane was prepared similarly but without attempt to remove the benzene–ethanol azeotrope and with only 3 min of reflux time. Under these circumstances the yield was only 14%, bp 51–65.5° (19 mm). Separation on the earlier mentioned 30-ft 6% TCEP column at 125° gave the two isomers in over 95% purity; a second pass produced nearly pure materials. The *cis* isomer had the following properties: $n^{20}D$ 1.4252; ir (neat), 1250, 1200, 1165, 1105, 995, 960, and 875 cm^{-1}; nmr, δ 5.02 ppm for H_2. The *trans* isomer had the following properties: $n^{20}D$ 1.4187; ir (neat), 1260, 1255, 1180, 1165, 1125, 1055 (broad), 1020, 1000, and 980 cm^{-1}; nmr, δ 5.23 ppm for H_2. The configurational assignment must be considered tentative.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.46; H, 9.65 (*cis* isomer). Found: C, 57.33; H, 9.61 (*trans* isomer).

Equilibrations.—In all cases, equilibrations were initiated with both *cis*-rich and *trans*-rich samples. Solutions in carbon tetrachloride and in acetonitrile were generally 1.4 *M*; those in alcohols were 0.35 *M*. The catalyst in CCl_4 was generated by adding 2 mol % of mutually equivalent amounts of acetyl chloride and the alcohol corresponding to the oxane; in acetonitrile and alcohol solvent the catalyst was 2 mol % *p*-toluenesulfonic acid; in ether the catalyst was 20 mol % boron trifluoride. Equilibrations were carried out in sealed ampoules at 25°; after the requisite time, the ampoules were opened and the acid was neutralized with methanolic sodium methoxide prior to gas chromatography. Response ratios (glpc) were determined for all compounds. Equilibrium was deemed to be reached when *cis*-rich and *trans*-rich starting samples came to the same composition. Each analysis was carried out at least four times (see also ref 1b for details of method).

Registry No.—2-Methoxy-6-methyloxane (*cis*), 17230-07-8; (*trans*), 17230-08-9; 2-ethoxy-6-methyloxane (*cis*), 17230-09-0; (*trans*), 17230-10-3; 2-isopropoxy-6-methyloxane (*cis*), 17230-11-4; (*trans*), 1927-76-0; 2-*t*-butoxy-6-methyloxane (*cis*), 17230-13-6; (*trans*), 17230-14-7; 2-(β,β,β-trifluoroethoxy)-6-methyloxane (*cis*), 17230-15-8; (*trans*), 17230-16-9; 2-(2-methyl-3-butyn-2-oxy)-6-methyloxane (*cis*), 17230-17-0; (*trans*), 17230-18-1; 2-methylthio-6-methyloxane (*cis*), 17230-19-2; (*trans*), 17230-20-5; 2-*t*-butylthio-6-methyloxane (*cis*), 17230-21-6; (*trans*), 17230-22-7; 2-ethoxy-4-methyl-5-oxene (*cis*), 17322-76-8; (*trans*), 17322-77-9; 2-ethoxy-4-methyloxane (*cis*), 17230-25-0; (*trans*), 17322-78-0; 2-methoxy-4-methyloxane (*cis*), 7429-27-8; (*trans*), 7429-28-9; 2,6-diethoxyoxane (*cis*), 17230-29-4; (*trans*), 17230-30-7; 2-methoxy-1,3-dioxane, 17230-31-8; 2-methoxy-4-methyl-1,3-dioxane (*cis*), 17230-32-9; (*trans*), 17230-33-0; 2-ethoxy-4-methyl-1,3-dioxane (*cis*), 17230-34-1; (*trans*), 17230-35-2.

Acknowledgment.—We express our thanks to Sr. M. Carmeline Knoeber who carried out the preparation and equilibrations of the 2-alkoxy-1,3-dioxanes described in this Article. We are indebted to Professor S. J. Angyal (Sydney), Professor J. D. Dunitz (Zurich), and Professor E. Havinga (Leiden) for helpful discussions regarding the origin of the anomeric effect.

The Synthesis of 1,4-Substituted Imidazoles[1a]

PRESTON K. MARTIN,[1b] H. RANDALL MATTHEWS, HENRY RAPOPORT, AND G. THYAGARAJAN[1c]

Department of Chemistry, University of California at Berkeley, Berkeley, California 94720

Received May 8, 1968

A specific and unambiguous synthesis of 1,4-substituted imidazoles is described. α-Amino-β-methylaminopropionic acid was cyclized in triethyl orthoformate with a catalytic amount of hydrochloric acid to 1-methyl-2-imidazoline-4-carboxylic acid, which was esterified and dehydrogenated, using active manganese dioxide, to methyl 1-methyl-4-imidazolecarboxylate. This ester was further converted into several other 1,4-substituted imidazoles. The same procedure has been used to synthesize 1,5-substituted imidazoles; *e.g.*, α-methylamino-β-aminopropionic acid was cyclized, esterified, and dehydrogenated under similar conditions to methyl 1-methyl-5-imidazolecarboxylate.

The wide biological occurrence and physiological importance of compounds incorporating the imidazole nucleus have stimulated considerable synthetic work on this heterocycle.[2] Methods of synthesis or of structural elucidation of unsymmetrical imidazoles are inadequate or ambiguous,[2-4] except for 1,5-substituted imidazoles. In the latter case,[5] only the procedure reported by Jones[5a] is unequivocal, reproducible, and versatile. We now report a general and unambiguous synthesis of 1,4-substituted imidazoles and its application to the synthesis of 1,5-substituted imidazoles as well.

(1) (a) Supported in part by the U. S. Army Research Office, Durham, N. C.; (b) U. S. Public Health Service Postdoctoral Fellow; (c) on leave from the Regional Research Laboratory, Hyderabad, India.

(2) (a) K. Hofmann in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1953 (Imidazoles and Derivatives, part I); (b) A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Russ. Chem. Rev.*, **35**, 122 (1966).

(3) (a) A. M. Crestfield, W. H. Stein, and S. Moore, *J. Biol. Chem.*, **238**, 2413 (1963); (b) T. E. Wagner, H. G. Chai, and M. E. Carlson, *Biochem. Biophys. Res. Commun.*, **28**, 1019 (1967); (c) E. B. Ong, E. Shaw, and G. Schoellman, *J. Biol. Chem.*, **240**, 694 (1965).

(4) L. B. Townsend, *Chem. Rev.*, **67**, 533 (1967).

(5) (a) R. G. Jones, *J. Amer. Chem. Soc.*, **71**, 644 (1949); (b) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 2028 (1948); (c) F. F. Blicke and H. C. Godt, Jr., *J. Amer. Chem. Soc.*, **76**, 3653 (1954); (d) P. M. Kochergin, *Zh. Obshch. Khim.*, **34**, 3402 (1964); (e) D. A. Shirley and P. W. Alley, *J. Amer. Chem. Soc.*, **79**, 4922 (1967).