NMR Studies of Anacomeric 2-Phenyl-5,5-Disubstituted-1,3-Dioxanes (I)

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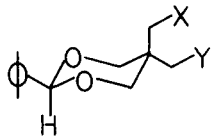
The chemical procedures for obtaining mixed functionalities of 5,5-substituents of 2-phenyl-1,3-dioxane (I) has been reported (2). Unequivocal stereochemical assignments of this series have been made on the basis of their nmr absorption positions.



I

It has been established (3) that alkyl and aryl substituents in the 2-position of 1,3-dioxane systems prefer the equatorial position thus rendering the molecule as being "conformationally biased" at normal temperatures. Even though these molecules are not "fixed" or "rigid" systems, a substituent at the 2-position is energetically sufficient to act as a "conformational locker" (4) and thus they are referred to as being anacomeric (5). Even when a large bulky atom (*i.e.*, *t*-butyl) resides at the 5-position this phenomenon predominates; it has been established by conclusive evidence that *cis*-2-methyl-5-*t*-butyl-1,3-dioxane exists exclusively with the methyl group equatorial and the *t*-butyl group axial (ref. cit.).

For geminal substituents at the 5-position, it has been shown (3,6,7) that the axial moiety absorbs at a lower field than its equatorial counterpart due to deshielding effects by the ring oxygen's lone pair electrons (3). In our studies we have similarly found that the ring oxygens have a marked effect on the position of absorption of the substituent methylene protons at the 5-position. It has been postulated that these non-bonding electrons are instrumental in directing nucleophilic substitution at functionalities attached at the 5-position (2).

In order to establish the conformation of our systems, the absorption position(s) of the axial C-2 methine proton, C-4 (or C-6) geminal coupling constants, and the C-5 substituent methylene protons were defined. The axial methine proton in the dioxanes studied absorb between 312-325 cps (Table I). The lower value for the C-2 methine proton of the *trans* compound VI may be attributed to the long range shielding effects from the equatorial *t*-butyl group at the C-5 position. The values observed in our systems (316.6-322.5 cps in carbon tetrachloride, Table I, and 317.5-324.9 cps in deuteriochloroform, Table II) are in excellent agreement with those reported.

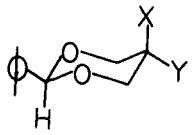
Reported geminal coupling (C-4 or C-6) varies from 10.8 to 12.5 cps and the "normal" value for the chair conformation when angular distortion is neglible is 11.2 to 11.5 cps (9-12). Our values, 11.2 to 12.3 cps (Table II) indicate that the conformers are of the chair and not the boat or twist boat form. Supportive evidence is also given by the single AB-quartet (12-14) produced by the ring protons at the C-4 and C-6 positions. The absorption for the equatorial C-4 or C-6 protons occurs at a lower field than the axial C-4 or C-6 protons, consistent with findings reported for similar 1,3-dioxanes (3-8, 15-17).

Axial methylene protons (C-5) absorb at a lower field than equatorial methylene protons in the 5,5-disubstituted dioxanes studied (Table I and II). For the monohydroxy-monotosylated isomers XII and XIII (Table II), the line positions of the axial C-5 methylene protons ($-CH_2OH$) and the equatorial C-5 methylene protons ($-CH_2OH$) are 235.1 cps and 208.6 cps respectively. For these isomers (XII; XIII) the absorption positions of the methylene protons adjacent to the tosylates correlate well with the corresponding positions of the ditosylated compound XI, (Table II). This same correlation is seen with the other mono- and disubstituted derivatives. The tosylate-bromide XIV has the axial methylene signal at 264.0 cps and the equatorial methylene absorption at 191.0 cps. The dibromide III has the C-5 axial absorption at 237.0 cps and the C-5 equatorial position at 196.0 cps. The change in the absorption positions in going from XIV to III, definitely show that the axial position is the centre at which substitution occured. The same phenomenon can be seen in going from the tosylate iodide XV to the diiodide IV. In each of these cases, the line position for the C-5 equatorial methylene substituents remain virtually unchanged except for small secondary electronic perturbations. These secondary effects account for the slight deviation in absorption positions in going from the dihalide to the monotosyl-monohalide derivatives.

