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STEREOCHEMISTRY OF FLAVAN-3,4-DIOLS

E.J. Corey
Department of Chemistry, Harvard University
Cambridge 38, Mass.
E.M. Philbin and T.S. Wheeler
Department of Chemistry, University College, Dublin

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THE stereochemistry of substituted flavan derivatives has been a more subtle and elusive matter than similar problems with saturated carbocyclic ring systems. This is mainly because the usual generalizations correlating reactivity and stereochemistry are not very reliable for a ring system containing a heteroatom and also aromatic unsaturation, features which conspire to produce unique complications.

This note reports the application of nuclear magnetic resonance to the clarification of the molecular configurations of the two known flavan-3,4-diols which have been prepared from flavan-3-ol-4-one: (1) the flavan-3,4-diol m.p. 145° prepared by direct reduction of the 4-ketone[1] and (2) the flavan-3,4-diol m.p. 160° synthesized from the same ketone via the 4-oxime by reduction to the amine followed by nitrous-acid deamination.[2] Although both diols might be expected to have the same configuration at C_3, differing simply at C_4 as _cis_ and _trans_ diols, _both_ can be converted to cyclic carbon-

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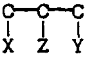
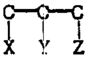
[1] R. Bognár and M. Rákosi, _Chem. & Ind._ 188 (1956); _Acta.Chim.Acad.Sci. Hung._ _14_, 369 (1958).

[2] R. Bognár, M. Rákosi, H. Fletcher, E.M. Philbin and T.S. Wheeler, _Tetrahedron Letters_ No. 19, 4 (1959).

ates: diol m.p. 145° → carbonate m.p. 127-128° and diol m.p. 160° → carbonate m.p. 157-158°. That one of these carbonates is, in fact, a <u>trans</u>-derivative is revealed clearly by NMR.

<u>Flavan-3,4-diol carbonate m.p. 127-128°</u>. Two of the heterocyclic ring protons (X,Y) appear together coincidentally as a doublet at -332.6 and -322 c.p.s.[3,4] (relative intensity ca. 1:1.7). The resonance of the third heterocyclic proton (Z) occurs as a triplet at -268.6, -258 and -247.5 c.p.s. (relative intensities 1:1.1:0.5). The only other peaks in the spectrum are due to the aromatic protons at lower field; the integrated intensities over the spectrum are, aromatic: 9.1 protons, heterocyclic (X,Y): 2.0 protons and heterocyclic (Z): 1.0 proton. The X, Y and Z resonances constitute a unique and unexpectedly simple pattern which reveals that this is a very special case. There are <u>only two possible</u> ways in which the lines observed for the three heterocyclic protons might arise: (1) X, Y and Z are disposed  $\underset{X}{C}-\underset{Z}{C}-\underset{Y}{C}$ with X and Y having the same chemical shift and also the same coupling constant to Z, i.e. $\sigma_X = \sigma_Y$ and $J_{XZ} = J_{ZY} = 10.6$ c.p.s., and (2) X, Y and Z are disposed  $\underset{X}{C}-\underset{Y}{C}-\underset{Z}{C}$ with $\sigma_X = \sigma_Y$, J_{XY} finite and $J_{YZ} = 21.2$ c.p.s. (J_{XZ} expected to be <0.5 c.p.s.).[5] The second alternative clearly is not tenable since it demands a coupling constant which is far too large for protons

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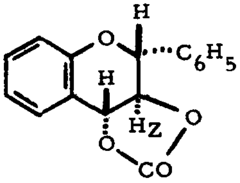
[3] Spectra were determined with a Varian 4300-B spectrometer in each case at 60 mc. Deuteriochloroform was used as solvent with tetramethylsilane as internal reference, solute concentration being in the range 10-15%. X, Y and Z refer to the proton resonances from low to high field respectively.

[4] All resonances expressed in c.p.s. from tetramethylsilane, negative values indicating lower field.

[5] This second and less obvious possibility represents a case which has not been recognized generally and which to our knowledge was first appreciated by Mr. J. Musher (Harvard Seminar, Feb. 1961). It is noteworthy that for this case the Z proton resonance will occur as a triplet even if $J_{XZ} = 0$ and $/\sigma_X-\sigma_Z/ = /\sigma_X-\sigma_Y/$ = a very large value.

attached to adjacent carbons.[6] In the first and only remaining interpretation the H_Z-C-C-H_Y and H_X-C-C-H_Z torsional (dihedral) angles must both be ca. 180°,[6] a condition which unequivocally fixes the stereochemistry of the carbonate m.p. 127-128° as I (plus mirror image):



I

Scale models of I demonstrate that the three trans-hydrogens are rigidly axial in type. The power of NMR as a tool in stereochemical analysis is vividly illustrated by this example in which a single measurement defines clearly the interrelationship of three asymmetric centers.

The dibenzoate m.p. 156-157° which corresponds to the carbonate m.p. 127-128° and the diol m.p. 145° displays quite a different NMR spectrum with each of the three heterocyclic protons appearing individually: a doublet (X) at -403, -397.2 c.p.s., a pseudo-triplet (Y) (whose end-peaks faintly show signs of further splitting) center at -360 c.p.s. with flanks at ca. -366.5 and -353.5 c.p.s., and a doublet (Z) at -332.7 and -325.3 c.p.s. This spectrum indicates a $\underset{X}{\overset{|}{C}}-\underset{Y}{\overset{|}{C}}-\underset{Z}{\overset{|}{C}}$ system with J_{XY} = 5.8 c.p.s. and J_{YZ} = 7.3 c.p.s., clearly consistent with the all-trans hydrogen assignment that follows from I and, moreover, indicating that the strictly axial arrangement of C-H bonds as found in the carbonate I has been somewhat relaxed to permit more nearly normal bond angles and to relieve repulsion between adjacent

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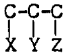
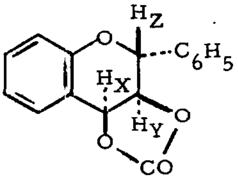
[6] See, for example, H. Conroy in Advances in Organic Chemistry Vol. II, pp. 308-311. Interscience, New York (1960); M. Karplus, J.Chem.Phys. 30, 6 (1959).

benzoyloxy groups.

