propane (Matheson), ethane (Matheson), trimethylsilane (Columbia), and methanethiol (Eastman).

Esr Line-Shape Calculations. Esr line shapes in the presence of exchange were calculated using the phenomenological density matrix equation of motion of Kaplan[28] and Alexander.[29] In those cases where the spectra are first order, considerable simplification is possible and the density matrix method reduces to the equations given by Sack.[30] Since the esr spectra in this study are very nearly first order (as is usually the case for organic free radicals), this approximation was used in the present analysis. Details concerning the esr line-shape calculations are given elsewhere.[31,32]

The spectra at the low- and high-temperature limits and the lines not affected by the exchange process at intermediate temperature could be fitted best by a Gaussian of Lorentzians. The Gaussian component is assumed to arise mainly from unresolved long-range proton couplings (the binomial coefficients of *n* approach a Gaussian function for large *n*). These long-range couplings should be invariant to the exchange process so that the esr line shapes in the presence of exchange can be obtained by first calculating the line shapes in the usual fashion using the Lorentzian line shape implied by the simple phenomenological density matrix equations of motion and then numerically convoluting the calculated spectrum with a Gaussian.

The exchange rates were obtained by a visual comparison of the observed and calculated spectra. The line shapes in the absence of exchange were first obtained by visually fitting one of the lines invariant to the exchange process. The exchange rate was then varied until a good fit at the exchanging lines was also obtained. In most cases the complete spectrum was not fitted; instead, several of the lines near the wings of the spectrum were used.

Calculated Stabilization of Radical 2. The energy by which the silicon-substituted radical, **2**, is stabilized due to hyperconjugation and p–d homoconjugation can be calculated with the aid of eq 4 and 5, respectively. The interaction between the odd electron orbital (the highest occupied orbital or the lowest half-occupied orbital) and the carbon–silicon bonding orbital or the silicon d orbitals is taken into account. To estimate the values of $H_{i\sigma}$ and H_{id}, the following equations were used

$$H_{i\sigma} = \frac{K}{2}S_{i\sigma}(H_{ii} + H_{\sigma\sigma})$$

$$H_{id} = \frac{K}{2}S_{id}(H_{ii} + H_{dd}) \qquad (6)$$

$$K = 1 \sim 2$$

where H_{ii}, $H_{\sigma\sigma}$, and H_{dd} are evaluated as the negative value of ionization potentials of the allyl radical (−8.15 eV),[33] that of $(CH_3)_4Si$ (−9.8 eV),[16] and the (negative) valence state ionization potential of the 3d orbital (−2.0 eV),[17] respectively. The overlap integral between the odd electron orbital ($\sqrt{1/2}\pi_1 - \sqrt{1/2}\pi_3$; π_1 and π_3 are the π atomic orbitals on C_1 and C_3) and the carbon–silicon bonding orbital ($\sqrt{1/2}\,\chi_4 + \sqrt{1/2}\chi_{Si}$; χ_4 and χ_{Si} are the sp^3 orbitals forming the carbon–silicon bond) is calculated to be 0.080 at the conformation of $\varphi = 10°$. The overlap integral between the odd electron orbital and the d orbitals is calculated as mentioned in the text. The odd electron orbital energy ϵ_i in eq 4 was equated to the negative value of the electron affinity of the allyl radical (−1.82 eV)[34] and ϵ_i in eq 5 to the negative value of the ionization potential of the allyl radical (−8.15 eV). Values of ϵ_σ and ϵ_d were evaluated as $H_{\sigma\sigma}$ and H_{dd}. The values obtained for the hyperconjugative and homoconjugative stabilizations of radical **2** at the eclipsed conformation are 1.5 ∼ 7 and 0.6 ∼ 3 kcal/mol (that is, the contribution to ΔE from the angular dependence of the p–d homoconjugation is 0.3 ∼ 1.5 kcal/mol), respectively. These calculated values are acceptable when compared with the observed energy barrier to the hindered internal rotation in Table II. Although the calculation of p–d homoconjugation is less reliable, the stabilization due to hyperconjugation and p–d homoconjugation would have the same order of magnitude.

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(28) J. I. Kaplan, *J. Chem. Phys.*, **28**, 278 (1958); **29**, 462 (1958).

(29) S. Alexander, *ibid.*, **37**, 967, 974 (1962); **38**, 1787 (1963); **40**, 2741 (1964).

(30) R. A. Sack, *Mol. Phys.*, **1**, 163 (1958).

(31) P. J. Krusic, P. Meakin, and J. P. Jesson, *J. Phys. Chem.*, **75**, 3438 (1971).

(32) P. Meakin, E. L. Muetterties, F. N. Tebbe, and J. P. Jesson, *J. Amer. Chem. Soc.*, **93**, 4701 (1971).

(33) J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. J. Herron, and K. Draxl, *Nat. Bur. Stand.* (*U. S.*), *Circ.*, **No. 26**, (1969).

(34) J. R. Hoyland and L. Goodman, *J. Chem. Phys.*, **36**, 21 (1962)

Conformational Analysis. XXVI. Conformational Equilibria in 5,5-Disubstituted 1,3-Dioxanes[1]

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Abstract: Thirteen pairs of diastereoisomers of 5,5-disubstituted 2-isopropyl-1,3-dioxanes were equilibrated by means of boron trifluoride or polystyrenesulfonic acid ("Amberlyst-15"). The geminal substituents were methyl–ethyl, methyl–isopropyl, methyl–cyclohexyl, methyl-*tert*-butyl, ethyl–isopropyl, methyl–phenyl, ethyl–phenyl, methyl–hydroxyl, methyl–methoxyl, methyl–nitro, methyl–hydroxymethyl, methyl–methoxymethyl, and methyl–carbomethoxyl. In most cases, conformational free energies for geminal substituents were found not to be additive. Potential reasons are discussed.

A large number of conformational energies (Scheme I, R = H) for monosubstituted cyclohexanes have been determined since 1955.[3] In contrast, little i known about geminally disubstituted cyclohexane and, in particular, whether the conformational en ergies for geminal substituents may be considered to b

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(1) Paper XXV: R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, *J. Amer. Chem. Soc.*, **94**, 1913 (1972).

(2) (a) Address correspondence to Department of Chemistry, University of North Carolina, Chapel Hill, N. C. 27514. (b) From the Ph.D. dissertation of R. M. Enanoza, University of Notre Dame, Notre Dame, Ind., 1970.

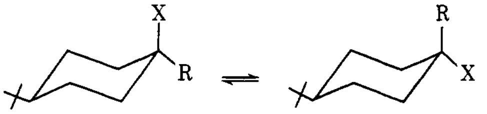
(3) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison "Conformational Analysis," Wiley-Interscience, New York, N. Y 1965; J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).

Table I. Experimental and Calculated[a] Free Energies for Isomerization of Geminally Disubstituted Cyclohexanes (Scheme I)

Groups		$\Delta G°$, kcal/mol			
X	R	Found	Calcd[a]	Ref	Method
OH	CH_3	0.24, 0.35;[b] 0.3;[b] 0.75[c]	0.8;[b] 1.1[c]	7, 8; 16	*d*; *e*
OH	C_6H_5	~0.5[b,c]	2.2;[b,f] 2.5[c,f]	16	*e*
OCH_3	CH_3	0.3	1.1	15	*d*
Cl	CH_3	1.1	1.2	6	*d*
OH	CH_2OH	0.46	1.05	15	*e*
OH	$CH{=}CH_2$	0.64	*g*	13	*e*
OH	$C{\equiv}CH$	−0.60	−0.3	14	*e*
COOH	CH_3	−0.5	+0.4	17	*h*
COOMe	CH_3	+0.16	+0.4	17	*e*
COO^-	CH_3	−0.25	−0.2	17	*h*
CHO	CH_3	0.14	0.3	18	*e*
NMe_2	C_6H_5	−0.9	1.0[f]	9	*h*
SCH_2[i]	OCH_2[i]	0.0 ± 0.2	−0.1;	5	*d*
OCH_2[j]	CH_2O[j]	0.15;[k] 0.27[l]	0.8;[k] 1.1[l]	10; 11	*m*; *n*
OCH_2[o]	CH_2[o]	0.46	1.1	12[p]	*q*
$OC{=}O$[r]	CH_2	0.28	1.1	12[p]	*d*

[a] Assuming additivity. [b] In hydrogen bonding solvent. [c] In nonbonding solvent. [d] Equilibration of 4-*tert*-butyl-substituted compounds. [e] Proton nmr using 4-*tert*-butyl-substituted models. [f] Using 3.1 kcal/mol for $\Delta G_{C_6H_5}°$; *cf.* ref 3. [g] No independent $-\Delta G°$ for alkyl group available. [h] Acidity measurement. [i] Ethylene monothioketal or trimethylene monothioketal. [j] Epoxide. [k] In H_2O–AcOH, ref 10. [l] In CS_2, ref 11. [m] Kinetic, ref 10. [n] Low-temperature nmr, ref 11. [o] $OCH_2CH_2CH_2$. [p] See also ref 15. [q] Infrared. [r] $OCOCH_2CH_2$.

