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CONFORMATIONAL ANALYSIS OF 3,4-EPOXYTETRAHYDROPYRAN BY N.M.R. SPECTROSCOPY

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ABSTRACT

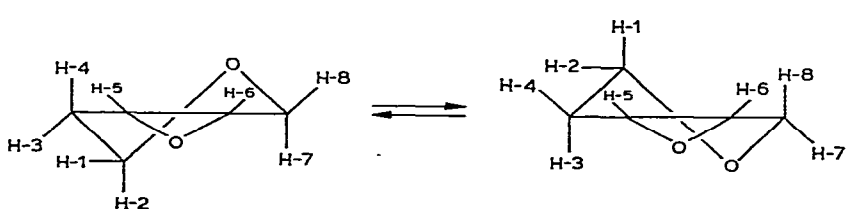
The conformational equilibrium of the title compound has been determined by correlating its n.m.r. parameters with those of its 2,2,6,6-tetradeuterio derivative and *trans*- and *cis*-2-*tert*-butyl-4,5-epoxytetrahydropyran. The high preference ($\Delta G \sim -0.8$ kcal/mol) for the half-chair conformation in which the pyranoid oxygen is furthest from the oxirane oxygen atom can be interpreted in terms of electrostatic interactions between the two oxygen atoms.

INTRODUCTION

The oxirane ring of 3,4-epoxytetrahydropyran can be opened in a highly regio- and stereo-selective manner[1,2], and epoxides have been used frequently as intermediates in synthesis. Conformational factors play a fundamental role in the reactions of sugar epoxides[3].

Spectroscopic methods (mainly n.m.r.) often allow a semiquantitative evaluation of the preferred conformations of these molecules[4], but the presence of substituents on one or more of the tetrahydropyran ring positions, their steric and polar interactions, the contribution of the anomeric effect, *etc.* usually complicate interpretation of the spectroscopic data.

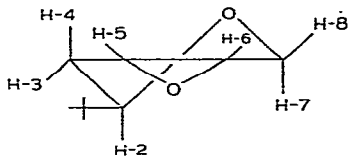
We have therefore investigated the conformational equilibrium of one of the basic compounds of this series, namely, 3,4-epoxytetrahydropyran (**1**). Whereas the conformational equilibrium for tetrahydropyran does not differ significantly from that of cyclohexane[5], no data are available for **1**, in which the two half-chair conformations **1a** and **1b** are not equivalent and may have different energies.



1a **1b**

RESULTS AND DISCUSSION

The conformational analysis of **1** has been performed by correlation of its n.m.r. parameters with those of the corresponding, rigid analogues **2** and **3**, which are models for conformations **1a** and **1b**.



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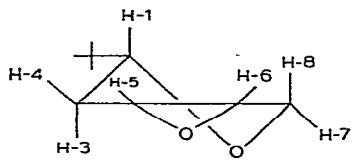

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The spectra of *trans*- (**2**) and *cis*-2-*tert*-butyl-4,5-epoxytetrahydropyran (**3**) in $CDCl_3$ were completely interpreted by using the LEQUOR programme[6], which is a special version of the LAOCOON/III programme[7] that can treat systems with up to 7 spins. The parameter sets thus obtained (Tables I and II) reproduce very well the experimental spectra (Figs. 1 and 2). The J values are compatible with slightly distorted chair conformations that are not entirely symmetrical around the epoxide ring, probably because of slight distortions caused by the tetrahydropyran oxygen and the bulky *tert*-butyl substituent. These J values are roughly in agreement with those calculated by Chmielewski and Zamojski[8] on the basis of the Karplus equation as modified by Abraham *et al.*[9], but it must be borne in mind that the latter data are based on a purely theoretical model and have only an indicative value.

The 100-MHz n.m.r. spectrum ($CDCl_3$) of **1** is more complicated (Fig. 3) because the difference in chemical shift between the signals of some protons is very

TABLE I

CHEMICAL SHIFTS CALCULATED FOR 3,4-EPOXYTETRAHYDROPYRANS[a]

Atom	**2** *($CDCl_3$)*	**3** *($CDCl_3$)*	**1** *($CDCl_3$)*	**1** *(C_6D_6)*
H-1	—	2.78	3.46	3.10
H-2	2.98	—	3.38	3.32
H-3	2.00	1.83	1.94	1.61
H-4	1.73	1.82	1.94	1.48
H-5	3.40	3.34	3.29	2.85
H-6	3.24	3.00	3.12	2.64
H-7	3.86	4.18	3.87	3.75
H-8	4.23	3.75	3.95	3.62

