HETEROCYCLES, Vol. 7, No. 1, 1977

DETERMINATION OF RING STEREOCHEMISTRY IN A SUBSTITUTED ISOXAZOLIDINE BY ^3J (^{13}C-C-C-^1H) DECOUPLING.

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The use of both ^{13}C n.m.r. and ^1H n.m.r. spectroscopy, together with specific long range carbon-proton decoupling experiments has permitted assignment of stereochemistry in a substituted isoxazolidine.

In a previous paper[1] we reported the application of ^{13}C n.m.r. spectroscopy, in conjunction with ^{13}C-^1H decoupling data, to assign unambiguously the chemical shifts in the p.m.r. spectra of the protons geminal to substituents at C-3, C-4 and C-5 in isoxazolidines (1) and (2), thereby allowing determination of the relative stereochemistry around the heterocyclic ring. The ^{13}C chemical shifts of (1) and (2) were assigned unequivocally by comparison with the data obtained from the analogues (3) and (4). However, the stereochemistry at C-5 in the isoxazolidines (3) and (4) could be discussed only on the basis of the anticipated stereoselectivity of the 1,3-dipolar addition of the nitrone to the alkene, the favoured transition state orientations being those in which repulsive steric interactions between the alkene and the substituent(s) on the nitrone carbon atom are minimised. We now report that C-5 stereochemistry can be determined experimentally using three-bond ^3J (^{13}C-C-C-^1H) values.

The isoxazolidine (3) was synthesised by reaction of the nitrone (5) with methyl methacrylate. Assignment of the signals due to the heterocycle carbon atoms and to the C-5 methyl substituent in the SFORD ^{13}C n.m.r. spectrum was readily made[1] from consideration of the observed multiplicities resulting from one-bond ^{13}C-^{1}H coupling (Table 1, signal multiplicities in parentheses). The C-4 proton of (3) for which $J_{3,4}$ is 8.6 Hz is designated H_A and is *cis* to the C-3 proton,[2] while the geminal C-4 proton, *trans* to the C-3 proton, is labelled H_B.

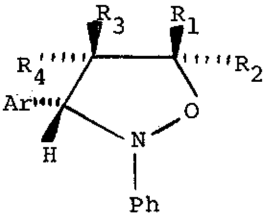
	3-C	4-C	5-C	CH_3-
δ ^{13}C	69.74 (2)	50.00 (3)	83.25 (1)	22.42 (4)
δ ^{1}H	5.10	2.13 H_A 3.30 H_B		1.56
$^{1}J(^{1}H-^{1}H)_{3,4}$	7.6 Hz *trans*, 8.6 Hz *cis*			

Table 1

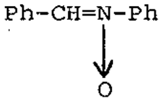
In addition to the one-bond ^{13}C-^{1}H coupling expected for the C-5 methyl substituent, resulting in a quartet, there is a further coupling of 3.90 Hz observed as the result of long-range ^{3}J (^{13}C-C-C-^{1}H) interaction with one of the C-4 protons. Specific irradiation of the signal due to H_A resulted in the disappearance of this fine coupling, whereas irradiation at the resonance frequency of H_B gave no observable effect. It is known[3] that, in general, three-bond carbon-proton coupling constants are smaller than the analogous proton-proton (vicinal) values. Furthermore, there is good correlation between the Karplus equation as applied to vicinal protons and as applied to the ^{13}C-C-C-H system.[4] From a consideration of the possible conformations of the heterocycle, together with the knowledge that the resolution of the spectrometer used (Jeol PFT-FX60, 4K core) does not permit observation of coupling constants of less than 1 Hz, it follows that the 3.90 Hz fine coupling corresponds to interaction of the C-5 methyl group with H_A, the dihedral angle being ca. 0°. The coupling constant resulting from interaction of the C-5 methyl group with H_B, with a dihedral angle of ca. 120°,[5] lies below the resolution of the instrument.

The product (3) of reaction between the nitrone (5) and methyl methacrylate is therefore confirmed as 5-cis-methoxycarbonyl-5-trans-methyl-2,3-diphenylisoxazolidine (stereochemical nomenclature is relative to the C-3 aryl group).

The carbonyl carbon atom of the C-5 methoxycarbonyl substituent is similarly coupled through to both H_A and H_B, and therefore should show corresponding simplifications under the specific proton irradiation experiments discussed above. However, the additional interactions of this carbon atom with both the C-5 methyl group and the ester methoxyl group lead to ten peaks, and the decoupling experiments gave residual patterns which could not be interpreted unambiguously in terms of J values and associated dihedral angles.



	Ar	R_1	R_2	R_3	R_4
(1)	2,5-dimethoxyphenyl	COOMe	H	H	COOMe
(2)	2,5-dimethoxyphenyl	H	COOMe	COOMe	H
(3)	phenyl	Me	COOMe	H_A	H_B
(4)	2,5-dimethoxyphenyl	Me	COOMe	H	H

(5) 

$\text{Ph-CH=}\underset{\overset{\downarrow}{\text{O}}}{\text{N}}\text{-Ph}$

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Received, 22nd June, 1977