Scheme I

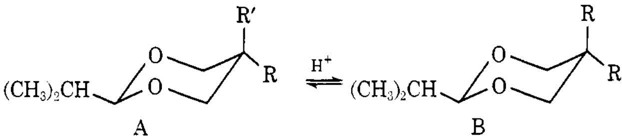


additive. The reason for the paucity of data is probably methodological: geminally disubstituted cyclohexanes are somewhat difficult to synthesize, configurational assignment is not straightforward, direct equilibration of diastereoisomers (assuming a holding group, such as 4-*tert*-butyl, to be present) is often impossible, and application of the popular nmr methods frequently founders on the lack of well-distinguishable signals for the two diastereoisomers.[4]

One of the earliest cases to be investigated was that of the 4-*tert*-butylcyclohexanone ethylene monothioketals[5a] and trimethylene monothioketals.[5b] In the case of the former, axial sulfur was slightly favored over axial oxygen, the reverse being true for the latter. In neither case was $\Delta G°$ equal to the difference of $\Delta G_{SR}°$ and $\Delta G_{OR}°$, although in the case of the six-membered ring it came close. The situation for the five-membered ring may have been affected by an outward distortion of the axial sulfur atom which may have diminished its nonbonded interaction below that of axial oxygen. A few other cases have since been investigated,[6–18] sometimes by rather indirect methods, and in two cases, that of vinyl[13] and that of ethynyl,[14] the $-\Delta G°$ value of the alkyl group has actually been deduced by assuming it to be additive with that of a gem-hydroxyl. Table I summarizes previous investigations on geminally disubstituted cyclohexanes; again lack of additivity is the rule.

The 1,3-dioxane system[19] provides an ideal opportunity to study equilibria involving geminal disubstitution, since dioxanes with a wide variety of substituents, including geminal substituents, are easy to synthesize and since equilibration with either boron trifluoride etherate or (more conveniently) an insoluble polystyrenesulfonic acid (Amberlyst-15) is facile, almost regardless of the nature of the substituent.[20–22] Our initial studies were directed toward 5,5-disubstituted dioxanes (Scheme II), for, although the $-\Delta G°$ values for 5 substituents in 1,3-dioxanes are quite different from those in cyclohexanes,[19,20,22] the vicinity of the 5 position is "cyclohexane-like," even down to geometric detail,[23] so that the 5 position would seem to afford a test of additivity of $-\Delta G°$ values which may be transferred to cyclohexanes.[24]

Scheme II



After this study was initiated,[25] Anteunis and co-

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(4) This last difficulty may be overcome by use of ^{13}C nmr.

(5) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962); (b) E. L. Eliel, E. W. Della, and M. Rogić, *J. Org. Chem.*, **30**, 855 (1965); (c) M. P. Mertes, H.-K. Lee, and R. L. Schowen, *ibid.*, **34**, 2080 (1969).

(6) N. L. Allinger and C. D. Liang, *ibid.*, **32**, 2391 (1967).

(7) N. L. Allinger and C. D. Liang, *ibid.*, **33**, 3319 (1968).

(8) J. J. Uebel and H. W. Goodwin, *ibid.*, **33**, 3317 (1968).

(9) S. Sicsic and Z. Welvart, *Bull. Soc. Chim. Fr.*, 575 (1967).

(10) J. J. Uebel, *Tetrahedron Lett.*, 4751 (1967).

(11) R. G. Carlson and N. S. Behn, *Chem. Commun.*, 339 (1968).

(12) P. Picard and J. Moulines, *Tetrahedron Lett.*, 5133 (1970).

(13) R. J. Ouellette, K. Liptak, and G. E. Booth, *J. Org. Chem.*, **31**, 546 (1966).

(14) R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964).

(15) J. J. Uebel, E. L. Nickoloff, W. T. Cole, and C. B. Grant, *Tetrahedron Lett.*, 2637 (1971).

(16) J. Alléon, J. R. Gessinger, P. Laszlo, and Z. Welvart, unpublished observations; *cf.* J. R. Gessinger, P. Laszlo, J. Alléon, and Z. Welvart, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, P-64.

(17) M. Malissard and Z. Welvart, personal communication.

(18) G. W. Buchanan, J. B. Stothers, and S.-T. Wu, *Can. J. Chem.*, **45**, 2955 (1967).

(19) *Cf.* E. L. Eliel, *Accounts Chem. Res.*, **3**, 1 (1970).

(20) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(21) F. W. Nader and E. L. Eliel, *ibid.*, **92**, 3050 (1970).

(22) E. L. Eliel and M. K. Kaloustian, *Chem. Commun.*, 290 (1970).

(23) *Cf.* A. J. de Kok and C. Romers, *Recl. Trav. Chim. Pays-Bas*, **89**, 313 (1970).

(24) 2,2-Disubstituted dioxanes [*cf.* E. L. Eliel, *Pure Appl. Chem.*, *Suppl.*, **7**, 219 (1971)] and 4,4-disubstituted dioxanes are under study.

(25) For preliminary results, see E. L. Eliel, *Pure Appl. Chem.*, **25**, 509 (1971), which is a summary of a paper presented at the Symposium on Conformational Analysis, Brussels, Belgium, Sept. 1969.

Table II.[a] Conformational Equilibria in 5-R,5-R′-Disubstituted 1,3-Dioxanes as Determined by Low-Temperature Nmr Study[b]

R	CH_3	CH_3	CH_3	CH_3	CH_3	C_2H_5[d]	C_2H_5
R′	NH_2	$COCH_3$	$(CH_3)_2CH$[c]	$(CH_3)_2CHCH_2$	C_6H_5	C_6H_5	$(CH_3)_2CH$
ΔG°, kcal/mol	0.16	−0.91	0.19	0.03	0.32	0.38	0.17

[a] See ref 26. [b] Equilibria written with the equatorial R′ group on the right. Solvent carbon disulfide. [c] Similar values for *sec*-Bu, 0.18; cyclopentyl, 0.12; cyclohexyl, 0.19. [d] Value for *n*-propyl, 0.29.

Table III. Equilibria in 5,5-Disubstituted 2-Isopropyl-1,3-dioxanes (Scheme II)

Entry no. (compd)	R	R′	Solvent[a]	K	ΔG_{25}° (exptl), kcal/mol	ΔG°, (calcd),[b] kcal/mol	$\Delta\Delta G^\circ$, kcal/mol[c]
1 (**1, 2**)	CH_3	CH_2CH_3	Ether	0.907	+0.06 ± 0.02	−0.14	+0.20
2 (**3, 4**)	CH_3	$CH(CH_3)_2$	Ether	1.66	−0.30 ± 0.05[d]	−0.33	+0.03
3 (**5, 6**)	CH_3	*c*-C_6H_{11}	Ether	1.60	−0.28 ± 0.01	−0.33	+0.05
4 (**7, 8**)	CH_3	$C(CH_3)_3$	Ether	3.91	−0.81 ± 0.07	−0.60	−0.21
5 (**9, 10**)	CH_2CH_3	$CH(CH_3)_2$	Ether	1.71	−0.32 ± 0.01[d]	−0.15	−0.17
6 (**11, 12**)	CH_3	C_6H_5	Ether	2.47	−0.54 ± 0.03[d]	−0.23	−0.31
7 (**13, 14**)	CH_2CH_3	C_6H_5	Ether	2.37	−0.51 ± 0.02[d]	−0.36	−0.15
8[e,f] (**15, 16**)	OH	CH_3	Ether	1.79	−0.41 ± 0.02	−0.49	+0.08
			DME	1.35	−0.18 ± 0.02	−0.39	+0.21
			$CHCl_3$	19.02	−1.74 ± 0.04	−1.89	+0.15
			i-PrOH	0.747	+0.09 ± 0.02	−0.19	+0.28
			CH_3CN	2.76	−0.60 ± 0.02	−0.97	+0.37
9 (**17, 18**)	CH_3	OCH_3	CCl_4	2.13	−0.45 ± 0.03	−0.03	−0.42
			Ether	1.78	−0.34 ± 0.04	+0.07	−0.41
			$CHCl_3$	0.716	+0.10 ± 0.01	+0.80	−0.70
			t-BuOH	1.47	−0.23 ± 0.02		
			CH_3OH	0.567	+0.39 ± 0.03	+0.77	−0.38
			CH_3CN	0.668	+0.12 ± 0.01	+0.91	−0.79
10 (**20, 19**)	NO_2	CH_3	CCl_4	2.07	−0.43 ± 0.07	−1.24	+0.81
			Ether	2.82	−0.62 ± 0.04		
			$CHCl_3$	4.51	−0.89 ± 0.03	−1.61	+0.72
			CH_2Cl_2	7.19	−1.17 ± 0.03	−1.79	+0.62
11[e] (**22, 21**)	CH_2OH	CH_3	CCl_4	5.68	−1.03 ± 0.04	−1.13	+0.10
			Ether	3.14	−0.68 ± 0.03	−0.87	+0.19
			$CHCl_3$	5.24	−0.98 ± 0.03	−1.13	+0.15
			DME	2.53	−0.55 ± 0.02	−0.79	+0.24
			CH_3OH	2.61	−0.57 ± 0.02	−0.90	+0.33
			CH_3CN	2.83	−0.62 ± 0.02	−0.81	+0.19
12 (**24, 23**)	CH_2OCH_3	CH_3	CCl_4	3.41	−0.73 ± 0.03		
			Ether	2.91	−0.63 ± 0.03	−0.85	+0.22
			DME	2.78	−0.61 ± 0.03		
			$CHCl_3$	3.20	−0.69 ± 0.03		
			CH_3OH	3.03	−0.66 ± 0.02		
13 (**25, 24**)	CO_2CH_3	CH_3	Ether	1.16	−0.09 ± 0.05	−0.08	−0.01
			CH_3CN	2.82	−0.63 ± 0.03	−0.68	+0.05