[a]Values expressed in p.p.m. (Me_4Si = 0)

TABLE II

COUPLING CONSTANTS (HZ) CALCULATED FOR 3,4-EPOXYTETRAHYDROPYRANS[a]

Coupling constant	**2** *($CDCl_3$)*	**3** *($CDCl_3$)*	**1** *($CDCl_3$)*	**1** *(C_6D_6)*	**4** *($CDCl_3$)*	**4** *(C_6D_6)*
$J_{1,2}$	—	—	−12.5	−11.2	—	—
$J_{1,3}$	— (0.8)	11.6 (10.0)	5.5[b]	5.5	—	—
$J_{1,4}$	— (3.5)	3.6 (3.5)	5.5[b]	5.5	—	—
$J_{2,3}$	2.4 (3.5)	— (3.5)	5.5[b]	4.5	—	—
$J_{2,4}$	11.4 (10.0)	— (0.8)	5.5[b]	8.2	—	—
$J_{3,4}$	−14.4	−13.4	—	−15.0	—	−15.0
$J_{3,5}$	2.3 (0)	0.0 (0)	2.2[b]	—	1.8	1.5
$J_{4,5}$	2.2 (1.5)	6.7 (4.5)	2.2[b]	3.0	3.0	2.9
$J_{5,6}$	4.4	3.9	4.1	—	4.4	4.4
$J_{6,7}$	0.0 (0)	0.0 (0)	0.0	0.0	—	—
$J_{6,8}$	4.0 (4.5)	0.0 (1.5)	3.1	3.1	—	—
$J_{7,8}$	−13.4	−13.4	−13.0	−13.5	—	—

[a]Values in parentheses are those calculated according to ref. 8. [b]Approximate values obtained by assuming H-3 and H-4 to be magnetically equivalent (see text).

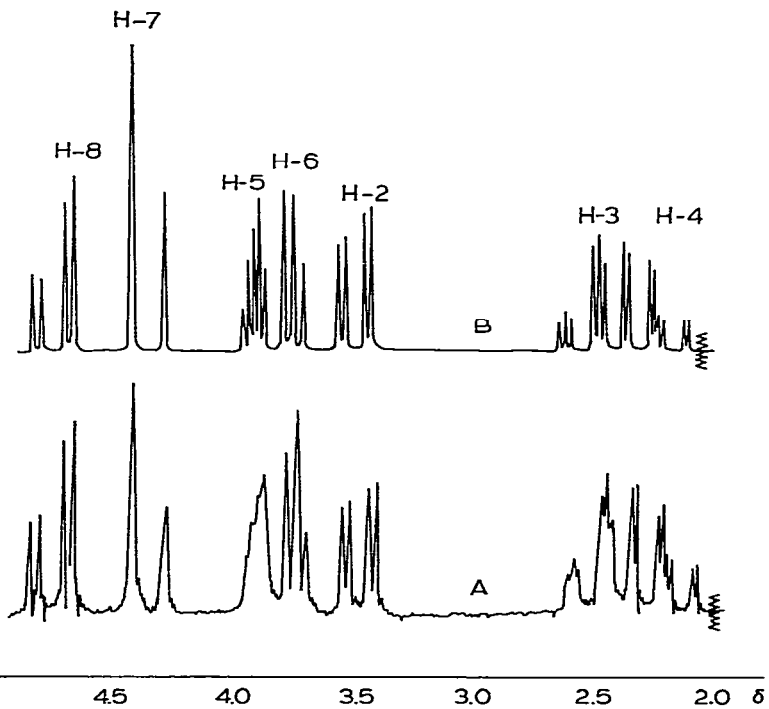


Fig. 1. Observed (A) and calculated (B) spectrum of *trans*-2-*tert*-butyl-4,5-epoxytetrahydropyran (**2**).