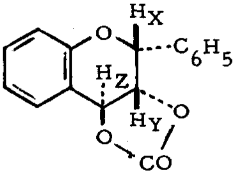
Flavan-3,4-diol carbonate m.p. 157-158°. One of the three heterocyclic protons (X) exhibits resonance as a doublet at -337 and -331 c.p.s., and the remaining two (Y, Z) appear at higher field as a merged multiplet with four distinct peaks at -304.5, -294.5 (shoulder at low-field side), -288.7 (shoulder both sides) and -279 c.p.s. (shoulder at high-field side) (signal ratio ca. 1:3:9:1). The partial overlapping of the Y and Z resonances which causes the appearance of unresolved shoulders on some of the bands complicates the interpretation of the spectrum of Y and Z. A simple analysis proceeds as follows: (1) proton X might be coupled to either Y or Z with a coupling constant of roughly 6 c.p.s., (2) Y and Z are mutually coupled and from the intensity and separation of the two bands at -288.7 and -279 c.p.s. it appears that Z is coupled only with Y and that $J_{YZ} \sim 9$ c.p.s. and (3) from (1) and (2) the proton arrangement can be seen to be



$\underset{X}{C}-\underset{Y}{C}-\underset{Z}{C}$ with $J_{XY} \sim 6$ c.p.s. and $J_{YZ} \sim 9$ c.p.s. for consistency with the observed spectrum. A more refined treatment following the general method of analysis for the ABX system[7] yields $J_{XY} = 6.4$, $J_{YZ} = 9.7$ and $/\sigma_Y - \sigma_Z/ \sim 8$ c.p.s.; in addition the spectra derived by calculation[7] from values close to these are in excellent agreement with that observed. These magnitudes of J_{XY} and J_{XZ} agree best with the assignments of stereoformula II (plus



II



III

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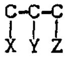
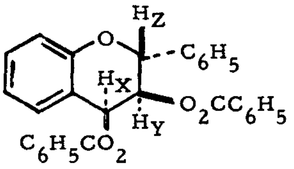
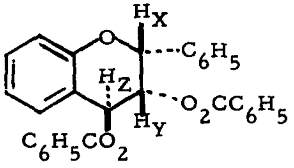
[7] J.A. Pople, W.G. Schneider and H.J. Bernstein, High-resolution Nuclear Magnetic Resonance Chap. 6. McGraw-Hill, New York (1959).

mirror image) for the carbonate m.p. 157-158°, for which the predicted coupling constants are J_{XY} = 7[8] and J_{YZ} = 10 c.p.s.,[6] but do not rigorously exclude the *trans* carbonate III (also less likely on chemical grounds). The alternative *cis* carbonate can be excluded on the basis that neither $J_{2,3}$ nor $J_{3,4}$ could reasonably be greater than 7 c.p.s.

The spectrum of the *dibenzoate* m.p. 121-122°, derived from flavan-3,4-diol m.p. 160° and in the same series with the carbonate m.p. 157-158°, adds strong support to the 3,4-*cis*, 2,3-*trans* arrangement of hydrogen, i.e. IV. The three heterocyclic protons occur as follows: one (X) a doublet at -398 and -401.5 c.p.s., a second (Y) as a quartet with peaks at -360, -356.5, -350 and -346.5 c.p.s. and the third (Z) as a doublet at -343 and -333 c.p.s. Simple analysis indicates the system  $\underset{X}{C}-\underset{Y}{C}-\underset{Z}{C}$ with J_{XY} = 3.5 c.p.s., J_{YZ} = 10 c.p.s. and $/\sigma_Y - \sigma_Z/$ = 11.6 c.p.s. These data are in disagreement with stereoformula V because the expected value of J_{XY} in V ($\sim$ 7 c.p.s.) is much greater than that observed.



IV



V

An independent argument in favor of II over III (or IV over V) is based on chemical shifts expected for these structures since the resonance of H_4 ought to occur at lower fields than the resonance of H_2 for both carbonate and benzoate. A definite proof of chemical shift assignments is desirable and this is contemplated using deuterium labelling.

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[8] P.L. Corio, *Chem.Rev.* **60**, 363 (1960).

The formation of a cyclic carbonate by the _trans_-3,4-diol indicates that the production of such derivatives can no longer be regarded as diagnostic for a _cis_ configuration. Doubt has already been cast on the specificity of such tests.[9] The bearing of this work on the configurations assigned on chemical evidence to flavan-3,4-diols synthesized from 3-hydroxyflavan-4-ones will be discussed in another communication.

A very recent note which appeared after this manuscript had been prepared also deals with stereochemistry and NMR spectra of flavan derivatives.[10] We are unable to ascertain whether our assignments are in agreement with this work because the NMR data cited[10] are not related to specific known substances, i.e. compounds are designated only by name and not by definitive and descriptive properties.

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[9] H. Kwart and G.C. Gatos, _J.Amer.Chem.Soc._ _80_, 881 (1958).

[10] J.W. Clark-Lewis and L.M. Jackman, _Proc.Chem.Soc._ 165 (1961).