

NMR-EXPERIMENTS ON ACETALS—PART 31 PMR-FEATURES AND CONFORMATIONS OF THE ISOMERIC 2,6-DIME-4-*t*.BU-1,3-DIOXANES

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Abstract—It is found from NMR data, that of the four possible isomeric 2,6-diMe-4-*t* Bu-1,3-dioxanes, only the 2,6-diaxial isomer (4) occurs in C₁ and C₂ twist-boat forms. A small amount of flexible forms may also be present in isomer (3), *r*-2-,*trans*-6-diMe,*trans*-4-*t*,Bu-1,3-dioxane. In extension of earlier findings,³ the *exo* coupling between the ring-proton and the C-2 substituent in dioxanes, is larger when this substituent has pronounced axial character.

IN ORDER to extend our knowledge about the NMR behaviour of 1,3-dioxanes¹⁻³ and especially those possessing potential flexible forms, we wished to amplify the data with a study of 2,6-diMe-4-*t*.Bu-1,3-dioxane, for which four isomers are possible, some being strained. The structures are depicted in Chart I, (1) to (4), in the order of expected decreasing stability. It was hoped to obtain a mixture of all of them by the acetalization of *threo*- and *erythro*-2,2-diMe-3,5-hexanediol with EtOH, under kinetically controlled conditions, thus preventing true thermodynamic equilibration of the epimerizable C-2 centre. Unexpectedly however under these conditions we could isolate, as well as the two other isomers, the least stable one 4, but not the more stable isomer 3, although it is the counterpart of 4 and must result from the *threo*-diol isomer. Even with capillary GC the isomer 3 (authentic sample prepared from a Grignard reaction) could not be detected, the amount being probably less than 0.1%. (Relative amounts of isomers obtained from a mixture of *threo*- and *erythro*-diol: $\approx 65\%$ (1), $\approx 20\%$ (2), $\approx 15\%$ (4)). Also the acetalization of 2,2-diMe-4,6-heptanediol was followed by GC, and although the *erythro*-diol reacts faster than the *threo*-derivative, *r*-2-,*trans*-6-dimethyl,*cis*-4-neopentyl-1,3-dioxane was never detected.⁴

We prepared the missing isomer (3) by a stereospecific Grignard reaction⁵ on the corresponding 2-methoxy derivative (5).

DISCUSSION OF THE NMR SPECTRA

The spectra were analyzed graphically, following the subspectral procedure⁶ for the ABXY spin systems (H-4, H-6, H-5, H-5'). The NMR data are gathered in Table 1.

For the isomers 1 and 2, classical *J*-values are obtained as for other *cis*- and *trans*-4,6-dialkyl-1,3-dioxanes, which occur in a chair form.¹⁻³ The spectrum for isomer 2 can be found under Fig 1. Some peculiarities are noteworthy. Firstly, as noticed earlier⁷ an *exo*-coupling constant involving axial CH₃ groups next to oxygen (Me-6 in (2)) is larger than for equatorial groups (Me-6 in (1)). Secondly a *syn*-axial

TABLE I. NMR SPECTRAL DATA FOR THE FOUR ISOMERS OF 2,6-diMe-4-t, Bu-1,3-DIOXANE (STRUCTURES (1), (2), (3) AND (4) ACCORDING TO CHART 1), OBTAINED IN 5% CCl₄ (VARIAN HA-100, TMS INT.). SHIFTS ν ARE IN δ FROM TMS. COUPLING VALUES IN HZ.