[a] Dielectric constants at 25°: ether, 4.22; DME (1,2-dimethoxyethane), 3.5–6.8; $CHCl_3$, 4.70; CH_3OH, 32.6; *i*-PrOH, 18.3; *t*-BuOH, 12.2; CH_3CN, 37.5 (20°); CCl_4, 2.23; CH_2Cl_2, 8.9. *Cf.* Landolt–Börnstein, "Zahlenwerte und Funktionen," Vol. II, 6th ed, Springer Verlag, Berlin, Germany, 1959, p 613. [b] See text. [c] Experimental minus calculated. [d] For nmr value, see Table II. [e] Concentration 0.2 *M* in each solvent. [f] Four-component equilibrium. Two dioxolanes are also formed. The same equilibrium was attained from the dioxolane side.

workers[26,27] reported on the conformational equilibria of some 5,5-disubstituted dioxanes (Scheme II, but without the isopropyl holding group) as measured by determination of nmr parameters at low temperature. Their values are summarized in Table II.

The ΔG° values for 5,5-disubstituted 1,3-dioxanes obtained by the chemical equilibration of diastereoisomers shown in Scheme II in the present study are summarized in Table III. Also indicated in the table are values calculated from the known $-\Delta G^\circ$'s of 5-monosubstituted 1,3-dioxanes.[20,22,28] For the 5,5-dialkyl-1,3-dioxanes the ΔG°'s were calculated taking into account the rotameric differences between monosubstituted and geminally disubstituted species, computing the population of all rotamers and then calculating $H^\circ_{\text{confo}} = \Sigma_i n_i H_i$ and $S^\circ_{\text{mix}} = -R\Sigma_i n_i \ln n_i$. G°_{confo} is then $H^\circ_{\text{confo}} - TS^\circ_{\text{mix}}$ and $\Delta G^\circ = G_r^\circ - G_s^\circ$ where G_r° and G_s° stand for the free energies computed for the right- and left-hand side of Scheme II, respectively.[29] The assumptions in this procedure are that only staggered conformations need be taken into account, that conformational energy differences adequately determine ΔH°, and that there are no contributions to entropy differences other than the entropy of mixing.[30] The values used for conformational energies are butane gauche, 0.85 kcal/mol ($^1/_2$ the value of axial

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[26] E. Coene and M. Anteunis, *Tetrahedron Lett.*, 595 (1970); *Bull. Soc. Chim. Belg.*, **79**, 25 (1970).

[27] See also M. Anteunis, E. Coene, and D. Tavernier, *Tetrahedron Lett.* 4579 (1966).

[28] In trying to check the values for 5-hydroxyl, earlier determined by Raney nickel equilibration,[22] by equilibration with acid (which yields a four-component mixture of 5-hydroxy-2-isopropyl-1,3-dioxanes and 4-hydroxymethyl-2-isopropyl-1,3-dioxolanes which is, however, readily analyzable by gas chromatography), we found some discrepancies; the new values used are shown in Table IV.

[29] *Cf.* ref 3, pp 23–25.

[30] For an excellent discussion of several of these points, see J. Reisse, "Conformational Analysis," G. Chiurdoglu, Ed., Academic Press, New York, N. Y., 1971, pp 219–228.

methyl in cyclohexane rather than the actual value in butane), axial 5 substituent with H inside the ring, 0.80 kcal/mol,[31] axial 5 substituent with methyl inside the ring, 3.10 kcal/mol.[31] For all other groups in Table III, the calculated values assume simple additivity for ΔG°, an assumption which is no doubt wrong for groups other than those of $C_{\infty v}$ or C_{3v} symmetry but which was made because no other basis for calculation is presently available. (This point will be further discussed below.) The ΔG° values for the 5-monosubstituted 1,3-dioxanes are those indicated in Table IV and ref 22.

Table IV. Equilibria in 5-Substituted 2-Isopropyl-1,3-dioxanes (Scheme II)

Entry	R	R′	Solvent[b]	*K*	ΔG_{25},° kcal/mol
1	H	CH_3	CCl_4	4.27	−0.86 ± 0.03
			Ether	4.54	−0.90 ± 0.03
			$CHCl_3$	5.27	−0.98 ± 0.02
			DME[c]	4.58	−0.90 ± 0.04
			CH_2Cl_2	5.21	−0.98 ± 0.02
			CH_3CN	4.82	−0.93 ± 0.03
2[a]	CH_2OH	H	Ether	0.954	+0.03 ± 0.04
			$CHCl_3$	1.31	−0.16 ± 0.04
			DME[c]	0.827	+0.11 ± 0.04
			CH_3OH	0.946	+0.03 ± 0.04
			CH_3CN	0.822	+0.12 ± 0.04
3[a]	OH	H	Ether	0.503	+0.41 ± 0.03
			$CHCl_3$	4.63	−0.91 ± 0.03
			DME[c]	0.427	+0.51 ± 0.03
			i-PrOH	0.309	+0.71 ± 0.03
			CH_3CN	1.08	−0.04 ± 0.01

[a] Concentration 0.2 *M* in each solvent studied. [b] For dielectric constants, see footnote *a*, Table III. [c] 1,2-Dimethoxyethane.

Synthesis. All the dioxanes shown in Table III were synthesized from the appropriate diols, $RR'C(CH_2OH)_2$, and isobutyraldehyde (*cf.* Scheme II); cis and trans isomers were separated by preparative gas chromatography except for the 5-methyl-5-nitro compound where the *cis*-nitro compound crystallized from the reaction mixture. The 5-methyl-5-cyclohexyl compounds were obtained both by direct synthesis and by hydrogenation of the 5-methyl-5-phenyl compounds. The diols in which R and R′ were alkyl or aryl groups were products of lithium aluminum hydride reduction of malonates, $RR'C(COOC_2H_5)_2$; diols with R = CH_3 and R′ = CH_2OH or NO_2 were commercially available. Oxidation of *cis*-2-isopropyl-5-methyl-5-hydroxymethyl-1,3-dioxane (**22**) with lead tetraacetate gave the cis aldehyde **29**, Scheme II, A, R = CH_3, R′ = CHO, and further oxidation with silver oxide the cis acid **30**, R = CH_3, R′ = COOH, which was converted to the methyl ester **25** by diazomethane; the *trans*-methyl ester **26** (Scheme II, B, R = CH_3, R′ = COOMe) was obtained from the cis epimer by equilibration. Reduction of the nitro compounds (**19**, **20**) gave the amines (which could not be equilibrated because the basic site in the molecule tied up the catalyst). Methylation of the hydroxymethyl compounds (**21**, **22**) gave the methoxymethyl derivatives **23** and **24**, Scheme II, R = CH_3, R′ = CH_2OMe. The 5-hydroxy-5-methyl compounds **15** and **16**, Scheme II, R = CH_3, R′ = OH, were obtained from the 5-methylene compound by oxymercuration–borohydride reduction[32] and were converted to the methoxy compounds **17** and **18**, Scheme II, R = CH_3, R′ = OMe, by methylation; a more direct route to the methoxy compounds involved oxymercuration–reduction using methanol instead of water as the solvent in the first step. The 2-methylene-1,3-propanediol required in the synthesis of 5-methylene-2-isopropyl-1,3-dioxane was kindly supplied by Professor J. P. Fleury of the University of Mulhouse, France.

Configurational and Conformational Assignments. Since the $-\Delta G^\circ$ value of the isopropyl group is 4.15 kcal/mol,[21] it may be safely assumed that this group remains in the equatorial position and acts as a "holding group," *i.e.*, that all the dioxanes here studied are "anancomeric."[33] Presumably all the molecules are in the chair or somewhat distorted chair forms, since the substituents in position 5 cause no strong compression[20,22] and since the twist–boat form in 1,3-dioxane is of very high energy.[34] Existence in the chair form was confirmed by the normal $(CH_3)_2CHCH(O-)_2$ coupling constant (4.2–5.0 Hz) and the relative constancy of the methyl shift of the isopropyl group (53.5–57 Hz at 60 MHz), these shifts being nearly the same in the two diastereoisomers. (Exceptions occurred in the presence of a strongly anisotropic 5 substituent, such as NO_2, where $\nu_{H\text{-}2}$ was 53.5 Hz for the 5-axial (**19**) and 57 Hz for the 5-equatorial (**20**) nitro compound, and phenyl, where the corresponding shifts between **12** and **13** are 52.5 and 60 Hz.)

