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HETERODIENE SYNTHESIS—VI[1]

CONFORMATIONAL STUDIES ON THE DIHYDROPYRAN RING IN 2,3-DIHYDROPYRANO[2,3-*d*]ISOXAZOLES, 2,3-DIHYDROPYRANO[2,3-*b*]INDOLES AND 2,3-DIHYDROPYRANO[2,3-*c*]PYRAZOLES USING A GRAPHICAL METHOD

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Abstract—A graphical treatment of coupling constant data from a number of substituted 2,3-dihydropyran systems has afforded information about the conformational equilibria within the series. Small changes in structure alter the conformational equilibrium significantly. Some trisubstituted dihydropyran rings prefer to exist in the conformer with all three groups in the pseudo-axial position.

IN PRECEDING papers, various aspects of reactions of arylidene-isoxazolones, -oxindoles and -pyrazolones with some vinyl ethers have been reported.[2-5] The reaction gives rise to products which contain a dihydropyran ring and the configurational assignments of the substituents on the ring have been established from a consideration of coupling constants and chemical shifts in the PMR spectra.[5] The assignments verified earlier conclusions obtained from chemical methods.[4] The variations in the magnitude of the coupling constants between *trans* protons on the saturated part of the ring indicated that not all the compounds have the same conformational preferences and this is the subject of the present investigation.

Conformational studies on other unsaturated heterocyclic systems lead to the conclusion that many 6-membered ring compounds including benzodioxans,[6] 2,3-dihydropyrans[7] and the dihydropyran rings in many flavan[8] derivatives prefer to exist in the rapidly inverting half chair forms. The sofa form appears to be limited to compounds where the unsaturated bond can conjugate with a CO group as in some flavanones,[9] or sometimes to a ring nitrogen, as in some dihydro 1,4-thiazines.[10] Clark-Lewis[9] has suggested that the energy difference between half-chair and sofa forms in some flavans could be small. For the purpose of the present work we assume that the dihydropyran ring in the compounds studied here exists in the rapidly interconverting half-chair forms but similar arguments would apply to interconverting sofa forms.

The coupling constants in the NMR spectra of the compounds considered (Fig 1) are abstracted from preceding papers[2,5] and are listed in the Table.

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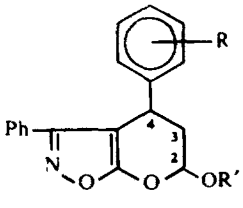
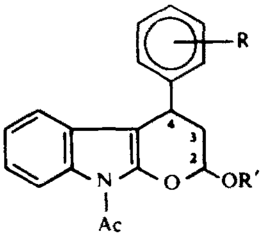


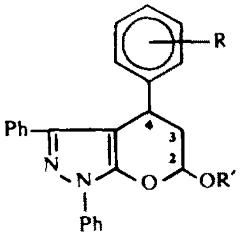
I: *cis*
II: *trans*

a: R = $o\mathrm{NO_2}$, R′ = Me
b: R = H, R′ = Et
c: R = $o\mathrm{NO_2}$, R′ = Et



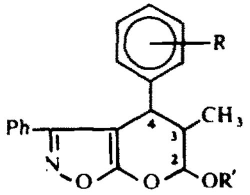
III: *cis*
IV: *trans*

a: R = H, R′ = Et

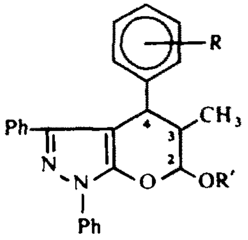


V: *cis*
VI: *trans*

a: R = H, R′ = Et
b: R = $o\mathrm{NO_2}$, R′ = Et
c: R = $p\mathrm{OCH_3}$R′ = Et
d: R = $o\mathrm{NH_2}$, R′ = Et
e: R = *o*NHAcR′ = Et



VII: *trans*-2,3-*trans*-3,4
VIII: *cis*-2,3-*trans*-3,4
a: R = H, R′ = *n*Pr
b: R = $o\mathrm{NO_2}$, R′ = *n*Pr



IX: *trans*-2,3-*trans*-3,4
X: *cis*-2,3-*trans*-3,4

a: R = H, R′ = *n*Pr
b: R = $o\mathrm{NO_2}$, R′ = *n*Pr
c: R = $p\mathrm{OCH_3}$, R′ = *n*Pr
d: R = $o\mathrm{NH_2}$, R′ = *n*Pr
e: R = *o*NHAc, R′ = *n*Pr