The position of absorption of these methylene protons also correlate with the electronegativity of the attached

TABLE I

Nmr Absorption of Some 2-phenyl-5,5-disubstituted-1,3-dioxanes

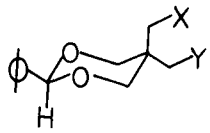


Cpd. No.	X	Y	ν 5 X (a)	ν 5 Y (e)	ν 2CH (a)	J_{gem}
II	$-CH_2Cl$	$-CH_2Cl$	239.1	203.5	320.0	12.0
III	$-CH_2Br$	$-CH_2Br$	233.6	195.6	322.5	11.5
IV	$-CH_2I$	$-CH_2I$	222.0	177.0	316.6	11.3
V (a)	*t*-Bu	H	62.9	–	325.5	–
VI (a)	H	*t*-Bu	–	55.1	312.4	–
VII (a)	H	H	–	–	321.0	–
VIII (b)	$COCH_3$	CH_3	–	–	322.8	–
IX (c)	H	H	–	–	319.2	–
X (c,d)	H	H	–	–	318.0	–

(a) ref 3; (b) ref 5; (c) ref 8; (d) substituent in 2-position *p*-NO_2-ϕ-
Values are in cps at 60 MHz; internal TMS at 0.1 *M*, carbon tetrachloride

TABLE II

Nmr Absorption Positions of 2-phenyl-5,5-disubstituted 1,3-dioxanes



Cpd. No.	X	Y	ν $5CH_2$ (a)	ν $5CH_2$ (e)	ν 2CH (a)	J_{gem}	ν 4 (6) e	ν 4 (6) a	$\Delta\nu$ $5CH_2$ (a-e)
XI	Ts	Ts	257.6	228.8	318.0	12.3	240.0	223.5	27.8
II	Cl	Cl	244.0	206.0	324.9	12.0	254.0	228.0	38.0
III	Br	Br	237.0	196.0	322.5	11.5	254.5	227.4	41.0
IV	I	I	225.5	181.6	319.0	11.2	252.0	227.0	46.0
XII	Ts	OH	266.0	208.6	321.5	11.9	246.5	224.9	57.4
XIII	OH	Ts	235.1	232.0	323.4	11.5	244.0	224.0	3.1
XIV	Ts	Br	264.0	191.0	318.2	12.0	244.8	219.5	73.0
XV	Ts	I	260.7	178.5	317.5	11.6	241.5	216.6	83.0

Values are in cps at 60 MHz using internal TMS at 0.1 *M*, deuteriochloroform. Complete nmr in ppm are reported in the Experimental.

heteroatom (*i.e.*, Cl > Br > I). The greater the electronegativity of the heteroatom, the greater is the deshielding effect on the adjacent nuclei, hence, the absorption position occurs at a lower field (18). This is in accord with the influence of the hetero-substituent on the chemical shift of the neighboring protons (19).

The dihydroxy compound (I, X = Y = OH) gives a complex multiplet in the regions of the AB pattern and the C-5 methylene absorption positions (d_6-Acetone and d_6-DMSO); consequently, no support could be given the positions for the C-5 axial and equatorial hydroxy methylene protons (*i.e.*, XII, XIII). Solubility factors also prevent

this compound from being compared in carbon tetrachloride or deuteriochloroform.