Configurational assignments rested, in the first instance, on the chemical shift of the 5-methyl substituent and also, where pertinent, on the other 5 substituent. It is known[35] that an axial 5-methyl is downfield, by 0.5–0.6 ppm, from an equatorial one, the situation being the opposite from that in methylcyclohexanes. As seen in Table V (Experimental Section), clear-cut assignments can always be made on this basis. In critical cases, notably those of the 5-methyl-5-isopropyl, 5-methyl-5-cyclohexyl, and 5-methyl-5-phenyl compounds, the assignment was confirmed by the slight but palpable broadening of the axial methyl signal over the equatorial as a result of long-range *W* coupling.[36] In all cases where the second substituent at C-5 displayed proton signals of its own, the chemical shift of these signals was consistent with the configurational assignment; *i.e.*, when the substituent was assigned the equatorial position (axial methyl), its signals were upfield from those in the stereoisomer in which the substituent was presumed axial (equatorial methyl). An additional empirical configurational criterion rests on the observation that in nearly all cases where one of the 5 substituents was methyl, the *trans*-5-methyl isomer

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(31) The former value is that of the 5-methyl axial (ref 20) and the latter is derived from the ΔG° for 5-*tert*-butyl which is 1.4 kcal/mol (ref 20), considering that equatorial 5-*tert*-butyl has four butane gauche interactions (3.4 kcal/mol) with C-4 and C-6 of the ring and the axial *tert*-butyl has two such interactions plus the methyl-inside interactions.

(32) H. C. Brown and P. Geoghegan, *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

(33) M. Anteunis, "Conformational Analysis," G. Chiurdoglu, Ed., Academic Press, New York, N. Y., 1971, p 32.

(34) K. Pihlaja, *Acta Chem. Scand.*, **22**, 716 (1968); K. Pihlaja and S. Luoma, *ibid.*, **22**, 2401 (1968); K. Pihlaja and J. Jalonen, *Org. Mass. Spectrom.*, **5**, 1363 (1971).

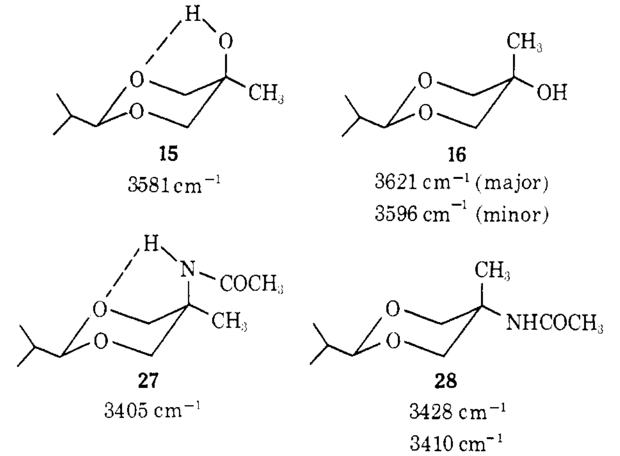
(35) E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 682 (1968); M. C. Knoeber, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Ind., 1967.

(36) *E.g.*, M. Anteunis, W. Vandenbroucke, and N. Schamp, *Bull. Soc. Chim. Belg.*, **76**, 552 (1967). The splitting in **6** could be clearly seen at 100-Hz sweep width, *J* = 0.8 Hz.

showed the H-4's and H-6's as a widely spaced AB pattern whereas the *cis*-5-methyl isomer displayed either a more narrowly spaced AB or a single, degenerate, signal for H-4,6. This is what one expects on the basis of the known[37] effect of axial methyl to shift the originally upfield axial cyclohexyl proton on the vicinal carbon downfield and the downfield equatorial proton upfield. (In contrast, an equatorial methyl group shifts both protons upfield and thus does not change their shift difference greatly.) The only exception to this empirical correlation was found in the 5-hydroxy-5-methyl compounds **15** and **16**.

It was considered desirable to achieve an independent assignment of configuration. This was simple in the 5-hydroxy-5-methyl compounds in which the isomer with axial hydroxyl (Scheme III, **15**) displayed intramolecular hydrogen bonding in the infrared whereas the equatorial one (Scheme III, **16**) did not. The configurations of the 5-methyl-5-methoxymethyl compounds (**17**, **18**) immediately follow by correlation (methylation).

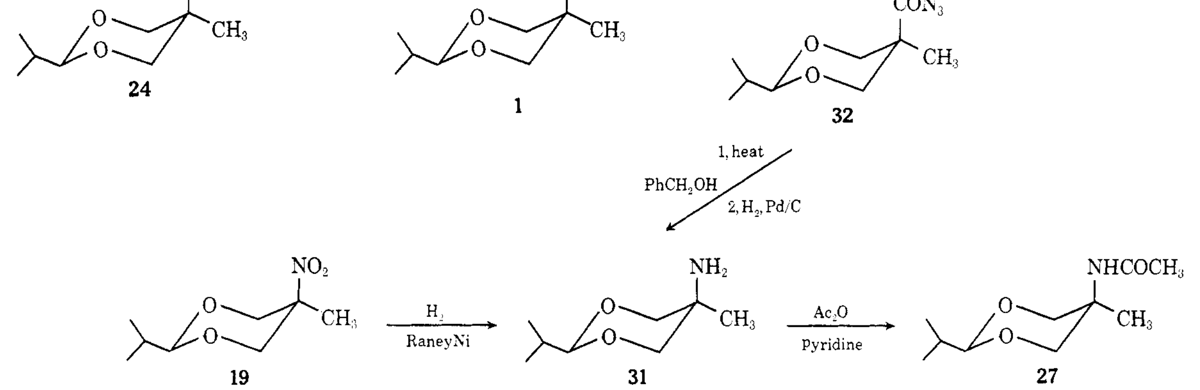
Scheme III



A similar, if somewhat less clear-cut, configurational assignment based on intramolecular hydrogen bonding can be made for the 5-methyl-5-acetamido compounds **27** and **28**, Scheme III. [For comparison, the 2-isopropyl-5-acetamido-1,3-dioxanes of known configuration show ir bands at 3383 (cis, bonded) and 3442 cm^{-1} (trans, nonbonded, shoulder at 3390 cm^{-1}).][38] The 5-methyl-5-acetamido derivative **27** was correlated with the *cis*-5-methyl-5-nitro (**19**), 5-methyl-5-carbomethoxy (**23**) and -carboxy **30**, 5-methyl-5-aldehydo (**29**), 5-methyl-5-hydroxymethyl (**21**),[39] 5-methyl-5-methoxymethyl (**24**), and 5-methyl-5-ethyl (**1**) compounds as shown in Scheme IV. A completely unimpeachable basis for the correlation shown in Scheme IV was subsequently provided through measurement of the dipole moment of nitro compound **19** (4.74 ± 0.05 D) and its stereoisomer **20** (2.13 ± 0.03 D); clearly the isomer with the higher dipole moment must have the axial nitro group.

For reasons to be discussed below, we were particularly concerned with the configurations of the 5-methyl-5-phenyl compounds **11** and **12**. The large anisotropy effect of the phenyl makes assignments based on chemical shifts suspect, especially since the rotational orientation of the phenyl groups was not known at the inception of this study. We therefore reduced a known mixture (31.6:68.4) of the phenyl compounds **11** and **12** to the corresponding cyclohexyl compounds **5** and **6** (31.0:69.0) which were then synthesized independently and equilibrated. Assignment of configuration to **5** and **6** on the basis of spectral criteria and position of equilibrium is unequivocal and that of the phenyl compounds **11** and **12** thus follows.

Scheme IV



Discussion

The equilibration data are summarized in Table III. Also indicated are the calculated $\Delta G°$ values taking

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(37) E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962).

(38) E. L. Eliel and N. Dennis, unpublished observations.

(39) This compound does *not* show intramolecular hydrogen bonding; *cf.* E. L. Eliel and H. D. Banks, *J. Amer. Chem. Soc.*, **94**, 171 (1972).

into account rotameric distribution of the substituent for the methyl–ethyl, methyl–isopropyl, and ethyl–isopropyl compounds (entries 1, 2, 4). For all other substituents the calculated values are simply additive, based on the known[1,20,22,38,39] $\Delta G°$ values for 5-substituted 1,3-dioxanes. (Some newly determined values for 5-methyl-, 5-hydroxy-, and 5-hydroxymethyl-1,3-dioxane are summarized in Table IV.) Since $\Delta G°$ for polar substituents is a function of solvent,[1,22,38] the values for 5,5-geminally substituted 1,3-dioxanes in which one substituent at least is polar (entries 8–13) are also solvent dependent.

For the sake of convenience, the equilibria are usually entered in Table III in such a way that the more stable isomer is on the right in Scheme II. Exceptions are the methyl–ethyl compounds (entry 1) as well as the methyl–hydroxy (entry 8) and methyl–methoxy (entry 9) compounds in certain polar solvents. Inspection of the table shows that in those cases where equatorial methyl is on the left in Scheme II ($R = CH_3$), the experimental $\Delta G°$ is almost invariably more negative than the calculated; *i.e.*, $\Delta\Delta G°$ is negative. On the other hand, when equatorial methyl is on the right in Scheme II ($R' = CH_3$), the $\Delta G°$ value is generally more positive than calculated; *i.e.*, $\Delta\Delta G°$ is positive. Almost invariably, therefore, the isomer with axial methyl is more prevalent (or that with equatorial methyl less prevalent) than is calculated on an additivity basis. *Grosso modo*, then, it appears that the substituent *other* than methyl is less favored in the axial position when there is a geminal methyl group at C-5 than when there is a geminal hydrogen. The reasons for this finding are, however, probably not the same for all the cases studied.