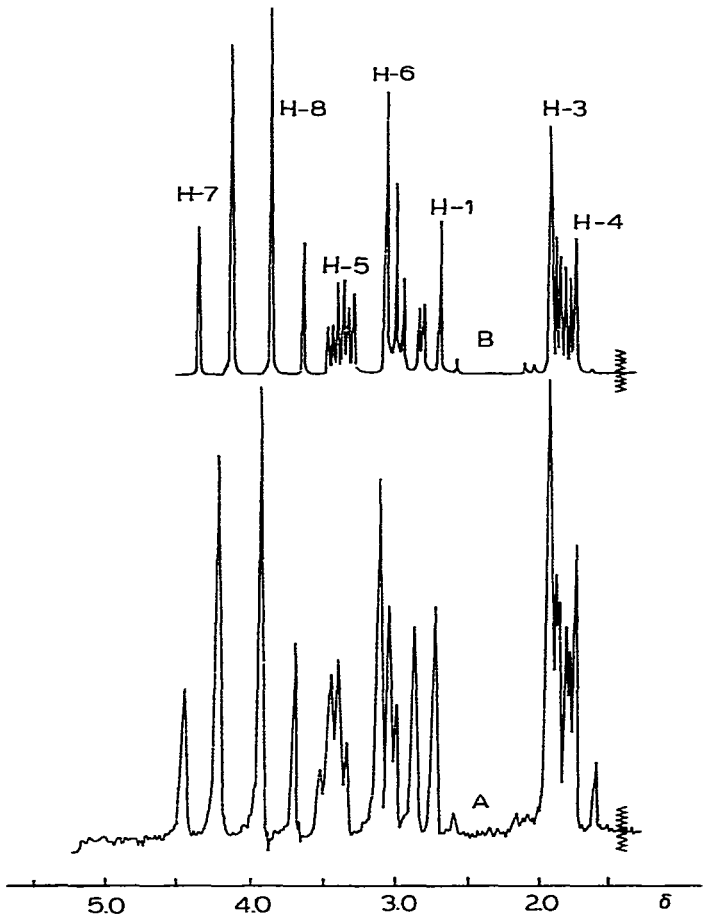


Fig. 2. Observed (A) and calculated (B) spectrum of *cis*-2-*tert*-butyl-4,5-epoxytetrahydropyran (3).

small. The analysis of this 8-proton system was not possible with the 7-spin LEQUOR programme. Although the use of C_6D_6 as solvent produced a better resolution of the signals[10], the spectrum was still too complicated for a direct analysis. However, the 360-MHz spectrum gave a complete resolution of the signals (Fig. 4), and a first-order analysis was possible, except for the unresolved signals H-3,5,6, which are probably broadened by small long-range couplings.

The 360-MHz spectrum ($CDCl_3$) of **1** was less well resolved. The signal for H-3,4 was a multiplet that had the same width at 360 and 100 MHz, thus indicating a fortuitous coincidence of their chemical shifts. An approximate analysis of these spectra was therefore undertaken with the LEQUOR programme, with the simplifying assumption of magnetic equivalence of the isochronous protons H-3 and H-4. The parameters thus obtained, although they involved incorrect average values for the couplings between H-3 and H-4 and the vicinal protons, reproduced surprisingly