With the exception of the ditosylate XI, and the hydroxytosylate XIII, the difference in the C-5 axial-equatorial methylene absorption positions ($\triangle\nu 5CH_2$) for each compound increases as the size of the substituents increase (Table II). The small $\triangle\nu 5CH_2$ for compound XI may be attributed to stacking or maximum accumulation of unsaturated centers, thereby making the magnetic environment of the methylene protons more similar. Absence of the epimeric relatives prevent any specific rationale for the small $\triangle\nu 5CH_2$ for XIII unless intramolecular associations are a contributing factor. The geminal coupling constants (C-4 or C-6) for the ditosylate XI are greater than other compounds in this series. This is possibly due to a slight deformation of the C_4-C_5-C_6 portion of the dioxane ring. This phenomenon has been previously discussed (4,8).

Temperature studies (-40 to +50 degrees; deuteriochloroform, for compounds II, III, IV, XI, XII, XIV, XV) also indicate that these systems exist virtually, if not exclusively as a single conformer within this temperature range. No change in the chemical shifts was observed, and the single AB pattern exhibited no conformational deformation. The axial tosylate equatorial hydroxy compound XII does show its C-5 equatorial methylene absorption as a somewhat broadened band at 34° and as a doublet at -40°. In view of the fact that nothing else in the spectrum changes, this can be rationalized on the basis of the nonequivalence of the two protons due to either intramolecular associations, or a rotameric species which is innate to the molecule in question. Another explanation could be that the catalytic exchange of the alcoholic proton at this temperature is now slow enough for the methylene protons on the adjacent carbon to be coupled with the hydroxyl proton thereby resulting in the observed doublet.

Isomer XII can theoretically form an intramolecular hydrogen bond with the axial tosylate moiety. In order for this compound to form an intramolecular association with the ring oxygens, inversion of the preferred conformation must occur. In view of the fact that no shift occurred with XII at several temperatures (-40° to +50°), the latter possibility was excluded. For compound XIII, the proton of the hydroxy moiety can exist as an intramolecular, "possibly bifurcated" (20), hydrogen bond with the ring oxygens, or it may hydrogen bond with the equatorial tosylate moiety (Figure 1).

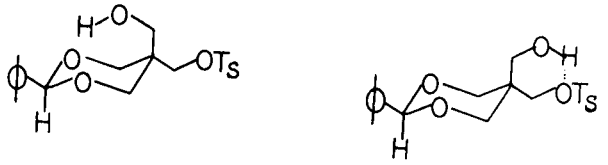
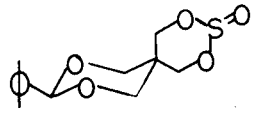


Figure 1

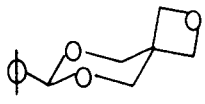
The difference in the environmental positions of the hydroxyl group in compounds XII and XIII is surprisingly characterized even by their solid state infrared spectra (potassium bromide). The axial CH_2OH (XIII) occurs as a strong sharp band at 3490 cm^{-1}. This gives good indication that the hydroxyl moiety is intramolecularly bonded, possibly with either the ring oxygens or with an oxygen of the tosylate substitutent (Figure 1). The hydroxyl band for the equatorial isomer XII is a strong broad band centered at 3250 cm^{-1}. This is characteristic of intermolecular association which would be favored in the solid state preparation.

As 10% solutions in methylene chloride, both compounds exhibit two hydroxy stretching frequencies. Compound XII showed an intense band at 3610 cm^{-1} and a weaker band (approximately half as intense) at 3540 cm^{-1}; XIII showed an intense band at 3610 cm^{-1} and a shoulder (about one-quarter to one-half as intense) at 3565 cm^{-1}. The higher frequency band is tentatively assigned the free -OH. The second band may be due to intramolecular associations (21-23) with the tosylate since both compounds can form this type bond. The lower frequency band could also be due to an alternative rotational conformation of the hydroxyl groups rather than due to intramolecular hydrogen bonding (4,23). These observations are in agreement with previous studies conducted on the hydrogen bonding capability of the hydroxyl group attached to substituents at the 5-position in *cis-trans* isomers (7,16,24,25).

