Configurations and Conformations of Epimeric 2,5-Dimethyl-5,6-dihydro-α-pyrans

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The high-resolution nmr spectra of epimeric esters of 2,5-dimethyl-5,6-dihydro-α-pyrans were studied. Configurational and conformational assignments were made using spin–spin decoupling, variable temperature, and shift reagent techniques. In the latter case, an appreciable changing of coupling constants was observed. The 5,6-dihydro-α-pyrans seem to exist in half-chair-like conformations exclusively (at room temperature). The conformational analyses of methylodihydropyrans show that they are more similar to cyclohexene than to alkoxycyclohexenes (or unsaturated sugars). A new J_0 for the Karplus equation was calculated and applied.

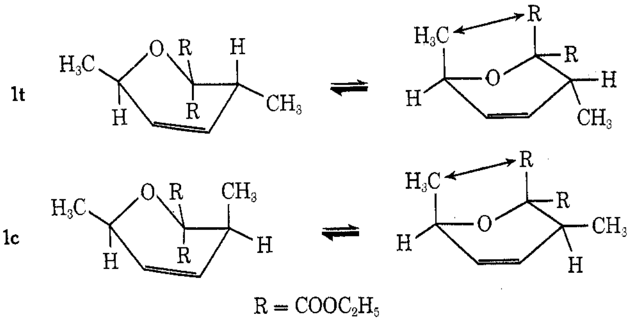
The present paper contains an analysis, by various nmr techniques, of the configurations and conformations of methylodihydropyrans, of which there have been relatively few conformational studies.[1–4]

The epimers diethyl 2β,5α-dimethyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**1t**) and diethyl 2β,5β-dimethyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**1c**), as well as the model compound diethyl 2β-methyl-5,6-dihydro-α-pyrano-6,6-dicarboxylate (**2**), were synthesized by the Diels–Alder reaction. The first two compounds were prepared by treating diethyl mesoxalate with *trans,cis*-2,4-hexadiene and *trans,trans*-2,4-hexadiene, respectively; the model compound was obtained by treating diethyl mesoxalate with *trans*-piperylene.[5–7]

The stereochemistries of the products obtained respect the Alder rules.

The conformations of the compounds **1t** and **1c** represent an equilibrium system (Scheme I).

SCHEME I



The equilibrium of the compound **1t** (two methyls trans) is pushed strongly to the left, the right-hand conformation being destabilized by both the 1,3-diaxial interaction and the axial positions of both methyl groups. For the compound **1c** (two methyls cis), conformational analysis shows a strong 1,3-diaxial interaction in the right-hand form which thus pushes the equilibrium to the left.

First of all, low-resolution nmr spectroscopy together with spin–spin decoupling permitted the identification of all proton signals.[8,9]

Since the 2-H of both the compounds **1t** and **1c** is partially masked by the carboxylate methylene quadruplets, our study was based on the 5-H, the observation of which is easier. For the compound **2**, the 2-H was used as a reference in view of the presence of two protons at the C-5 position.

The low-temperature nmr analysis of the compound **2** showed no coalescence in the 25 to −180° temperature range, indicating conformational homogeneity.

A coupling constant $J_{2,3} = 2.2$ Hz was observed for the compound. On the other hand, using the Karplus equation and angles obtained from Dreiding models, this $J_{2,3}$ was calculated to be only 1.90 Hz.[11] It is this discrepancy which prompted us to introduce a modified J_0 for the Karplus equation;[9–13] a value of $J_0 = 10.6$ Hz was found to correlate the calculated angles and observed coupling constants, and was used in further calculations. This modified Karplus parameter is about the same as that of other authors for a similar system.[2]

The analysis of the low-temperature spectra of **1t** and **1c** (Table I) also showed the absence of coalescence in the temperature range mentioned above. Furthermore, the modified $J_0 = 10.6$ Hz was applied as it afforded better justification of the coupling constants found.