FIG 1

TABLE 1

cis Compds	J_{23}	$J_{23'}$	J_{34}	$J_{3'4}$	*trans* Compds	J_{23}	$J_{23'}$	J_{34}	$J_{3'4}$
●	J_{trans}	J_{cis}	J_{trans}	J_{cis}	▲	J_{cis}	J_{trans}	J_{trans}	J_{cis}
I a	4·5	2·5	4·7	7·2	II a	2·4	3·1	9·85	5·8
I b	5·0	2·8	6·1	6·1	II b	2·5	4·8	8·05	6·0
I c	4·2	2·75	4·55	7·05	II c	2·55	3·3	9·65	5·8
III a	7·9	2·5	9·5	7·0	IV a	2·7	3·3	9·5	6·1
V a	5·2	2·7	6·5	6·5	VI a	2·2	5·9	6·95	5·6
V b	4·7	2·5	5·5	6·9	VI b	2·4	3·7	9·0	6·0
V c	5·2	2·5	6·6	6·6	VI c	2·3	5·8	6·2	6·2
V d	----4·2----		----6·7----		VI d	----3·9----		----6·5----	
V e	5·0	2·8	6·3	6·3	VI e	2·5	4·4	8·1	6·5
VIIa	5·3	---	5·95	--	VIIIa	2·15	--	8·7	--
VIIb	2·8	--	2·5	--	VIIIb	2·1	-	8·7	-
IX a	5·4	--	6·1	-	X a	2·1	--	8·1	--
IX b	2·8	--	2·6	--	X b	2·0	-	7·95	-
IX c	5·4	--	6·0	--	X c	2·0	--	7·6	--
IX d	5·7	--	6·3	--	X d	2·15	--	7·7	--
IX e	5·0	--	5·5	-					

The measured values of J_{34} can therefore be located on a straight line (*line* 1) arbitrarily drawn across a graph of Coupling Constant versus x where the x scale is not graduated, Fig 3. From such a graph a relative value of x, of unknown magnitude, is defined for each compound.

Using the same axes, the other *trans* couplings J_{23} (in the *cis* series) and $J_{23'}$ (in the *trans* compounds) are each plotted against their corresponding relative values of x, and this is found to give two fairly good straight lines which supports our earlier assumptions. The equations for the lines are:

$$\textit{line}\ 2;\quad J_{23} = x(J_{2_a3_a} - J_{2_e3_e}) + J_{2_e3_e} \tag{2}$$

$$\textit{line}\ 3;\quad J_{23'} = x(J_{2_e3'_e} - J_{2_a3'_a}) + J_{2_a3'_a} \tag{3}$$

The slopes of the lines are found to be approximately equal but of opposite sign and this is in accord with the further assumption used below that $J_{2_a3_a}$ equals $J_{2_a3'_a}$ and $J_{2_e3_e}$ equals $J_{2_e3'_e}$, and that each pair remains constant within the compounds studied. Since a large number of compounds are investigated, minor variations in $J_{2_a3_a}$ (or $J_{2_a3'_a}$), $J_{2_e3_e}$ (or $J_{2_e3'_e}$) as well as in $J_{3_a4_a}$ and $J_{3_e4_e}$ from one compound to another are averaged out.

By equating Eqns (2) and (3) and using the approximations that $J_{2_a3_a} = J_{2_a3'_a}$ and $J_{2_e3_e} = J_{2_e3'_e}$, it is found that x equals 0·5 where the *lines* 2 and 3 intersect. Having established the point on the x scale where $x = 0{\cdot}5$ we obtain values of $\frac{1}{2}(J_{3_a4_a} + J_{3_e4_e}) = 6{\cdot}5$ Hz, and $\frac{1}{2}(J_{2_a3_a} + J_{2_e3_e}) = 5{\cdot}55$ Hz; values which are compatible with those predicted from the Karplus equation.[13] Furthermore, since J_{aa} is always larger than J_{ee}, x increases from left to right, and it is immediately clear which compounds preferentially exist in conformer *a* ($x > 0{\cdot}5$) and which prefer conformer *b* ($x < 0{\cdot}5$).

