NMR 1,3-Diaxial Deshielding Effect of the Hydroxyl Group on Ring Hydrogens Studied from Partially Deuterated Six-Membered Ring Compounds

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The deshielding effect of the hydroxyl group on axial ring protons through 1,3-diaxial spatial interaction has been studied in *trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol-3,3,6,6-d_4 (II) and *trans*-2-*o*-tolyl-*cis*-4-hydroxycyclohexanol-3,3,6,6-d_4 (III) in deuterated chloroform, acetone-d_6, methanol-d_4, acetic acid, and pyridine; in 4-*tert*-butyl-*trans*-1,4-cyclohexanediol-3,3,5,5-d_4 (VI) in methanol-d_4 and pyridine; and in 4-*tert*-butyl-*cis*-1,4-cyclohexanediol-3,3,5,5-d_4 (VII) in pyridine. A consistent downfield shift of about 0.50 p.p.m. was found for the signal of H-1 of II in the first 4 solvents, but a considerably larger shift of 0.90 p.p.m. was obtained in pyridine. A downfield shift of about 0.58 ± 0.05 p.p.m. was found for the signal of H-2 in III in the first 4 solvents while a shift of 0.97 p.p.m. was obtained in pyridine. The deshielding effect of the tertiary hydroxyl groups in VI and VII was found to be smaller than that of the secondary hydroxyl in II and III in a given solvent, but the magnitude of the pyridine solvent effect was about the same in the 2 series.

THE DESHIELDING effect of the hydroxyl group through 1, 3-diaxial spatial interaction is well established in NMR spectroscopy of 6-membered ring compounds. The effect was observed on the NMR signals of angular methyl groups in steroid molecules by Shoolery and Rogers in 1958 (1) and has since been the object of systematic investigations by several authors (2–6). Much of the work has centered around the effect on angular methyl groups in steroids, where the average downfield shift for a large number of steroids measured in chloroform was found to be in the neighborhood of 0.25 p.p.m. (2) but examples of deshielding of axial protons are also known (6). Bhacca and Williams give tabulated data covering both cases (7).

A number of partially deuterated 6-membered ring compounds have been synthesized in this laboratory in recent years (8, 9). Some of these compounds provide excellent models for the investigation of the deshielding effect of an axial hydroxyl group on ring protons in 1,3-diaxial orientation to the hydroxyl group. Remote deuteration greatly simplifies the spectra and often allows more reliable chemical shifts and coupling constants. This is demonstrated in Fig. 1. The deshielding was investigated by comparing the chemical shifts of H-1 in compounds I and II, and H-2 in I and III in 5 different solvents, and by comparing the chemical shifts of the axial protons at positions 2 and 6 in IV and VI in pyridine and deuterated methanol, and V and VII in pyridine. The results are given in Tables I and II.

The origin of the magnetic anisotropy responsible for the 1,3-diaxial long-range deshielding by a hydroxyl group is not clearly understood. Early in the course of this investigation a large difference was observed in the deshielding effect in compounds II and III in pyridine compared to deuterated chloroform. Additional solvents were therefore selected in order to determine if a pattern of solvent effects could be found on the deshielding effects of the axial hydroxyl group in solvents that can associate with the hydroxyl group through hydrogen bonding only by acting as proton acceptors *versus* solvents which can hydrogen bond by acting as proton donors as well as proton acceptors. No such pattern was found in comparing the shift in acetone with that in methanol, acetic acid, and chloroform. In compound II the shift is identical in these 4 solvents; in III there is a slightly larger shift in acetone than in methanol and acetic acid, but the variation is not very large. A much larger difference in the shift was found between pyridine and all other solvents used. It is interesting to note that the downfield shift is not so large in VI and VII as in II or III in the corresponding solvents, but that the difference in the shift between pyridine and methanol is of similar magnitude for VI as for II and III. The smaller shift caused by a tertiary hydroxyl group in the *cis* and *trans* isomers of 4-*tert*-butylcyclohexanediol compared to the shift caused by a secondary hydroxyl

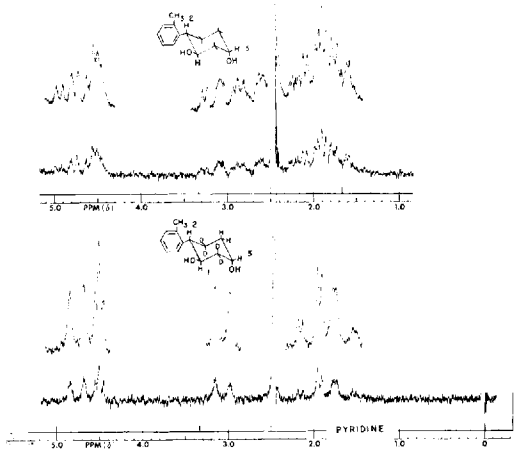

Fig. 1.—NMR spectra of *trans*-2-*o*-tolyl-*trans*-5-hydroxycyclohexanol and the corresponding 3,3,6,6-tetradeutero analog; 60 mc., about 1 *M* in pyridine with TMS as internal reference.