G.C. fraction	Structure	$\nu(\text{H-2})$	$\nu(\text{H-6})$	$\nu(\text{H-4})$	$\nu(\text{H-5a})$	$\nu(\text{H-5e})$	$\Delta(5a \rightarrow 5e)$	$\nu(\text{Me-2})$	$\nu(\text{Me-6})$	$\nu(t, \text{Bu})$
1	1	4.56 (ax)	3.56 (ax)	3.08 _s (ax)	1.17	1.33	0.158	1.23 (eq)	1.16 (eq)	0.86
3	2	4.88 (ax)	4.20 (eq)	3.31 (ax)	1.82 ₄	1.14 ₅	-0.68	1.16 (eq)	1.29 (ax)	0.88
4	3	5.20 (eq)	3.93 (ax)	3.43 _s (ax)	1.28	1.37	0.09 ₁	1.32 (ax)	1.16 (eq)	0.86
2	4 ^a	4.99 ^a	3.82 ^a	3.45 (ax ^a)	1.80 ₆ ^a	1.35 ^a	-0.40 ₂	1.16 (ax ^a)	1.17 (ax ^a)	0.86
		$^2J(\text{H-5})^b$	$^3J(\text{Me-2, H-2})$	$^3J(\text{Me-6, H-6})$	$^3J(\text{4a, 5e})$	$^3J(\text{4a, 5a})$	$^3J(\text{4e, 5e})$	$^3J(\text{4e, 5a})$	$^3J(\text{6a, 5a})$	$^3J(\text{6a, 5e})$
1	1	12.8	5.0 ₄ ^c	6.2 ₄ ^c	2.3	11.5 ₄	—	—	11.5 ₄	2.3
2	2	12.8	5.0 ₇	6.4 ₁						
3	3	13.7	5.1 ₇	7.0 ₆ ^d	3.0 ₈	11.5 ₆	1.5 ₆	6.0 ₆	11.8	2.5 ₇
4 ^a	4 ^a	13.3	5.7 ₅ ^d	6.1 ₂ ^d	5.6 ₈	10.2 ₆	—	—	11.5 ₆	3.0 ₈
			5.6 ₈	6.0 ₈						
			5.2 ₇	6.3 ₄					6.4 ₂	7.4 ₆

^a Essential twist form 4A see text and figure 2

^b Mean value from eq. and ax. part.

^c From 60 MHz spectrum

^d Exo coupling with axial Me-group.

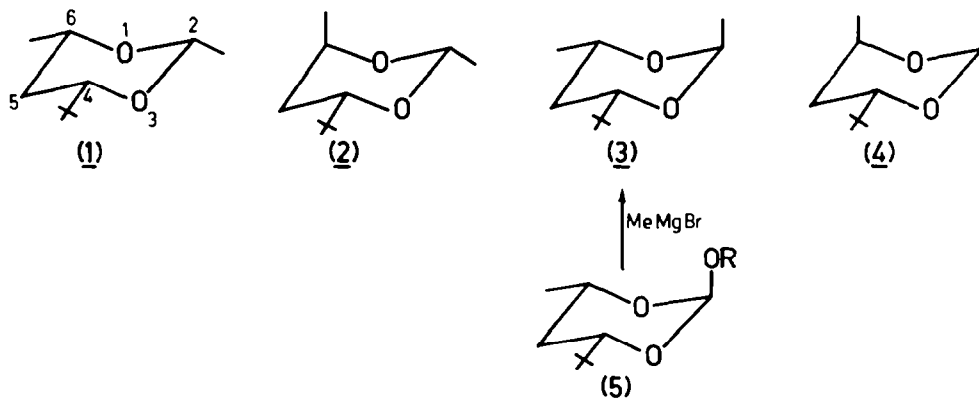


CHART I

substituent causes a deshielding, a fact allowing easy configurational assignment. This is verified when comparing $\nu(\text{H-2})$ and $\nu(\text{H-4})$ in **3** with the corresponding values found in **1**.

In 1,3-dioxane itself¹ and in many derivatives the axial H-5 atom is found at lower field than the equatorial counterpart. This is also true in *trans*-4,6-disubstituted-1,3-dioxanes. In this case the shift difference $\delta(5a \rightarrow 5e)$ may be quite large, often leading to high first order character of the spin systems. In *cis*-4,6-disubstituted-1,3-dioxanes however, the H-5a and H-5e atoms are very tightly coupled and generally H-5e is now found at lower field. This behaviour is also reflected in the second-order character of the X and Y parts (H-4 and H-6) (see Fig 2, inset; compare CH-t Bu X-part obtained at 100 MHz with the same obtained at 60 MHz).

r-2,-*trans*-6-DiMe,*trans*-4-t.Bu-1,3-dioxane (**3**)

The fact that the GC fraction 4 epimerizes into **1** (GC fraction 1), shows immediately the structural relationship between these two isomers. The coupling constants extracted from the analysis of the H-5 pattern (Fig 2 and Table 1) agree well with those of a chair form, although the sum of the vicinal coupling constants ($\Sigma^3J = 14.7_7$ cps (14.6₄ cps from H-5 pattern and 14.9 cps from the outer lines of the Y-part) is 1 cps larger than for the all-*cis* derivative (**1**) ($\Sigma^3J = 13.6_7$ cps (13.8₄ cps from H-5 pattern and 13.5 cps from outer lines of the Y-part). This might indicate the presence of a minor amount of twist-boat conformations,* or alternatively a change in ring shape. The *exo*-coupling $^3J(\text{Me-2}, \text{H-2}) = 5.7$ cps corresponds with pronounced chair character with an axial Me-2 group. The value observed shows that the criterium⁷ $^3J^{\text{exo}}(\text{Ra}, \text{He}) > ^3J^{\text{exo}}(\text{Re}, \text{Ha})$ holds also for substituents at C-2 in 1,3-dioxanes, which allows a choice in the assignment between diastereoisomers. This trend however, vanishes with the loss of axial resp. equatorial character of the substituent, which happens when the molecule escapes into flexible forms. Therefore the present value, being larger by about 0.5–0.6 cps than for typical Me-2e groups, illustrates the essential axial character for Me-2 in a chair form of isomer **3**. The difference in *exo*-coupling