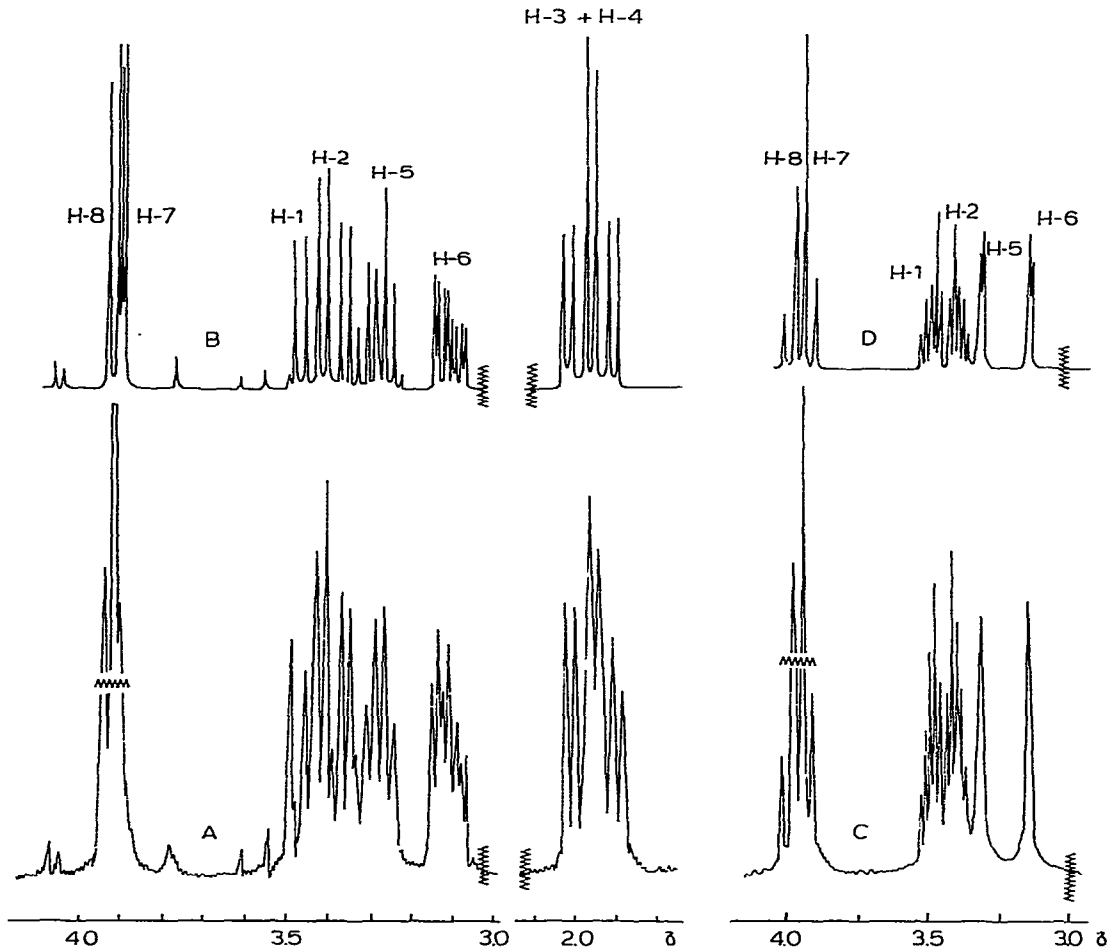
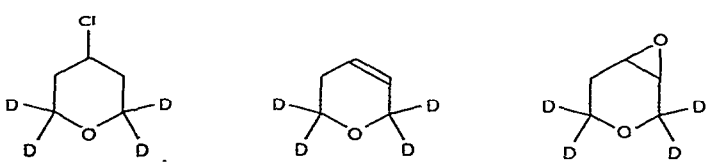


Fig. 3. Spectra of 3,4-epoxytetrahydropyran (**1**) in $CDCl_3$: observed (A) and calculated (B) at 100 MHz; observed (C) and calculated (D) at 360 MHz.

well the experimental spectra (Fig. 3). The values of $J_{6,7}$ and $J_{6,8}$, which should not be influenced by the approximation, have the same values in C_6D_6 and in $CDCl_3$, indicating similar contributions of conformations **1a** and **1b** in these solvents.

In order to obtain more-precise values for $J_{3,5}$ and $J_{4,5}$, the 2,2,6,6-tetra-deuterated derivative **6** was synthesised by Prins cyclisation of 3-buten-1-ol-*2,2-d*$_2$



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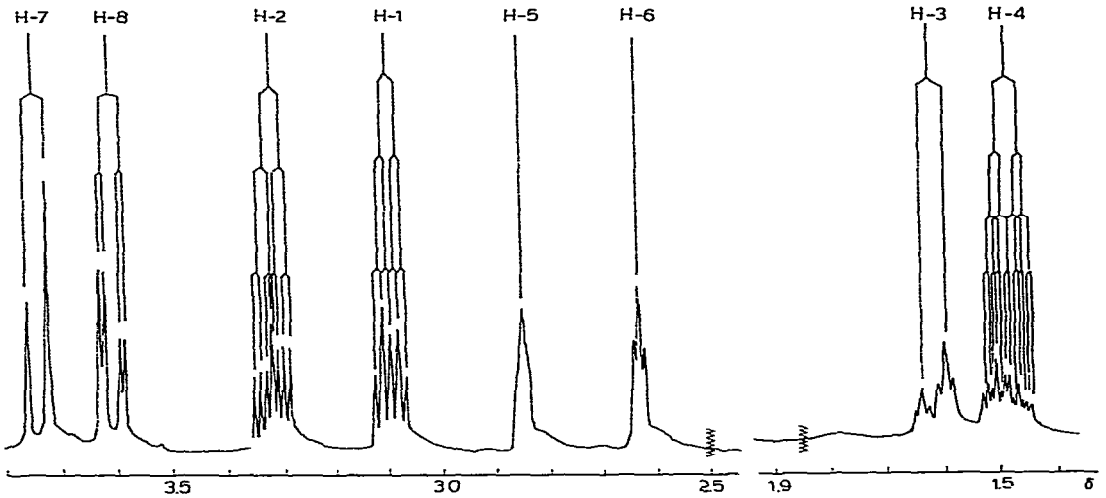

Fig. 4. 360-MHz Spectrum of 3,4-epoxytetrahydropyran (1) in C_6D_6.