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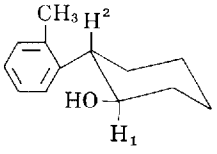
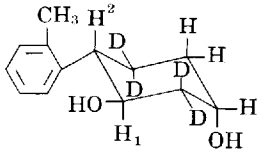
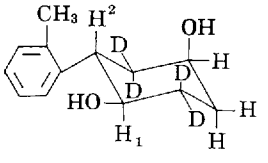
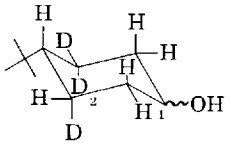
TABLE I.—CHEMICAL SHIFTS (ν) IN C.P.S. AT 60 MC. AND DESHIELDING EFFECT OF AXIAL HYDROXYL GROUP ON AXIAL HYDROGENS

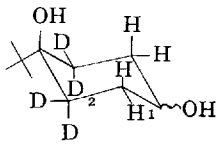
	Solvents	ν, c.p.s. at 60 mc. H-1	H-2	CH_3	Deshielding by Axial OH
 I	$CDCl_3$	220	161	138	
	Acetone-d_6	225	165	138	
	Methanol-d_4	222	163	138	
	AcOH	232	168	139	
	Pyridine	232	173	140	
					($\nu_{II} - \nu_I$) for H-1
 II	$CDCl_3$	249	162	140	29 c.p.s.
	Acetone-d_6	255	167	140	30
	Methanol-d_4	252	165	140	30
	AcOH	261	171	140	29
	Pyridine	285	184	148	53
					($\nu_{III} - \nu_I$) for H-2
 III	$CDCl_3$	228	198	143	37
	Acetone-d_6	232	203	140	38
	Methanol-d_4	226	196	141	33
	AcOH	236	200	140	32
	Pyridine	246	231	145	58

group in II and III in a given solvent could possibly be the result of a greater restriction to rotation about the C—O bond in the 4-*tert*-butyl compounds, causing the OH group to have a different preferred conformation on a time average than in II and III. Any deshielding effect resulting from the anisotropy of the O—H bond or of the unshared electrons of the oxygen atoms will be affected by the orientation of the hydroxyl group.



IV, *cis*, OH axial

V, *trans*, OH equatorial



VI, *trans*-diol, OH-1 axial

VII, *cis*-diol, OH-1 equatorial

TABLE II.—CHEMICAL SHIFTS (ν) IN C.P.S. AT 60 MC. AND DESHIELDING EFFECT OF AXIAL HYDROXYL GROUP ON AXIAL HYDROGENS

Solvent	ν, c.p.s. at 60 mc. Axial H-2 and H-6	Equatorial H-2 and H-6	Deshielding by Axial OH
IV Pyridine	86	119	
Methanol-d_4	85	109	
V Pyridine	83	129	
			($\nu_{VI} - \nu_{IV}$), axial H-2 and H-6
VI Pyridine	132	112	46
Methanol-d_4	110	95	25
			($\nu_{VII} - \nu_V$), axial H-2 and H-6
VII Pyridine	127	121	44

Table I indicates that the introduction of an axial hydroxyl group at C-5 in II has a negligible effect on the chemical shift of H-2, and the introduction of an axial hydroxyl group on C-4 of III has a negligible effect on the chemical shift of H-1 in III in all but the pyridine solvent. The chemical shift of the aromatic methyl group shows very little variation in all solvents for all 3 compounds. Although not given in Table I, the chemical shift of H-5 in II was found to be 251, 254, 252, 260, and 270 c.p.s. in deuterated chloroform, acetone-d_6, methanol-d_4, acetic acid, and pyridine, respectively, and that of H-4 in III was 246, 244, 238, 248, and 257 c.p.s. in the respective solvents.