The methyl–ethyl (entry 1) and methyl–isopropyl (entry 2) compounds are exceptions to the rule of stabilization of axial methyl. The value for methyl–isopropyl agrees with the calculated value within limits of experimental error. For methyl–ethyl, contrary to calculation, the axial ethyl predominates; this predominance is outside of the error limit. While it does not agree with the calculation based on first principles (see above), it is in accord with the fact[20] that $-\Delta G°$ for 5-ethyl is smaller (0.67 kcal/mol) than for 5-methyl (0.90 kcal/mol). It would appear that the compression of the methyl group of $CH_3–CH_2$ with the gauche ring atoms of the 4 and 6 positions is larger when the ethyl group is equatorial than when it is axial.

When methyl or ethyl are juxtaposed with the larger alkyl groups or with phenyl (entries 4–7), the smaller methyl (or ethyl) group has a greater preference for the axial position than additivity would predict. We can see two possible reasons for this behavior. (1) The geminal substituent exercises a buttressing effect, preventing the axial substituent from bending outward. This is energetically more serious when the larger substituent is axial. (2) The normally flattened 1,3-dioxane ring[23] becomes more puckered when C-5 is quaternary rather than tertiary, since the ring angle is closed from 111 to 109.5°. This puckering enhances the compression of the axial substituent, and the resultant enhancement of the effective conformational energy of the substituent is more important for the larger group which thus is less likely to be axial. It is not entirely clear whether (1) and (2) are really independent explanations any more than it is clear whether there are independent steric compression and bond hybridization factors causing the C–C–C angle in propane to be larger than tetrahedral.

The greater-than-calculated preference for axial methyl and ethyl when juxtaposed with phenyl was a cause for surprise, since calculations for 1-methyl-1-phenylcyclohexane[40] have recently indicated that it is the phenyl group which should show enhanced preference for the axial position in the presence of geminal methyl; this is in accord with the earlier cited observations[16] for phenyl *vs.* hydroxyl. The reason[40] for the nonadditivity of $\Delta G°$ values is that in phenylcyclohexane the equatorial phenyl is "parallel" (or bisecting), whereas the axial phenyl is "perpendicular" (or flatside-on) in order to avoid severe interactions with the syn-axial hydrogens. Under these circumstances, the major cause for the large $\Delta G°$ value of phenyl is the interaction of the ortho hydrogens of the axial phenyl group with the equatorial hydrogens at C-2 and C-6 of the cyclohexane ring. In a 1-phenyl-1-methylcyclohexane, the conformational energy of the axial phenyl is not affected but that of the equatorial phenyl is much enhanced, since the parallel phenyl has its *o*-hydrogen interfere badly with the *gem*-methyl hydrogens; as a result the phenyl turns into the equatorial perpendicular conformation with its attendant *o*-hydrogen compression and there is then actually some gain in shifting it to the axial perpendicular conformation (since the *gem*-methyl then becomes equatorial). It follows from our experiments that the same argument does not apply in 5-methyl-5-phenyl-1,3-dioxane; and while we cannot, in the absence of calculations, pinpoint the exact cause, it must surely be related to the absence of the compression by syn-axial hydrogens in the oxygen-containing ring.

The equilibrium data in Table III, entries 2, 5, 6, and 7, are in only modestly good numerical agreement with the nmr data in Table II. This may be due to the difference in temperature and solvent, since the presence of the isopropyl holding group at C-2 in our study does not change the geometry.[41] Moreover the signs reported in Table II for the four entries we have checked should be reversed; the nmr study does not lead to a clear choice as to which isomer predominates.[42]

In the case of hydroxyl (Table III, entry 8) the deviation from additivity is strongly solvent dependent, becoming more pronounced in the more polar solvents. Since specific solvation (which does favor equatorial OH) should be less important for the pair of tertiary alcohols than for the pair of secondary alcohols in Table IV, it cannot account for the enhanced preference for equatorial OH in the tertiary series. We prefer to believe that the cause is a less specific local dielectric effect. A high dielectric constant favors the more polar axial isomer (*cf.* Table IV).[1,22] It would appear reasonable that the *effective* dielectric constant of the medium in the vicinity of the functional group is less for a tertiary than for a secondary compound, because of sterically less facile access of solvent molecules to the functional

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(40) N. L. Allinger and M. T. Tribble, *Tetrahedron Lett.*, 3259 (1971).

(41) H. R. Buys and E. L. Eliel, *ibid.*, 2779 (1970).

(42) Our values are, however, in good agreement with those recently reported by A. V. Bogatskii, A. I. Gren, Yu. Yu. Samitov, I. M. Krinitzkaya, L. H. Vostrova, V. I. Somchinskaya, B. P. Mamontov, and T. I. Davidenko, *Khim. Geterotsikl. Soedin*, 7, 582 (1971); $CH_3/(CH_3)_2CH$, -0.36 to -0.38 kcal/mol; CH_3/CH_2OCH_3, 0.85 kcal/mol.

site. As a result, the favoring of the axial polar group by a high dielectric solvent is depressed by the presence of a *gem*-methyl substituent.

A similar effect may be seen in the 5-methoxy compound (entry 9). In this case, strong nonadditivity is noted even in the nonpolar solvent, carbon tetrachloride. However, it must be taken into account that no allowance has been made (unlike in entries 1, 2, and 5) for the unequal rotamer population for axial and equatorial OCH_3. Presumably axial OCH_3 will always exist largely in the "methyl out" conformations, because of very unfavorable steric interactions when the *O*-methyl points into the ring. However, the equatorial methoxyl, which probably prefers the unsymmetrical conformations in the secondary model, becomes nearly equally distributed between three conformations when there is a *gem*-methyl group, with a resulting increase in entropy of mixing. This effect will lead to a favoring of equatorial methoxyl when the geminal substituent is methyl rather than hydrogen, apart from all other considerations. In addition, the already invoked depression of general solvation, which disfavors the axial polar substituent in the tertiary compound, is clearly seen in the polar solvents, *tert*-butyl alcohol and acetonitrile. (Specific hydrogen bonding effects may counteract this factor in solvent methanol.)

For the 5-nitro compound (entry 1) axial nitro is considerably less favored in all solvents than predicted on the basis of the known preference of nitro for the axial position[21] combined with that of methyl for equatorial. We have reason to believe[24,35] that the conformation of the axial nitro group is such that it bisects the ring, *i.e.*, that one of the oxygen atoms of NO_2 points into the ring and the other out of it. It is clear that the outer oxygen in this conformation interferes strongly with a *gem*-methyl group, leading either to a destabilization by a steric compression (which is not present in the equatorial nitro group which presumably is placed "broadside-on" to the ring) or to a forcing into an electronically less favored rotameric arrangement. The large $\Delta\Delta G°$ for 5-nitro in all solvents studied thus far provides support for our hypothesis[24,35] regarding the conformation of axial NO_2.

For hydroxymethyl (entry 11) and methoxymethyl (entry 12) any preference for the equatorial conformation over that calculated is modest and not strongly solvent dependent. What preference exists may readily be accounted for by the already explained rotameric advantage of equatorial over axial CH_2X.

No such advantage exists for the (flat) $COOCH_3$ group, nor do we have any evidence that this group, when axial, has any other than broadside-on conformation. Therefore, the special effects postulated for nitro do not exist and $\Delta G°$ for the 5-methyl-5-carbomethoxy (entry 13) group is very nearly that calculated on the basis of additivity. It might also be noted that solvent effects are not pronounced either in this case or in that of the nitro group (they were less extensively studied with the latter). Perhaps solvation of an sp^2 hybridized substituent is less affected by a *gem*-methyl substituent than that of an sp^3 hybridized one.

In summary, the present rather extensive experimental material seems to confirm what already appeared from more scattered data in the literature (Table I). Conformational energies of geminal substituents are usually not additive, to the point where even the predominant isomer at equilibrium may not be that predicted (*e.g.*, Table III, entries 8 in *i*-PrOH and 9 in ether). Three reasons are suggested for nonadditivity, the first two of which have already previously been stated.[9,43] (1) The rotameric preference of the substituent may be altered by a geminal group and this, in turn, may alter its conformational energy contribution. (2) For nonpolar substituents, change of hybridization or buttressing in the geminally disubstituted species tends to increase the conformational energy of a large substituent more than that of a small one. (3) Change from a secondary to a tertiary center may interfere with local solvation and may thus discriminate against the isomer of higher dipole moment.

Experimental Section

Melting points were determined on a Sargent "Mel-Temp" variable temperature heating block. Nmr spectra were recorded on a Varian A-60A instrument; pertinent data are summarized in Table V and, for the isopropyl and C-2 protons, in the Discussion. Infrared spectra were recorded on a Perkin-Elmer Model 457 grating infrared spectrometer except for the hydrogen bonding studies (Scheme III) for which a Perkin-Elmer Model 521 instrument equipped with 10-cm quartz cells was employed. Preparative gas chromatography was effected with a Nester-Faust Model 850 Prepkromatic automatic preparative gas chromatograph equipped with 3-ft "bi-wall" $^3/_4$-in. annular column for large samples and on a Varian Aerograph Series 1520 instrument using $^3/_8$-in. aluminum columns of 7–20-ft length for samples less than 0.5 ml. The carrier gas was He and the coolant liquid nitrogen. Microanalyses were performed by Midwest Microlab, Inc.