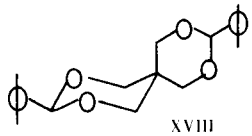
As a corollary to the 5,5-disubstituted systems, 2-phenyl-1,3-dioxane spiro compounds (XVI, XVII, XVIII) were compared for the position of their C-2 methine protons



XVI



XVII



XVIII

and effects of cyclization on the AB pattern. Dibenzalpentaerythritol XVIII (26) should have two axial methine protons for the most thermodynamically stable chair-chair conformer. In deuteriochloroform the sharp singlet which integrates for two protons occurs at 322.5 cps clearly demonstrating that the two methine protons are in the axial positions. The oxetane systems XVII (1) has its designated axial C-2 methine absorption at 324.0 cps and a geminal coupling for the C-4 or C-6 protons of 12.0 cps. The disulfurous acid ester XVI (2) exhibits a C-2 methine absorption at 325.0 cps. Possible secondary and long range

coupling effects cause the C-4 (or C-6) and C-5 methylene protons in both XVI and XVIII to be overlapping complex multiplets; subsequently no support could be given to these absorption positions.

The above mentioned absorption positions for compounds XVI, XVII, XVIII lend excellent additional support to the previously described chair conformation of 2-substituted-1,3-dioxanes, and the position of the axial C-2 protons in these systems.

EXPERIMENTAL

Nuclear magnetic resonance spectra were obtained at 34 degrees on a Hitachi Perkin-Elmer R 20A at 60 MHz. Solutions are in deuteriochloroform (0.1 *M*) and carbon tetrachloride (0.1 *M*) using internal tetramethylsilane. The simplicity of the nmr splitting patterns allowed for first order analysis. The infrared spectra were obtained on a Perkin-Elmer Model 237 B Grating Spectrometer in potassium bromide and methylene chloride (1.01 mm sodium chloride cell path length). Syntheses are reported elsewhere (2). Nmr values have been converted from cps to ppm and the complete spectra are reported.

2-Phenyl-5,5-*bis*(chloromethyl)-1,3-dioxane (II) (27).

Nmr (deuteriochloroform) δ 3.43 [s, 2, C_5 (e) methylene], 3.80 [AB broad d, 2, J = 12.0 cps, C_4 and C_6 (a)], 4.07 [s, 2, C_5 (a) methylene], 4.23 [AB broad d, 2, J = 12.0 cps, C_4 and C_6 (e)], 5.42 [s, 1, C_2 (a) methine], and 7.42 (m, 5, C_2Ar).

2-Phenyl-5,5-*bis*(bromomethyl)-1,3-dioxane (III).

Nmr (deuteriochloroform) δ 3.27 [s, 2, C_5 (e) methylene], 3.79 [AB broad d, 2, J = 11.5 cps, C_4 and C_6 (a)], 3.95 [s, 2, C_5 (a) methylene], 4.24 [AB broad d, 2, J = 11.5 cps, C_4 and C_6 (e)], 5.38 [s, 1, C_2 (a) methine], and 7.40 (m, 5, C_2Ar).

2-Phenyl-5,5-*bis*(iodomethyl)-1,3-dioxane (IV).

Nmr (deuteriochloroform) δ 3.03 [s, 2, C_5 (e) methylene], 3.76 [s, 2, C_5 (a) methylene], 3.78 [AB broad d, 2, J = 11.2 cps, C_4 and C_6 (a)], 4.20 [AB broad d, 2, J = 11.2 cps, C_4 and C_6 (e)], 5.32 [s, 1, C_2 (a) methine], and 7.42 (m, 5, C_2Ar).

2-Phenyl-5,5-*bis*(*p*-toluenesulfonylmethyl)-1,3-dioxane (XI).

Nmr (deuteriochloroform) δ 2.42, 2.49 (2s, 6, CH_3OTs), 3.73, 4.00, 3.81 [m, 6, AB C_4 and C_6, J = 12.3 cps, C_5 (e) methylene], 4.29 [s, 2, C_5 (a) methylene], 5.30 [s, 1, C_2 (a) methine], and 7.10-7.90 (m, 13, C_2Ar, Ts).