The dihedral angles between the protons 4-H, 5-H and 2-H, 3-H measured for the chair conformations presented were found to be about 80° for the 5-H_{ax}, C-5, C-4, 4-H (or 2-H_{ax}, C-2, C-3, 3-H) system and about 40° for the 5-H_{eq}, C-5, C-4, 4-H (or 2-H_{eq}, C-2, C-3, 3-H) system.[9,14] These values were calculated for a simple system substituted by an alkoxy group, whereas our system is one substituted by two alkyl groups. For the boat conformations, the corresponding angles are 110 and 18°, respectively.[9] The values found, using $J_0 = 10.6$ Hz, after the examination of the various coupling constants (see Table II, Scheme II) confirm a more folded conformation, with angle values closer to those of cyclohexene calculated by Garbisch[8,15] and Corey,[16] being about 60 and 45°, respectively, than to those of the mentioned 2-alkoxy carbohydrates.[1] Using the modified Karplus equation[9,10,17] and the measured values of the dihedral angles between 4-H

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(1) R. J. Ferrier and G. H. Sankey, *J. Chem. Soc.*, 2339, 2345 (1966).

(2) O. Achmatowicz, J. Jurczak, A. Konowal, and A. Zamojski, *Org. Magn. Resonance*, **2**, 55 (1970).

(3) R. J. Ferrier and N. Parsad, *J. Chem. Soc.*, 581 (1969), 1417 (1967).

(4) R. J. Ferrier, G. H. Sankey, and W. G. Overend, *ibid.*, 2830 (1965).

(5) O. Achmatowicz and A. Zamojski, *Rocz. Chem.*, **35**, 1251 (1961).

(6) K. Jankowski, J. Couturier, and R. Tower, *Can. J. Chem.*, **50**, 1539 (1972).

(7) J. Couturier, These CH 4000, Université de Moncton, 1969.

(8) E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **86**, 5561 (1964).

(9) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, New York, N. Y., 1969, pp 280–310.

(10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(11) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *Chem. Ind. (London)*, 213 (1962); *J. Chem. Soc.*, 3699 (1969).

(12) R. J. Abraham, H. Gottschalck, H. Paulsen, and W. A. Thomas, *J. Chem. Soc.*, 6268 (1965); M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

(13) R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 335 (1965).

(14) L. D. Hall, *J. Org. Chem.*, **29**, 297 (1964).

(15) E. D. Garbisch, Jr., *ibid.*, **27**, 4243, 4249 (1962).

(16) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955).

(17) G. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963).

TABLE I

PROTON CHEMICAL SHIFTS OF **1t** AND **1c**, WITH (δ_{SR}) AND WITHOUT (δ_0) SHIFT REAGENTS[a] ($CDCl_3$)

	1c				1t			
		δ_{SR} After addition of E-FOD[a]				δ_{SR} After addition of E-FOD[a]		
	δ_0	0.5 mol	1 mol	$\Delta\delta_{SR}$[b]	δ_0	0.5 mol	1 mol	$\Delta\delta_{SR}$[b]
H-2	4.37	5.22	6.14	1.77	4.25	4.95	6.05	1.80
H-3	5.51	5.82	6.28	0.77	5.50	5.74	6.20	0.70
H-4	5.84	6.20	6.62	0.78	5.86	6.10	6.52	0.66
H-5	3.04	3.80	4.62	1.58	3.03	3.62	4.60	1.57
H_3C-2	1.39	1.80	2.38	0.99	1.33	1.66	2.32	0.99
H_3C-5	1.02	1.42	1.90	0.88	0.99	1.38	1.82	0.83
H_3C–**H_2**C ax	1.27				1.17			
		1.36	1.54	0.27		1.52	1.48	0.30
eq	1.28				1.19			
H_3C-H_2C ax	4.26	4.52			4.24	4.40		
			4.78	0.51			4.70	0.45
eq	4.28	4.55			4.26	4.44		

[a] E-FOD = Eu(fod)$_3$-d_{27}. [b] Molar $\Delta\delta_{SR} = \delta_{SR} - \delta_0$.