1,3-Diols. Diethyl dialkylmalonates were synthesized by methylation or ethylation of the available monoalkyl malonates using sodium hydride and the appropriate alkyl iodide in DMF–benzene solvent.[44] Properties agreed with those reported in the literature. The methylphenyl and ethylphenyl compounds were obtained from J. T. Baker and Matheson Coleman and Bell, respectively. Reduction to the corresponding diols $RR'C(CH_2OH)_2$ was effected with lithium aluminum hydride exactly as previously described for monoalkyl malonates.[26] Melting points: methylisopropyl, 63–64° (lit.[45] 64–65°); ethylisopropyl, bp 72–73° (0.2 mm) [lit.[46] 72–74° (0.2 mm)]; methyl-*tert*-butyl, 190–194° (reported in lit.[47] without mp); methylphenyl, 77–79° (lit.[48] 80–81°); ethylphenyl, 78–78.5° (lit.[49] 79°). The methylcyclohexyldiol, mp 72.5–73.5° (lit.[50] mp 79–80°) [nmr δ 0.67 (s), *ca.* 3.43 (broad), 3.36 and 3.62 (AB pattern, J = 4.2 Hz), 3.49 ppm (s)] was obtained by catalytic hydrogenation of the methylphenyl compound at 1500 psi and 70° over 5% rhodium on alumina in ethanol containing a few drops of acetic acid. The methylethyl and methylnitro compounds were obtained from Aldrich Chemical Co., 2-Methylene-1,3-propanediol was supplied by Professor Fleury.[51]

1,3-Dioxanes. A solution of 9.1 ml (7.2 g, 0.1 mol) of isobutyraldehyde, 0.1 mol of the appropriate diol, and 0.8 g of *p*-toluenesulfonic acid monohydrate in 50 ml of petroleum ether (bp 30–60°) was boiled under reflux in a 200-ml round-bottom flask equipped with a magnetic stirrer and a reflux condenser with a Dean–Stark trap.

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(43) J. P. Mazaleyrat and Z. Welvart, *Chem. Commun.*, 485 (1969).

(44) E. L. Eliel, P. H. Wilken, and F. T. Fang, *J. Org. Chem.*, **22**, 231 (1957).

(45) H. Yale, E. J. Pribyl, W. Braker, J. Bernstein, and W. A. Lott, *J. Amer. Chem. Soc.*, 72, 3716 (1950).

(46) S. Searles, R. G. Nickerson, and W. K. Witsiepe, *J. Org. Chem.*, **24**, 1839 (1959).

(47) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **83**, 1368 (1961). The infrared spectrum of our sample was identical with one kindly provided by Professor Schleyer.

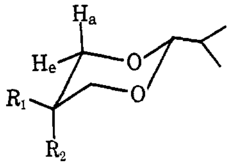
(48) A. L. Mndzhoyan, *et al.*, *Izv. Akad. Nauk Arm. SSR, Ser. Fiz.-Mat. Nauk*, 7, 79 (1954); *Chem. Abstr.*, **49**, 12371*a* (1955).

(49) L. A. Pohoryles, S. Sarel, and R. Ben-Shoshan, *J. Org. Chem.*, **24**, 1878 (1959).

(50) G. Ferrari and C. Casagrande, *Farmaco, Ed. Sci.*, **18**, 780 (1963); *Chem. Abstr.*, **60**, 2811*e* (1964).

(51) F. Weiss, A. Isard, and R. Bensa, *Bull. Soc. Chim. Fr.*, 1355 (1965).

Table V. Chemical Shifts of Geminal Groups and Chemical Shift Difference between Axial and Equatorial C-4(6) Hydrogens (at 60 MHz)[a]



Compd no.	Geminal groups R₁	Geminal groups R₂	Chemical shift, Hz R₁	Chemical shift, Hz R₂	$\Delta\nu_{ae}$, Hz
1	CH_3	CH_2CH_3	36.0^{b}	A 98.0^{b}	25.2^{b}
		A B		B $\sim 53^{b}$	
			18.0	A 102.0^{c}	30.9^{c}
				B 47.0^{c}	
2	CH_2CH_3	CH_3	$54^{b,d}$	67.5^{b}	16.2^{b}
			$40^{c,d}$	68.0^{c}	20.2^{c}
3	CH_3	$CH(CH_3)_2$	29.0	A 144.0	44.4
		A B		B 55.0	
			13.0^{c}	A 151.0^{c}	50.2^{c}
				B 50.0^{c}	
4	$CH(CH_3)_2$	CH_3	~ 48	65.0	20.2
			$\sim 35^{c}$	64.5^{c}	26.8^{c}
5	CH_3	C_6H_{11}	28^{b}	$68–80, 90–125^{b}$	49.7^{b}
6	C_6H_{11}	CH_3	$70–120^{b}$	63.5^{b}	21.1^{b}
7	CH_3	$C(CH_3)_3$	37.0	63.0	55.3
			21.0^{c}	61.0^{c}	60.9^{c}
8	$C(CH_3)_3$	CH_3	53.0	71.0	0
			41.5^{c}	70.5^{c}	0^{c}
9	CH_2CH_3	$CH(CH_3)_2$	$\sim 70^{c,d}$	A $\sim 145^{c}$	36.9^{c}
		A B		B 56.5^{c}	
10	$CH(CH_3)_2$	CH_2CH_3	39.5^{c}	A 107.0^{c}	22.2^{c}
		A B		B 60.0^{c}	
11	CH_3	C_6H_5	61.0	~ 444	12.6
12	C_6H_5	CH_3	434.5	94.0	0
13	CH_2CH_3	C_6H_5	A 88.0	440	45.6
	A B		B 33.0		
14	C_6H_5	CH_2CH_3	435	A 126.0	29.5
		A B		B 40.5	
15	CH_3	OH	58.5		12.7
16	OH	CH_3		83.5	16.4
17	CH_3	OCH_3	55.5	202.0	34.5
18	OCH_3	CH_3	194.5	85.0	22.1
19	CH_3	NO_2	82.0		62.5
20	NO_2	CH_3		110.0	10.6
21	CH_3	CH_2OH	43.5	225.0	30.2
22	CH_2OH	CH_3	219.5	71.0	0
23	CH_3	CH_2OCH_3	42.5	A 209.0	38.5
		A B		B 202.0	
24	CH_2OCH_3	CH_3	A 180.0	71.0	0
			B 195.0		
25	CH_3	CO_2CH_3	56.5	225.5	65.5
26	CO_2CH_3	CH_3	219.5	87.0	0

[a] Solvent $CDCl_3$ unless otherwise indicated. [b] Solvent carbon tetrachloride. [c] Solvent benzene. [d] Overlapping peak.

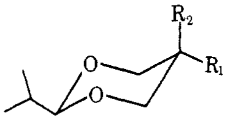
When *ca.* 1.8 ml (0.1 mol) of water had been collected in the trap, the solution was cooled, buffered by addition of 0.7 g of anhydrous sodium acetate, stirred for an additional 20 min, filtered, diluted with 100 ml of ether, and washed with two 50-ml portions of water. The solution was dried over $MgSO_4$, filtered and flash-evaporated and the residue was distilled. Diastereoisomers were separated by preparative gas chromatography, using a He flow of 2 ml/sec (Varian 1520 instrument) unless noted otherwise. Yields and properties of products are listed in Table VI. Compounds **22** and **23** have been previously described.[39]

2-Isopropyl-5-methylene-1,3-dioxane. A mixture of 20 g (0.22 mol) of 2-methylene-1,3-propanediol,[51] 20 ml (15.8 g, 0.22 mol) of isobutyraldehyde, 10 g of anhydrous $CuSO_4$, 100 ml of methylene chloride, and a small amount of *p*-toluenesulfonic acid hydrate was refluxed for 5 hr. The hydrated copper salt was filtered and washed twice with 10-ml portions of methylene chloride. The filtrate was buffered with 1 g of sodium acetate, filtered, and washed twice with 25-ml portions of water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Distillation of the residue gave 25.3 g (80%) of 2-isopropyl-5-methylene-1,3-dioxane: bp 58–60° (9 mm), $n^{25}D$ 1.4409 [lit.[51] bp 80–81° (50 mm), $n^{25}D$ 1.445)]; ir (neat) 6.80, 9.08 μm (strong); nmr ($CDCl_3$) δ 0.92 (d, 6 H), 1.75 (m, 1 H), 4.30 (s, 4 H), 4.32 (d, 1 H), 4.86 (m, 2 H).

2-Isopropyl-5-hydroxy-5-methyl-1,3-dioxanes (15, 16). To a 500-ml flask equipped with a magnetic stirrer containing a solution of 22.8 g (0.07 mol) of mercuric acetate in 70 ml of water and 70 ml of tetrahydrofuran was added, slowly and with cooling in an ice water bath, 9.9 g (0.07 mol) of 5-methylene-2-isopropyl-1,3-dioxane. After an additional 30 min of stirring, 70 ml of 3 *M* aqueous NaOH followed by 70 ml of 0.5 *M* aqueous $NaBH_4$ in 3 *M* NaOH was added. The mercury was allowed to settle and the solution saturated with NaCl. The THF layer was separated, dried over $MgSO_4$, and concentrated. Separation of the isomers was effected on the Nester-Faust instrument, *cf.* Table VI. Configurational assignment rests on the ir spectrum in 0.005–0.0005 *M* CCl_4 solution (Scheme III).