* For a discussion of a genuine twist-boat form with the implications on Σ^3J , see under isomer **4**.

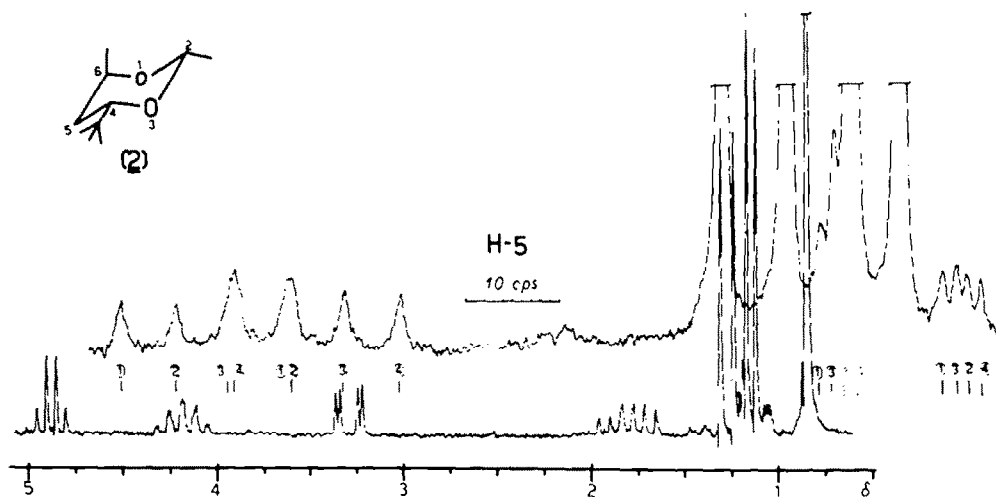


FIG 1. NMR Spectrum (VARIAN HA-100; 10% in CCl_4 , TMS int.) of *r*-2,-*trans*-6-diMe-*cis*-4-*t* Bu-1,3-dioxane (2). Inset: detailed pattern for H-5-atoms (250 sw.w.). The four subspectral ab-systems are indicated.

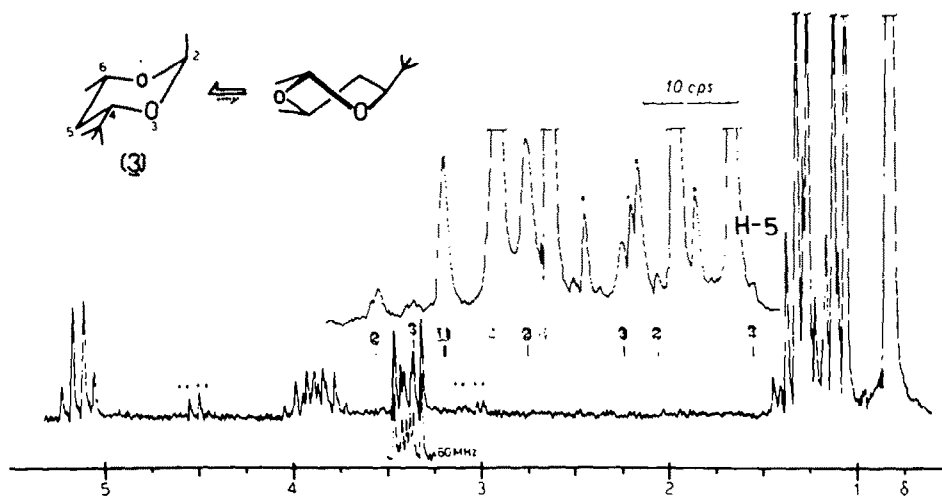


FIG 2. NMR Spectrum (VARIAN HA-100; 10% in CCl_4 , TMS int.) of *r*-2,-*trans*-6-diMe-*trans*-4-*t* Bu-1,3-dioxane (3). The dashes indicate peaks belonging to epimer (1). Inset: detailed pattern for H-5 atoms (250 sw.w.); subspectral ab-systems are indicated.