The spectra of the deuterated compounds II and III allow the determination of accurate coupling constants between H-1 and H-2 from simple AX systems. Compound II gave J_{12} values of 10.5, 10.3, 10.3, 10.4, and 10.5 c.p.s. in chloroform-*d*, acetone-d_6, methanol-d_4, acetic acid, and pyridine, respectively; compound III gave J_{12} values of 10.0, 10.2, 10.3, 10.5, and 10.5 c.p.s. in the same respective solvents. These constant values of J_{12} indicate that there is practically no difference in conformation of these 2 compounds in the various solvents used. The coupling constants of about 10 c.p.s. indicate that H-1 and H-2 have a diaxial orientation and that II and III exist almost exclusively in a chair conformation with the aromatic group in an equatorial orientation in the 5 solvents used (8).

EXPERIMENTAL

trans-2-*o*-Tolylcyclohexanol (I) is a known compound (10).

trans-2-*o*-Tolyl-*trans*-5-hydroxycyclohexanol-3,3,-6,6-d_4 (II) and *trans*-2-*o*-tolyl-*cis*-4-hydroxycyclohexanol-3,3,6,6-d_4 (III) were prepared by the method previously reported for the corresponding nondeuterated compounds (11) except that butadiene-1,1,4,4-d_4 (12) was used in the Diels-Alder condensation step.

cis-4-*tert*-Butylcyclohexanol-3(axial)4,4-d_3 (IV) and the corresponding *trans* isomer (V) have been reported in a previous communication (13). Detailed synthesis of these 2 compounds will be reported in a subsequent publication.

4-*tert*-Butyl-*trans*-1,4-cyclohexanediol-3,3,4,5-d_4 (VI) and the corresponding *cis*-diol (VII) have been reported previously (9).

The NMR spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal reference.

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Elucidation of the Configuration of an Intermediate in the Synthesis of *cis*-β-Acetoxystyrene II

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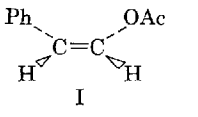
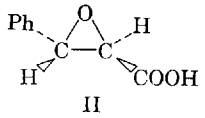
The configuration of *erythro*-α-hydroxy-β-toluene-*p*-sulfonyloxypropionic acid (III) was proved through conversion to the known methyl *erythro*-β-phenyl-α,β-ditoluene-*p*-sulfonyloxypropionate (VIII). Compound III represents the key intermediate in the conversion of *trans*-β-phenylglycidic acid (II) to *cis*-β-acetoxystyrene (I) and elucidation of the *erythro* configuration for III substantiates the original proposal that decarboxylative elimination of the probable acetate derivative (IV) occurred *trans*.

RECENTLY, the authors reported (1) a stereoselective synthesis for *cis*-β-acetoxystyrene (I) from *trans*-β-phenylglycidic acid (II). The key intermediate in the synthesis involved formation of the α-hydroxy-β-tosyloxy compound (III) through reaction of *trans*-β-phenylglycidic acid with *p*-toluenesulfonic acid in dry ether.

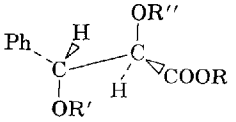
Assignment of the *erythro* configuration to compound III was originally based on the stereoselective formation of *cis*-β-acetoxystyrene (I) which was proposed to have formed by *trans* decarboxylative elimination of the corresponding α-acetoxy derivative (IV). Since the α-acetoxy derivative (IV) was not isolated when compound III was treated with acetic anhydride in pyridine (1)[1] and since some openings of benzylic epoxides with various Bronsted acids in nonpolar medium have been shown to occur with retention of configuration (2) independent evidence for the configuration of the β-tosyloxy-α-



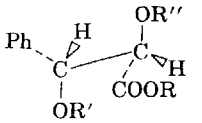
I



II



III, R = R'' = H, R' = Ts
IV, R = H, R' = Ts, R'' = Ac
V, R = R' = R'' = H
VII, R = CH_3, R' = Ts, R'' = H
VIII, R = CH_3, R' = R'' = Ts
IX, R = CH_3, R' = R'' = H



VII, R = R' = R'' = H
X, R = CH_3, R' = R'' = Ts
XI, R = CH_3, R = R'' = H

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‡ Supported by grant GY-339, Undergraduate Research Participation Program, National Science Foundation.
[1] *cis*-β-Acetoxystyrene was formed directly from compound III. Formation of the enol acetate was rationalized on the basis of the instability of the α-carboxy-β-tosyloxy system.