2-Isopropyl-5-methoxy-5-methyl-1,3-dioxanes (17, 18). Method A. In the preceding preparation, the 70 ml of water was replaced by reagent grade methanol. The remainder of the procedure was unchanged. The compounds are listed in Table VI. **Method B.** The appropriate 5-hydroxy compounds **13**, **14** (Table VI) were

Table VI. Properties and Preparative Data of 1,3-Dioxanes



Compd no.	R_1	R_2	Yield, %^{a}	Column^b (temp, °C)	Ret,^{c} min	Prop, %^{d}	Bp, °C^e	$n^{20}D$	Ir bands, cm^{-1}	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	CH_3	CH_2CH_3	57	A (115)	51	60	82–84.5	1.4328	1459, 1388, 1111	69.72	11.70	69.45	11.55
2	CH_2CH_3	CH_3	57	A (115)	63	40	(16 mm)	1.4318	1471, 1398, 1388, 1111	69.72	11.70	69.52	11.45
3	CH_3	$CH(CH_3)_2$	47	B (100)	35	50	91–93	1.4375	1460, 1391, 1110	70.92	11.90	70.75	11.57
4	$CH(CH_3)_2$	CH_3	47	B (100)	52	50	(11 mm)	1.4355	1471, 1395, 1099	70.92	11.90	70.70	11.67
5	CH_3	C_6H_{11}	72	C (185)	10	29	145–150		1121, 1090, 1031	74.29	11.58	74.28	11.66
6	C_6H_{11}	CH_3	70	C (185)	15	71	(13 mm)		1127, 1085, 1029	74.29	11.58	74.02	11.59
7	CH_3	$C(CH_3)_3$	57	A (132)	42	38	106–107	1.4472	1470, 1398, 1095, 1122	71.97	12.07	71.70	11.85
8	$C(CH_3)_3$	CH_3	57	A (132)	64	62	(12 mm)	1.4470	1475, 1398, 1095	71.97	12.07	71.78	11.97
9	C_2H_5	$CH(CH_3)_2$	83	A (137)	60	35	124–127	1.4335	1471, 1117, 1077, 1035	71.97	12.07	71.74	12.02
10	$CH(CH_3)_2$	C_2H_5	83	A (137)	69	65	(23.5 mm)	1.4452	1470, 1458, 1395, 1110, 1035	71.97	12.07	71.77	11.71
11	CH_3	C_6H_5	58	D (175)	67		136–140	1.5055	1149, 1100, 1040	76.32	9.15	76.21	9.52
12	C_6H_5	CH_3	58	D (175)	128		(7 mm)	1.5072	1110, 1073, 1035	76.32	9.15	76.37	9.01
13	C_2H_5	C_6H_5	100	D (163)	135	60	92.5–95	1.4994	1138, 1101, 1025	76.88	9.46	76.60	9.01
14	C_6H_5	C_2H_5	100	D (163)	150	40	(0.17 mm)	1.5055	1115, 1090, 1035	76.88	9.46	77.03	9.38
15	CH_3	OH	69	E^f	28	(86)	nd^g	1.4338	1395, 1124, 1087	59.97	10.07	60.03	10.06
16	HO	CH_3	11	E^f	60	(14)	nd^g	1.4431	1395, 1100	59.97	10.07	59.92	10.30
17	CH_3	OCH_3	61^h	F (150)	62	(88)	nd^g	1.4351	1465, 1395, 1110	62.04	10.41	61.86	10.32
18	OCH_3	CH_3	8^h	F (150)	34	(12)	nd^g	1.4282	1470, 1450, 1392	62.04	10.41	62.05	10.30
19	CH_3	NO_2	82	*i*			Mp 55–55.5^j		1540, 1105				
20	NO_2	CH_3	6	G (120)	10		55–56 (0.15)^j	1.4428 (25)^j	1550, 1460, 1115				
21	CH_3	CH_2OH	60	H (148)	36	90	78–80	1.4527	1469, 1391, 1102, 1040	62.04	10.41	62.19	10.42
22	CH_2OH	CH_3	60	H (148)	56	10	(0.3 mm)	1.4515	1470, 1102, 1050	62.04	10.41	61.90	10.41
23	CH_3	CH_2OCH_3	94	E (139)^k			85.5–87 (12 mm)	1.4321	1471, 1450, 1392, 1106	63.80	10.71	63.68	10.65
24	CH_2OCH_3	CH_3	56	I (123)			87–88 (9 mm)	1.4315	1471, 1450, 1395, 1101	63.80	10.71	63.97	10.62
25	CH_3	CO_2CH_3	87^l	I (143)	48	52^m	nd^g	1.4385	1462, 1390, 1240, 1099	59.39	8.97	59.36	8.93
26	CO_2CH_3	CH_3		I (143)	34	48^m	nd^g	1.4380	1471, 1450, 1260, 1098	59.39	8.97	59.80	9.02

[a] Combined yield of diastereoisomers. [b] A, 20 ft × 3/8 in. 20% TCEP on Chromosorb P (60–80 mesh); B, same as A but 10% TCEP; C, 9-ft Carbowax 20M on Firebrick (80–100 mesh); D, 7 ft × 3/8 in. 20% UCON 50LB 550X on Chromosorb W (60–80 mesh); E, 6 ft × 3/4 in. "bi-wall" 20% FFAP on Chromosorb W (40–60 mesh); F, 12 ft × 3/4 in. 20% Carbowax 20M on Chromosorb W (45–60 mesh); G, 6 ft × 3/4 in. "bi-wall" 10% SE-30 on Chromosorb W (40–60 mesh), He flow 5 ml/sec; H, 3 ft × 3/4 in. "bi-wall" 20% FFAP on Chromosorb W (40–60 mesh), He flow 5 ml/sec; I, 20 ft × 3/8 in. 5% FFAP on Chromosorb W (40–60 mesh). [c] Retention time. [d] Proportion of diastereoisomers, recorded as per cent of cis-trans mixture. [e] Cis-trans mixture. [f] Programmed: 0–20 min, 135°; 20–46 min, 150°; 46–64 min, 175°. [g] Not distilled. [h] Method A. [i] Crystallized. [j] C. Rondestvedt, *J. Org. Chem.*, **26**, 2247 (1961), reports mp 55–55.5° for the cis isomer, bp 107–137° (18 mm), $n^{25}D$ 1.4443–1.4460 for the trans. [k] He flow 200 ml/min. [l] From acid. [m] Sample equilibrated in ether.

methylated with sodium hydride and methyl iodide in dry 1,2-dimethoxyethane.[52] In this way, the *cis*-hydroxy compound yielded the *cis*-methoxy and the *trans*-hydroxy yielded the *trans*-methoxy, each in 92% yield. The corresponding compounds obtained by methds A and B were identical in ir and nmr spectra.

2-Isopropyl-5-methoxymethyl-5-methyl-1,3-dioxanes (23, 24). The 2-isopropyl-5-hydroxymethyl-5-methyl-1,3-dioxanes, **21** and **22**,[39] were methylated with a slight excess of methyl iodide and sodium hydride in 1,2-dimethoxyethane.[52] The products were distilled and further purified by glpc as indicated in Table VI.

***r*-2-Isopropyl-*cis*-5-carbomethoxy-5-methyl-1,3-dioxane (25).** To a solution of 17.2 g (0.1 mol) of *r*-2-isopropyl-*cis*-5-hydroxymethyl-5-methyl-1,3-dioxane (**21**) in 140 ml of anhydrous pyridine and 140 ml of dry benzene was added 44.3 g (0.1 mol) of lead tetraacetate with stirring.[53] After 48 hr of stirring the dark red solution had turned yellow. About three-fourths of the solvent was removed at water aspirator pressure and the remaining solution was filtered and the solid residue washed twice with 100 ml of ether. The combined ether layers were washed three times with 100-ml portions of water, dried over Na_2SO_4, filtered, and concentrated. Distillation of the residue gave *r*-2-isopropyl-*cis*-5-formyl-5-methyl-1,3-dioxane (**29**) as the first fraction [bp 101–116° (9 mm), yield 16.1% g (94%)] followed by unreacted alcohol: bp 120–146° (9 mm); ir (neat) 3.68, 5.82 μm; nmr ($CDCl_3$) δ 0.78 (s, 3 H), 0.90 (d, 6 H), 1.75 (m, 1 H), 3.9 (m, 4 H), 4.25 (d, 1 H), 9.86 (s, 1 H).

To silver oxide, prepared from 7.8 g (0.046 mol) of silver nitrate and 3.7 g (0.092 mol) of sodium hydroxide, each in 16 ml of water,[54] 4 g (0.023 mol) of the above aldehyde **29** was added dropwise with stirring and after a few minutes the black suspension was suction filtered through sintered glass, the residue being washed three times with 50-ml portions of hot water. After a second gravity filtration, the filtrate was clear and, upon acidification with HCl, deposited crystals of the acid **30** which were thoroughly chilled and then collected, yield 2.0 g. An additional 0.5 g was recovered from the mother liquor: total yield 2.5 g (58%); mp 158–160°; ir (CCl_4)

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[52] U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, **44**, 1591 (1966).

[53] *Cf.* R. E. Partch, *Tetrahedron Lett.*, 3071 (1964).