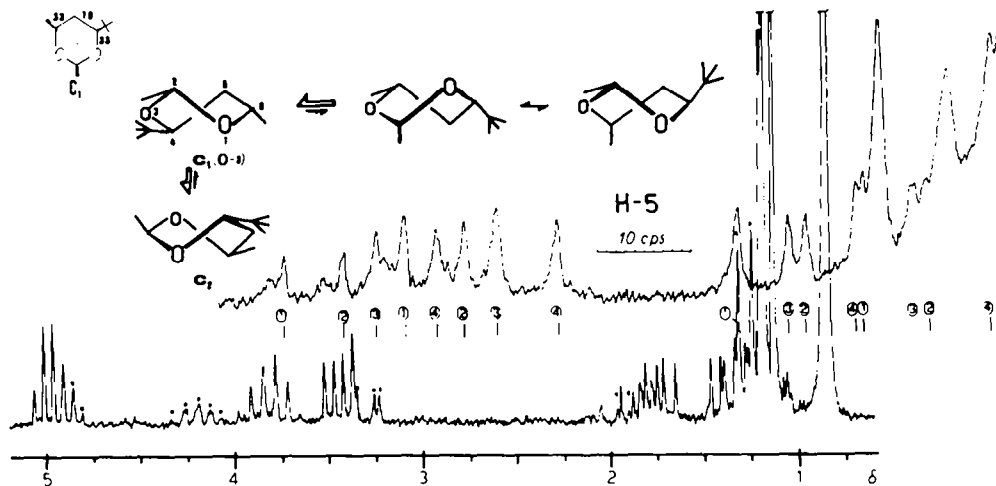


FIG 3. NMR Spectrum (VARIAN HA-100; 10°, in CCl₄, TMS int.) of *r*-2-*cis*-6-diMe-*trans*-4-*t*-Bu-1,3-dioxane (4). Dashed peaks belonging to the epimer (2). Cf. Fig. 1. Inset: details of H-5 region (250 sw.s); the four sub-spectral ab-systems are indicated.

for a Me-2 group is to be compared with almost the same order found when Me-4(6) substituents are involved (e.g. 2 against 1, Table 1).

r-2-*cis*-6-DiMe,*trans*-4-*t*-Bu-1,3-dioxane 4

The spectrum of isomer 4 is displayed in Fig 3. It contains (dashed peaks) a small amount of the epimer 2 (spectrum, Fig 1), to which it is quantitatively transformed in the NMR tube after a few days, proving the 4,6-dialkyl-*trans* relationship. This follows also from inspection of the vicinal ring-coupling constants. We would have expected analogous relative differences for 3J values at the CH₃ side ($^3J(5,6)$: 7.5 and 6.4 cps) as for the *t*.Bu side ($^3J(5,4)$: 10.3 and 5.7 cps) if both alkyl groups were orientated similarly (e.g. *cis* to each other). This is not the case. However the relatively large values found for both $^3J(5,6)$ show appreciable deviation from the classical chair conformation. The twist \leftrightarrow chair interconversion is governed at room temperature by a free energy difference of about $\Delta G^\circ = 5.0$ Kcal/mole ($\Delta H^\circ = 6.2$ Kcal/mole; $\Delta S^\circ \approx 4$ e.u.).⁸ Taking the sum of the conformational energies of a Me-6 group (3.0 Kcal/mole)⁹ and that of a Me-2 group (3.9 Kcal/mole)¹⁰ as a point of comparison, one indeed predicts a substantial amount, if not an exclusive twist population for the isomer 4 ($\Delta G^\circ(\text{Me-2}) + \Delta G^\circ(\text{Me-6}) > 6.8$ Kcal/mole).

For all possible C₁ and C₂ twist forms, we shall retain only those having bisectonal and/or pseudo-equatorial occupations (Chart II), e.g. C₂ and C₁ (0-3). The fact that the $^3J^{\text{exo}}$ coupling values for both H-2 and H-6 protons are in the lower range, gives indeed no indication of the occurrence of conformations with (pseudo) axial character for the corresponding Me-groups involved.