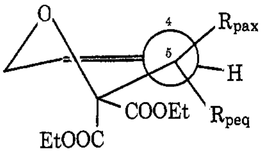
TABLE II

COUPLING CONSTANTS OF PROTONS OF **1c** AND **1t** (CPS)

J	1t	1c
3,4	10.15	10.35
2,5	2.45	2.0
4,5	2.70	5.25
2,3	2.20	1.40
2,4	−1.55	−1.80
3,5	−1.67	−0.74
2,CH_3-2	7.10	7.07
5,CH_3-5	7.25	6.85
CH_2,CH_3	7.15	7.02
After the Addition of 1 mol of E-FOD		
4,5	3.0 (0.3)[a]	5.85 (0.6)[a]
2,3	2.5 (0.3)[a]	1.8 (0.4)[a]

[a] Differences between $J_{2,3}$ and $J_{2,3}$ in the presence of the shift reagent.

SCHEME II



	1t	1c
R_{pax}	H	CH_3
R_{peq}	CH_3	H

and 5-H, we were able to calculate the coupling constants, which had, however, an orientational value only.

The comparison of the relative values of observed coupling constants, *i.e.*, compound **1c**, with the calculated values further establishes the existence of the product in the conformation where the 5-CH_3 is in an axial position (calcd 5.30 Hz, obsd 5.25 Hz). This places, respecting the Alder rule, the 2-CH_3 in an equatorial position.

It is not possible to apply experimental equations derived for coupling constants in a cyclohexene system in view of the fact that the presence of the oxygen atom in the cycle changes considerably and, unpredictably,[2,8,15] the coupling constant values (especially $J_{2,3}$). Nevertheless, the C-4, C-5 part of the molecule is similar to cyclohexene and therefore the application of the above-mentioned equations gives but little deviation.[1,8] Our study of the conformations of **1t** and **1c** is primarily based on $J_{4,5}$ rather than other coupling constants.

Some of the coupling constants (allylic, homoallylic) were obtained by the use of high-resolution nmr spectrometry. First of all, the homoallylic $J_{2,5}$ for the compound **1t** (2.45 Hz) was found to be larger than that for the **1c** compound (2.00 Hz). As it is, a coupling constant between two pseudoaxial protons 2-H, 5-H is predicted to be greater than the coupling between a combination of pseudoaxial and pseudoequatorial protons, this latter being larger than that between two pseudoequatorial protons.[18] For the compound **1c**, the homoallylic coupling constant calculated was $J_{2,5}$ = 2.0 Hz.[12]

The allylic coupling constant on the oxygen side of the molecule is of little significance. Using Corey's values,[16] we were able to calculate the angles on the C-4, C-5 face of the molecule.

The allylic coupling, which is equally angularly dependent, calculated by Abraham's equation is in good agreement with the obtained data.[12,13]

At the outset of this analysis, we now have a more complete picture of the molecules **1t** and **1c** by evaluating the angles indicated in Tables III and IV, and by Scheme II.

TABLE III

DIHEDRAL ANGLES CALCULATED FROM *J*[a]

			After addition of 1 mol of E-FOD	Δ∢
H-2,C-2,C-3,H-3	1c	64°40′	61°40′	3°
	1t	63°	61°	2°
H-4,C-4,C-5,H-5	1c	39°30′	35°30′	4°
	1t	50°20′	53°30′	1°50′

[a] Karplus equation using J_0 = 9.3.

TABLE IV

DIHEDRAL ANGLES CALCULATED FROM *J*[a]

			After addition of 1 mol of E-FOD	Δ∢
H-2,C-2,C-3,H-3	1c	66°20′	64°	2°20′
	1t	61°10′	59°10′	2°
H-4,C-4,C-5,H-5	1c	43°30′	40°20′	3°10′
	1t	57°50′	56°10′	1°40′

[a] Karplus equation using modified J_0 = 10.6 (from product **2**).

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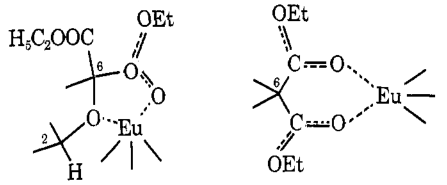
[18] D. W. Cameron, D. G. I. Kingston, N. Sheppard, and L. Todd, *J. Chem. Soc.*, 98 (1964).