[54] E. Campaigne and W. M. LeSuer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 919.

5.92 μm; nmr ($CDCl_3$) δ 0.92 (d, 6 H), 1.01 (s, 3 H), 1.8 (m, 1 H), 3.95 (m, 4 H), 4.30 (d, 1 H), 10.6 (s, 1 H).

Treatment of the acid **30** with excess diazomethane in ether yielded the ester **25**, further purified on column G (Table VI) at 145°, yield 87%. Properties are listed in Table VI.

To obtain the trans isomer **26**, the cis ester (**25**) was equilibrated as indicated below and the resulting mixture separated gas chromatographically (see Table VI).

r-2-Isopropyl-*cis*-5-amino-5-methyl-1,3-dioxane (31) and Its Acetyl Derivative 27. Method A.[55] The cis acid described above (2.80 g, 14.9 mmol) dissolved in 10 ml of reagent grade acetone was treated with 1.88 g (18.6 mmol) of anhydrous triethylamine in 1 ml of acetone followed, after 30 min of stirring, by 2.22 g (20.5 mmol) of ethyl chloroformate in 1 ml of acetone, which was added dropwise. After another 30 min of stirring at 0°, sodium azide (1.57 g, 24.2 mmol) in 10 ml of water was added and the mixture stirred at room temperature for 1 hr, after which it was diluted with 50 ml of ice water and extracted with two 15-ml portions of ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to yield 2.2 g (70%) of a yellowish oil (assigned structure **30**), the ir spectrum of which showed a strong azide band at 4.70 μm and carbonyl band at 5.87 μm.

The azide **32** was dissolved in 10 ml of toluene and 1.4 g (13.0 mmol) of benzyl alcohol added.[56] After stirring at reflux for 8 hr the solution was cooled and concentrated at reduced pressure and the residue distilled at a bath temperature of 120–130° to give 2.0 g (68%) of the benzylurethane, ir (neat) 2.95, 5.82 μm.

The benzylurethane was dissolved in 20 ml of absolute methanol and hydrogenolyzed in the presence of 5% Pd on charcoal at a pressure of 40 psi of hydrogen for 3 hr. The catalyst was filtered and the filtrate concentrated at reduced pressure to give 0.9 g (83%) of the amine **31**: $n^{17}D$ 1.4454; ir (neat) 3.0 μm; nmr ($CDCl_3$) δ 0.88 (s, 3 H), 0.95 (d, 6 H, $J = 6.5$ Hz), 1.8 (m, 1 H), 2.05 (s, 2 H), 3.58 (m, 4 H), 4.18 (d, 1 H, $J = 4.5$ Hz).

Method B. A solution of 9.5 g of *r*-2-isopropyl-*cis*-5-nitro-5-methyl-1,3-dioxane (**19**) in 150 ml of absolute ethanol was shaken with a small amount of Raney nickel and filtered. The filtrate was reduced with hydrogen at 100 atm in the presence of 2 g of Raney Ni for 4 hr. The catalyst was filtered and the solvent removed at reduced pressure, yield of amine **31** 7.0 g (87%). The material was identical in spectral characteristics with that obtained by method A.

Acetyl Derivative. To a solution of 2.4 g (15.1 mmol) of the above amine in 15 ml of anhydrous pyridine was added 2.0 g (20.0 mmol) of acetic anhydride and the solution was refluxed for 12 hr. It was then cooled, washed three times with 10-ml portions of water, and dried over anhydrous $MgSO_4$. Filtration and concentration, followed by recrystallization from petroleum ether (bp 60–90°), yielded 2.0 g (66%) of needle-like crystals which, after sublimation, melted at 101–102°: ir (CCl_4) 2.92, 3.05, 6.05 μm; nmr ($CDCl_3$) δ 0.93 (d, 6 H), 1.24 (s, 3 H), 1.8 (m, 1 H), 1.98 (s, 3 H), 3.85 (m, 4H), 5.9 (s, 1 H).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52. Found: C, 59.62; H, 9.15.

r-2-Isopropyl-*trans*-5-acetamido-5-methyl-1,3-dioxane (28) was prepared from the *trans*-nitro compound **20** in the same way as its cis isomer described above. The amine was obtained in 80% yield: ir (neat) 3.0 μm; nmr ($CDCl_3$) δ 0.96 (d, 6 H, $J = 6.5$ Hz), 1.30 (s, 2 H), 1.37 (s, 3 H), 1.8 (m, 1 H), 3.5 (m, 4 H, $J_{gem} = 10.0$ Hz), 4.15 (d, 1 H, $J = 4.0$ Hz). Acetylation as described above yielded the amide **28** in 80% yield: mp 92–94°; ir (CCl_4) 3.05, 6.06 mμ; nmr ($CDCl_3$) δ 1.05 (d, 6 H, $J = 6.5$ Hz), 1.65 (s, 3 H), 1.8 (m, 1 H), 2.04 (s, 3 H), 4.06 (s, 4 H), 4.36 (d, 1 H, $J = 4.5$ Hz).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52. Found: C, 59.78; H, 9.60.

r-2-Isopropyl-*cis*-5-ethyl-5-methyl-1,3-dioxane (1) from the Aldehyde 29. To a 100-ml three-necked flask equipped with a reflux condenser, mechanical stirrer, addition funnel, and gas inlet tube was added 4.25 ml (0.011 mol) of a 2.37 *M* solution of *n*-butyllithium in hexane while a gentle flow of dry nitrogen was maintained in the flask. Anhydrous ether (50 ml) was added with stirring, followed by 3.57 g (0.01 mol) of triphenylmethylphosphonium bromide[57] over a 5-min period. Stirring was continued for 4 hr. The aldehyde **29** (1.9 g, 0.11 mol) was then added dropwise, resulting in decolorization of the solution and formation of a white precipitate. The mixture was boiled overnight, cooled, and filtered, the residue being washed with 10 ml of ether. The filtrate was extracted with 5 ml of water, dried over $MgSO_4$, filtered, concentrated in a stream of nitrogen, and distilled, bp 94–96° (40 mm) [lit.[58] 75–78° (12 mm)]. Further purification was effected over a 10 ft × 0.25 in. 20% FFAP on Chromosorb W (40–60 mesh) column at 80° to give *ca.* 0.9 g (60%) of *r*-2-isopropyl-*cis*-5-vinyl-5-methyl-1,3-dioxane: ir (neat) 3.26, 6.12, 9.05, 10.0 μm; nmr δ 0.76 (s, 3 H), 0.92 (d, 6 H, $J = 6.5$ Hz), 1.80 (m, 1 H), 3.63 (m, 4 H, $J_{gem} = 10.5$ Hz), 4.18 (d, 1 H, $J = 4.5$ Hz), 5.10 (double doublet, 1 H, $J_{cis} = 10.5$, $J_{gem} = -2.0$ Hz), 5.15 (double doublet, 1 H, $J_{trans} = 18$, $J_{gem} = -2.0$ Hz), 6.25 (double doublet, 1 H, $J_{trans} = 18$, $J_{cis} = 10.5$ Hz).

Hydrogenation of the vinyl compound (0.9 g in 10 ml of absolute ethanol) over 5% Pd at 30 psi for 2 hr gave the ethyl compound, identical in nmr spectrum with a sample of **1** obtained by glpc of the isomeric dioxane mixture obtained from the diol as listed in Table VI.

An alternative synthesis of the 5-cyclohexyl-5-methyl-2-isopropyl-1,3-dioxanes **5** and **6** involved hydrogenation of the mixture of the corresponding phenyl compounds **11** and **12** over 5% rhodium on alumina in ethanol at 2000 psi and 70°.

Equilibration was carried out in the solvents listed in Table IV using 0.05–1.1 g of compound in 0.5–1.0 ml of solvent. For alkyl- and aryl-substituted dioxanes, 1 drop of boron trifluoride etherate was used as catalyst. For all other compounds, Amberlyst-15 (Rohm and Haas, beaded polystyrenesulfonic acid) was employed. Anhydrous potassium carbonate was used for quenching and the quenched solutions were analyzed directly by gas chromatography. The results are shown in Table VII.[59] Response ratios were determined at the same time and under the same conditions as the analyses. All equilibria were approached from both sides, that for the 5-hydroxy and 5-methyl-5-hydroxy (**15**, **16**) compounds also from the dioxolane side. Each sample was analyzed three to ten times using an F & M Model 810-19 or 810-29 dual thermal conductivity analytical research chromatograph equipped with a Honeywell Brown Elektronik Model 15 1.0-mV recorder and Disc Instrument Co. integrator. Some integrations were checked by measurement with a Keuffel and Esser Co. compensating polar planimeter, Model 4242. Detector temperature was 230 (Model 810-29) or 295° (810-19). The injector block was maintained at 220°. Stainless steel columns (1/8 in. i.d.) were used for analytical work. The errors given in Tables IV and VII[59] are standard deviations.

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(55) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

(56) *Cf.* M. Bergmann and L. Zervas, *J. Biol. Chem.*, **113**, 341 (1936).

(57) G. Wittig and U. Schöllkopf, *Org. Syn.*, **40**, 66 (1960).

(58) C. Rondestvedt, *J. Org. Chem.*, **26**, 2247 (1961).

(59) Table VII will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JACS-72-8072. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.