In the C₂ form, we discussed previously^{2, 8} the fact that the sum of the vicinal coupling constants $^3J(5,4) + ^3J(5,6)$ equals $2 \times (15.7-16.4)$ cps. In the actual compound 4 the total sum is found to be 29.8 cps (Me-side and *t*.Bu side), a value somewhat lower than in our C₂ model compounds (e.g. 31.4-32.8 cps). It is striking that

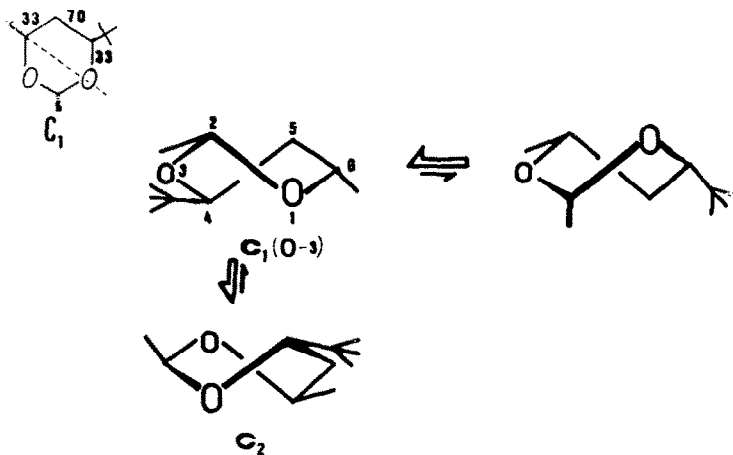


CHART II

$\Sigma^3 J$ involving the Me-side (${}^3 J(5,6) = 13.9$ cps) is lower than at the t.Bu side (${}^3 J(5,4) = 15.9$ cps), indicating the presence of forms other than C_2 . From inspection of other possible twist forms, only a C_1 (Chart II: $C_1(0-3)$) may be retained. The trend in the observed differences between ${}^3 J(5,4)$ and ${}^3 J(5,6)$ is well rationalized by this C_1 form. From idealized Bucourt diagrams (see Chart II) of C_1 with ring torsion angles of 33° , resp. 70° the following torsion angles between the coupled hydrogens H-4, H-6, and H-5 may roughly be estimated: 190° and 70° (H-4/H-5; t.Bu side) and 87° and 33° (H-6/H-5; Me-side). These torsional changes with respect to the C_2 form must result in a lowering of the vicinal coupling values, as follows qualitatively from the Karplus rule. The net result will be a lowering of $\Sigma^3 J$ if in the flexible family the C_1 form is also present. The relatively small difference between the observed value (29.8 cps) and the one expected for a C_2 form (31.4–32.8 cps) suggests a smaller population of C_1 (0–3) compared with C_2 (e.g. $\approx 20\%$).

EXPERIMENTAL

Preparation of isomers 1, 2, and 4. Phenyl acetate (b.p. $115^\circ/25$ mm, yield 90% from CH_3COCl) was condensed with pinacolone with NaH in ether; 26.6 g of the β -diketone so obtained (purified as Cu-salt; b.p. $80^\circ/20$ mm; yield 50%) was reduced with Ra-Ni at 100° and 100 atm affording crude diol 27.5 g, which without further purification was treated under reflux with paraldehyde 9 g in C_6H_6 200 ml in the presence of a trace of pTsoH. After boiling for 1 hr (1.6 g H_2O from Dean-Stark separator; 50% of theoretical), the reaction was interrupted distilling a fraction of ca. 12 g (b.p. 70 – $90^\circ/25$ mm) of an isomeric mixture (GC: 65% (1), 15% (4), 20% (2)) of the 2,6-diMe-4-t.Bu-1,3-dioxanes. These isomers were separated (GC) into the three compounds (QF₁ 20 m, $T = 120^\circ$ shots of 100 μ l).

r-2,-trans-6-DiMe,trans-4-t.Bu-1,3-dioxane (3). The procedure of Eliel⁵ is followed. From 5.9 g of a mixture of erythro and threo-2,2-diMe-3,5-hexanediol (ca. 50:50), 7 g of a mixture (ratio in increasing order of GC retention 18.5:12:27:42.5) of the 2-methoxy-4-t.Bu-6-Me-1,3-dioxanes (5) is obtained. After treatment with MeMgBr in ether and working up with K_2CO_3 ,⁵ the evaporated ether extract gave 4.1 g of the 2-methylated 1,3-dioxanes (ratio 3.2:14:3.8:79 in the order 1:4:2:3). The two major components are the isomers 3 and 4, as expected for preferential attack (with retention) of Grignard reagents on axial MeO-2 groups.⁵ Identification was checked by comparison with the three fractions obtained from the acetalization. The fourth peak was isolated by GC and is the *r-2,-trans-6-diMe,trans-4-t.Bu-1,3-dioxane (3)*.

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