The molecules show a great resemblance to Corey's propositions for cyclohexenes,[16,17] in opposition to Reeves's proposition—therefore half-chair-like conformations for a like system.[19]

The application of shift reagents such as E-DPM, P-DPM, E-FOD, and P-FOD enabled us to better identify certain protons and coupling constants, *i.e.*, 2-H (Table I). E-FOD, or Eu(fod)$_3$-d_{27} was preferred by us for use with ester-type compounds.[20] Praseodymium derivatives, in shifting signals to already occupied regions, are clearly less useful.

The addition of E-FOD (in chloroform) displaces differently relative shifts in epimers, especially for the protons 3-H and 4-H. For example, in the compound **1t**, the 3-H signal is the most displaced, whereas, in the compound **1c**, it is the 4-H signal which is the most displaced. The addition of the complexing agent displaces appreciably in decreasing order the 2-H, 5-H, and 2-CH$_3$ signals. The simplification of two ester ethyl signals (axial and equatorial) after the addition of an equimolar quantity of shift reagent was also noticed. This may indicate the formation of a complex involving both carboethoxy groups or, more probably, one of the two carboethoxy groups and the oxygen atom of the cycle. According to Buckingham and Sargeson,[21] the oxygen of the cycle must participate in the formation of such a complex [five-membered cycle, large $\Delta\delta_{SR}$(2-H)] which undoubtedly causes a greater rigidity in the molecule (Scheme III).

SCHEME III



Therefore, we are proposing the introduction of a quantity referred to earlier in Table I, that is, the molar shift reagent chemical shift, $\Delta\delta_{SR}$(molar). This would be a unit chemical shift/mole shift reagent, and could be determined for different classes of compounds such as ethers, amines, pyrans, and pyridines. This value would permit the determination of the exact influence of the soluble mole:mole complex on the conformation of a molecule in a given solvent.

Another interesting observation was that of the changing of coupling constants under the influence of shift reagent. Indeed, E-FOD in chloroformic solution changes the value of certain coupling constants, *i.e.*, by 0.6 Hz for $J_{2,3}$ of the compound **1c** and by 0.3 Hz for the same coupling in the compound **1t** (Table II). This indicates a changing of conformation in the neighborhood of the oxygen atom in the molecule. These changes, corresponding to dihedral angle variation with the overall effect of flattening the molecule, are shown in Tables III and IV. We have used both the normal Karplus J_0 (Table III) and the modified Karplus J_0 (Table IV).

The changes in coupling constants mentioned above illustrate that many conformational conclusions drawn with the help of shift reagent application must be verified, and that the technique itself must be applied with greater caution and in limited cases. In fact, it must be realized that it is the complex's coupling constants that are being measured, and not those of the original compound. Nevertheless, the application of shift reagents can become a useful method in the study of conformers or epimers.

A correct interpretation of data is difficult if the products are left in an even lightly acidic solution. The epimerization of the C-2 is observed even in chloroformic solution.

Experimental Section

The nmr spectra, in CCl$_4$, CS$_2$, or CDCl$_3$, were registered on Varian A-60, T-60, HA-100, and HR-220 MHz, as well as Bruker XL-60 and XL-90 spectrometers. Spin–spin decouplings were carried out on HA-100 and HR-220 MHz instruments; variable-temperature measurements were obtained on a Bruker XL-60 spectrometer. The shift reagent Eu(fod)$_3$-d_{27} was purchased from Merck Sharp and Dohme, Canada Ltd., and was added gradually up to equimolar quantities, in CDCl$_3$.

The compounds **1c**, bp 82° (0.17 mm), 47% yield, **1t**, bp 84° (0.12 mm), 34% yield, and **2**, bp 79° (0.1 mm), 45% yield, were prepared by ourselves[5,7] in bomb tubes, at 120–140° for 24 hr. These were purified by vpc preparative and their purity was verified on a Varian MAT-Gnom 411 VPC-MS system.[6]

Registry No.—*cis*-**1**, 36736-30-8; *trans*-**1**, 36736-31-9; **2**, 36749-08-3.

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[19] R. E. Reeves, *Advan. Carbohyd. Chem.*, **6**, 107 (1951); see also C. J. Bushweller and J. W. O'Neil, *Tetrahedron Lett.*, 4713 (1963).

[20] R. E. Rondeau and R. E. Sivers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

[21] D. A. Buckingham and A. M. Sargeson, *Top. Stereochem.*, **6**, 219 (1971).