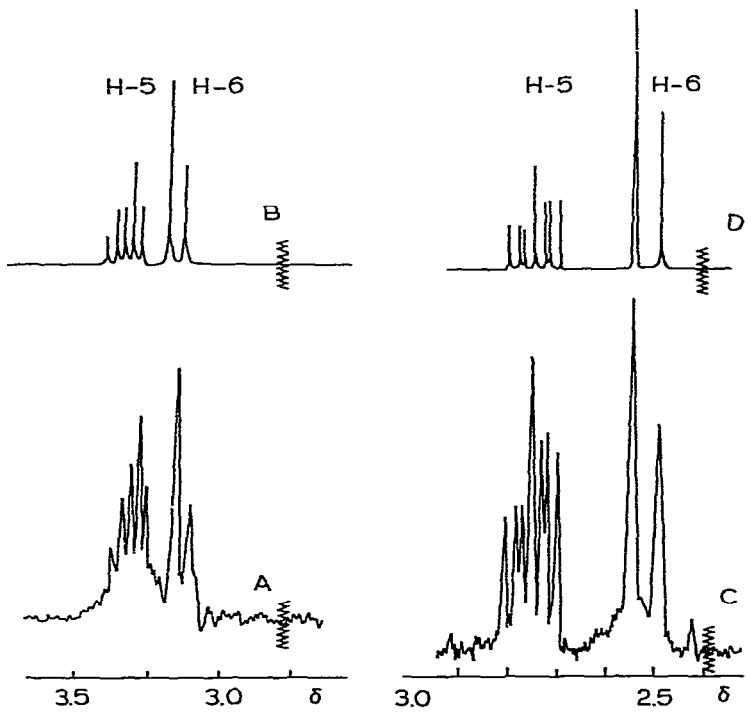

Fig. 5. Low-field portions of spectra of 2,2,6,6-tetradeuterio-3,4-epoxytetrahydropyran-d_4 (6): observed (A) and calculated (B) in $CDCl_3$; observed (C) and calculated (D) in C_6D_6.

with formaldehyde-d_2 in the presence of HCl, to give **4**, followed by dehydrochlorination to **5** and epoxidation.

The 80-MHz spectra of **6** in C_6D_6 and in $CDCl_3$ were easily interpreted by using the LEQUOR programme, and the calculated parameters reproduced well the experimental signals for the epoxide protons H-5 and H-6 (Fig. 5). Excessive broadening of the signals for H-3 and H-4, due to coupling with deuterium, prevented a good resolution of these signals.

Since chemical shifts are sensitive to the long-range effects of substituents, the conformational equilibrium for **1** was calculated on the basis of the equation:

$$J_{\text{mobile}} = X_a J_a + X_b J_b.$$

Only $J_{4,5}$ and $J_{6,8}$ are sufficiently different in the two rigid model-compounds to allow this equation to apply with a reasonable accuracy. The values for the conformational equilibrium deduced from these coupling constants are given in Table III, and indicate a preference for conformation **1a**. The data for $J_{3,5}$, although they are affected by a higher error because of the small value of J, confirm this preference. The data for $J_{6,8}$ in C_6D_6 and $CDCl_3$ are self consistent, whereas those for $J_{4,5}$ indicate somewhat higher percentages of conformer **1a**. This could be due to deformation of the six-membered ring by the *tert*-butyl substituent, so that **2** and **3** are not ideal models for conformations **1a** and **1b**. However, this should not seriously affect the data and, even if quantitative evaluation of the conformational equilibrium is made difficult, there is no doubt that the preference for conformation **1a** is ~80%, corresponding to a ΔG of 0.82 kcal/mol. Also, there do not appear to be pronounced differences between the spectra obtained with $CDCl_3$ and C_6D_6 as solvents, although these solvents can influence conformational equilibria, often unpredictably[11-12].

The observed preference for conformation **1a** over **1b** is probably not due to steric effects, since the (very small) repulsive interaction between the epoxide oxygen and the vicinal axial protons should disfavour conformer **1a** (one axial and one pseudo-axial *cis* proton) with respect to **1b** (one pseudo-axial proton). The preference for conformer **1a** is therefore due to repulsion between the dipoles associated with the oxygen atoms, an effect favouring the conformer **7** in which their interaction is minimised.