2(e)-Phenyl-5(e)-hydroxymethyl-5(a)-*p*-toluenesulfonylmethyl-1,3-dioxane (XII).

Nmr (deuteriochloroform) δ 2.05 (broad s, 1, OH), 2.42 (s, 3, CH_3OTs), 3.48 [s, 2, C_5 (e) methylene], 3.78 [AB broad d, 2, J = 11.9 cps, C_4 and C_6 (a)], 4.11 [AB broad d, 2, J = 11.9 cps, C_4 and C_6 (e)], 4.43 [s, 2, C_5 (a) methylene], 5.38 [s, 1, C_2 (a) methine], and 7.2-7.9 (m, 9, C_2Ar, Ts).

2(e)-Phenyl-5(a)-hydroxymethyl-5(e)-*p*-toluenesulfonylmethyl-1,3-dioxane (XIII).

Nmr (deuteriochloroform) δ 1.84 (broad s, 1, OH), 2.43 (s, 3, CH_3OTs), 3.73 & 4.07, 3.87 & 3.92 [m, 6, J = 11.5 cps, AB C_4 and C_6, C_5 (e) and C_5 (a) methylenes], 5.42 [s, 1, C_2 (a) methine], and 7.22-7.94 (m, 9, C_2Ar, Ts).

2(e)-Phenyl-5(e)-bromomethyl-5(a)-*p*-toluenesulfonyl-1,3-dioxane (XIV).

Nmr (deuteriochloroform) δ 2.40 (s, 3, CH_3OTs), 3.18 [s, 2, C_5 (e) methylene], 4.08 [AB broad d, 2, J = 12.0 cps, C_4 and C_6 (e)], 3.65 [AB broad d, 2, J = 12.0 cps, C_4 and C_6 (a)], 4.40 [s, 2, C_5 (a) methylene], 5.31 [s, 1, C_2 (a) methine], and 7.20-7.95 (m, 9, C_2Ar, Ts).

2(e)-Phenyl-5(e)-iodomethyl-5(a)-*p*-toluenesulfonylmethyl-1,3-dioxane (XV).

Nmr (deuteriochloroform) δ 2.41 (s, 3, CH_3OTs), 2.98 [s, 2, C_5 (e) methylene], 3.61 [AB broad d, 2, J = 11.6 cps, C_4 and C_6 (a)], 4.03 [AB broad d, 2, J = 11.6 cps, C_4 and C_6 (e)], 4.35 [s, 2, C_5 (a) methylene], 5.29 [s, 1, C_2 (a) methine], and 7.15-7.95 (m, 9, C_2Ar, Ts).

3-Phenyl-9-oxo-2,4,8,10-tetroxa-9-thiaspiro[5.5]undecane (XVI).

Nmr (deuteriochloroform) δ 3.86 (m, 4), 4.65 (m, 4), 5.41 [s, 1, C_2 (a) methine], and 7.40 (m, 5, C_2Ar).

7(e)-Phenyl-2,6,8-trioxaspiro[3.5]nonane (XVII).

Nmr (deuteriochloroform) δ 3.84 [AB broad d, 2, J = 12.0 cps, C_4 and C_6 (a)], 4.24 [s, 2, C_5 (e) methylene], 4.54 [AB broad d, 2, J = 12.0 cps, C_4 and C_6 (e)], 4.76 [s, 2, C_5 (a) methylene], 5.41 [s, 1, C_2 (a) methine], and 7.38 (m, 5, Ar).

3,9-Diphenyl-2,4,8,10-tetroxaspiro[5.5]undecane (XVIII) (26).

Nmr (deuteriochloroform) δ 3.60 (m, 6), 4.82 (broad d, 2), 5.38 [s, 2, C_3 and C_9 (a) methine], and 7.38 (m, 10, Ar).

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