In order to locate $x = 0$ or $x = 1$ a knowledge of any *one* of $J_{3_a4_a}$, $J_{2_a3_a}$, $J_{3_e4_e}$ or $J_{2_e3_e}$ is required. Whilst none of these is known, clearly $J_{2_e3_e}$ is less than 2·8 Hz and $J_{3_e4_e}$ is less than 2·5 Hz, the couplings found in VIIb. A consideration of other systems e.g. dioxans,[14] suggests that a value of 2 Hz for the $J_{2_e3_e}$ coupling constant is reasonable. Extrapolation of *line* 2 to 2 Hz on the coupling constant axis locates the value of $x = 0$ on the x axis; this and a graduation of the x scale is included on the graph.

The present approach assumes that variations in the *trans* couplings is solely dependent upon the conformational equilibrium, and neglects effects arising from electronegative groups at C_2. Variations in the *cis* couplings show that these effects may not be insignificant. Such effects may account for the scatter of some of the points about *lines* 2 and 3. The order of the error in the location of $x = 0{\cdot}5$ on the x scale, which arises from the approximations, can be estimated. Thus, if $J_{2_a3_a} = J_{2_a3'_a} \pm 0{\cdot}5$ Hz and $J_{2_e3_e} = J_{2_e3'_e} \pm 0{\cdot}5$ Hz, the error in the location of $x = 0{\cdot}5$ is of the order of 0·04 units (using $J_{2_a3_a} = 9$ Hz and $J_{2_e3_e} = 2$ Hz). Further, if $J_{3_a4_a}$ is smaller in the *trans* series than in the *cis* series as discussed earlier, then the relative x values of the *trans* compounds are all fractionally too low. A "*corrected line* 3," which would be drawn further to the right than at present, would displace the location of $x = 0{\cdot}5$ by about 0·05 units for a difference of 1 Hz between $J_{3_a4_a}$ in the two series.

Whilst the errors in the location of $x = 0{\cdot}5$ are not large, error in evaluation of individual x values may be more significant. Added to the uncertainty in $x = 0{\cdot}5$, is the uncertainty in the choice of J_{2e3e} to locate $x = 0$, plus the deviation of the compounds from *line* 2 or 3. For these reasons it is felt that it is not strictly proper to determine individual equilibrium constants. We prefer to consider semiquantitatively the variations in the conformational preferences within the series as a whole, for which purpose the graph is well suited.

The compounds are members of a class in which small changes in structure alter the conformational equilibrium significantly. Although there are too many factors involved to enable a complete analysis of the interactions to be made, some points do clearly emerge. Most of the *trans* compounds prefer the form with the C_4-aryl group pseudo-equatorial and the 2-alkoxy group pseudo-axial whilst the *cis* compounds in general have a slight preference for the form with both substituents pseudo-axial. This indicates that a 2-alkoxy group prefers the pseudo-axial position; a preference arising from dipole–dipole interactions and well known in carbohydrate chemistry (the anomeric effect),[15] and observed in a number of other systems also, e.g. phenanthrodioxans,[16] dioxans[17] and tetrahydrochromans.[18]

The *cis* and *trans* indole derivatives IIIa and IVa show a stronger preference for the C_4-aryl equatorial conformer than the majority of the other compounds. This suggests that the phenyl substituent on the adjacent ring in these other compounds destabilises the 4-aryl group in the pseudo-equatorial position; an interesting result in that a small attractive force between *syn* periplanar 1,2-diphenyl groups has been calculated for 1,2-diphenylethane.[19]

The nature of the substituent on the C_4-aryl group significantly affects the conformational equilibrium of the dihydropyran ring. This is illustrated by a comparison of the relative x value for the *cis* compounds Va, Vb, Vc, and Ve, and the *trans* compounds VIa, VIb, VIc, and VIe which suggests that an *ortho* nitro group effectively increases the preference for the *trans* compounds to exist in conformer *a* and the *cis* to exist in conformer *b*. The reason for this is not clear but it appears to be a function of the nitro group rather than of a generally substituted *ortho* position since the effect is reduced when the group is converted to NHCOMe. This phenomenon is even more pronounced in the 2,3,4-trisubstituted compound. Whereas the *ortho* amino, *ortho* acetamido and *para* methoxy *trans trans* compounds (IX, c, d and e) have no particular conformational preferences, the corresponding *ortho* nitro derivative IXb, as well as the analogous VIIb, probably exist almost exclusively with all three groups in the pseudo-axial positions.

These latter results in particular emphasise the complexities of the interactions involved in these systems where reduced 1,3 interactions and field effects strongly modify the well known conformational rules of cyclohexane.

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