TABLE III

CONFORMATIONAL EQUILIBRIUM FOR 3,4-EPOXYTETRAHYDROPYRAN[a]

Coupling constant	**1** *(C_6D_6)*	**1** *($CDCl_3$)*	**6** *(C_6D_6)*	**6** *($CDCl_3$)*
$J_{4,5}$	82	—	84	80
$J_{6,8}$	78	78	—	—

[a]Expressed as the percentage of conformer **1a**. If a maximum error of ±0.2 Hz is assumed in the J values, the error in the percentage value (standard deviation) should be ±4%.

7 8

For 3,4-epoxytetrahydrofuran, in which the boat form is more stable than the chair form, the situation is different, since eclipsing between hydrogen atoms makes the conformer in which the oxygen atoms are more distant less stable[13].

Although the conformational situation in tetrahydropyran derivatives having an electronegative substituent at position 2 can be explained on the basis of the anomeric effect[14], the situation associated with a polar substituent at positions 3 or 4 is less clear. 3-Halo derivatives[15] exhibit a marked preference for conformations having the halogen equatorial, in accordance with the predominance of dipole–dipole repulsion, whereas other substituents, such as a 3-acetoxy group, have practically no influence on the conformational equilibrium[16].

Studies aimed at obtaining a more precise evaluation of the conformational situation of **1**, using dipole moment measurements, and extension to derivatives of **1** carrying substituents in different ring positions are planned.

EXPERIMENTAL

N.m.r. spectra were recorded for 10% solutions in $CDCl_3$ or C_6D_6 with JEOL C-60HL (**3**), JEOL PS-100 (**2** and **1**), Varian CFT-20 (at 79.9 MHz for **6**), and Bruker HXS-360FT (at 360 MHz for **1**) instruments. I.r. spectra were recorded with a Perkin–Elmer 197 instrument. G.l.c. was performed on a Carlo Erba Fractovap GV instrument equipped with a glass column (2 m) and a flame-ionisation detector.

To compute the final chemical shifts, proton–proton couplings, and theoretical spectra, an iterative program (LEQUOR[6]), based on the method of Castellano and Bothner-By[7], was applied and solved with an IBM 370/155 computer equipped with a Calcomping accessory. The parameters obtained should be correct to within ±0.2 Hz.

Compounds **1–3** were prepared as previously reported[1–2].

4-Chlorotetrahydropyran-2,2,6,6-d_4 (**4**). — Dry, gaseous HCl was bubbled into a stirred mixture of 3-buten-1-ol-*1,1-*d_2[17] (3.29 g, 45.6 mmol) and perdeuterated paraformaldehyde (1.37 g, 45.6 mmol) at −10° until the solid had completely dissolved (2 h). The solution was stirred for 2 h, poured into ice (20 g), and extracted with ether (3 × 20 ml). The dried ($MgSO_4$) extract was concentrated and the residue was distilled, to give **4** (2.55 g), b.p. 50–53°/18 mmHg; ν_{max} 2200, 2080, 1160, and 1060 cm^{-1}; lit.[17] b.p. 150/760 mmHg for the nondeuterated compound.

3,4-Epoxytetrahydropyran-2,2,6,6-d_4 (**6**). — Compound **4** (2.5 g) was treated with a solution of 85% KOH (5 g) in ethylene glycol (10 ml) and boiled under reflux for 4 h. The mixture was distilled and the fraction having b.p. 75–105°/760 mmHg was extracted with ether (50 ml). The extract was dried ($MgSO_4$) and concentrated,

to give 5,6-dihydro-2*H*-pyran-*2,2,6,6-d*$_4$ (5, 1.83 g); ν_{max} 3000, 2170, 2050, and 1190 cm^{-1}. Without further purification, this product was dissolved in dry $CHCl_3$ (50 ml) and treated at 0° with 85% 3-chloroperbenzoic acid (3.6 g). After 24 h at 5°, the solution was cooled to −10°, filtered, washed with aqueous Na_2CO_3 (2 × 20 ml), dried ($MgSO_4$), and concentrated, to give **6** (1.56 g), b.p. 55–60°/18 mmHg; ν_{max} 2200, 2070, and 1050 cm^{-1}. G.l.c. (1% of NPGS on 80–100 mesh silanised Chromosorb W, 170°) showed a single peak having the same retention time as **1**.

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