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STEREOCHEMISTRY AND P.M.R. SPECTRA OF β-LACTAMS

K.D. Barrow and T.M. Spotswood
Department of Organic Chemistry, University of Adelaide,
Adelaide, South Australia.

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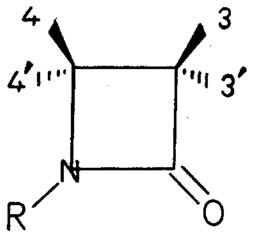
The synthesis and P.M.R. spectra of some 1-phenyl-3,4-disubstituted β-lactams has recently been reported (1) and marked magnetic non-equivalence of benzylic CH_2 protons in a number of N-benzyl cyclic amides has been recorded (2,3). We now report the P.M.R. spectra of fourteen β-lactams (Fig. 1) which show a number of interesting spectral features.

In these compounds (Table 1) $J_{cis} > J_{trans}$, and these vicinal coupling constants are of the same sign and opposite in sign to the two geminal couplings $J_{33'}$ and $J_{44'}$. Comparatively large cross-ring couplings between N-substituents and H_3 or $H_{3'}$ are observed; and in the N-benzyl compounds, marked magnetic non-equivalence of the benzylic protons and stereospecific coupling to the C-3 protons in 4-substituted compounds suggests highly preferred conformations of the N-benzyl grouping.

We assume in the following discussion that the β-lactam ring is planar, but that the N-substituent is not coplanar with the ring atoms, a conclusion which is almost inescapable on the spectral evidence presented. Chemical shift data are summarised in Table 1, coupling constants in Table 2, and long-range coupling constants in Table 3.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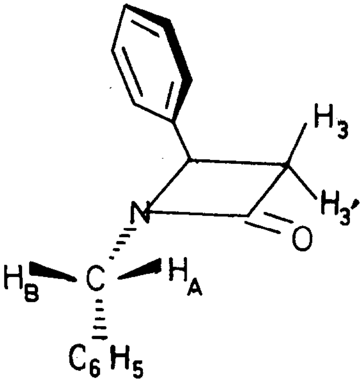
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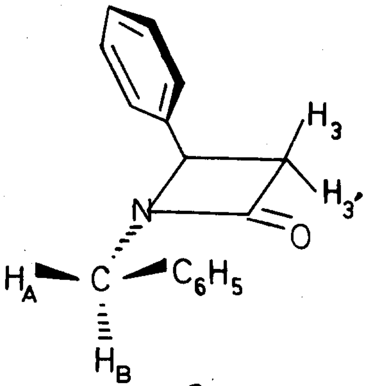
C$_6$H$_5$

2A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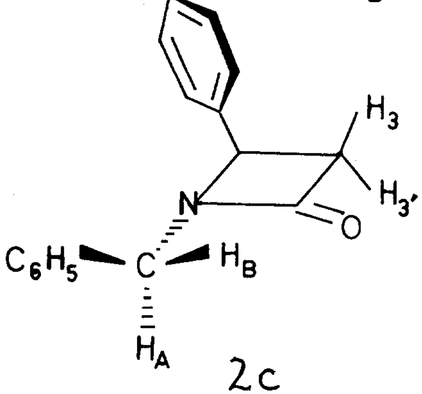
2B


H$_3$
H$_3$'
N
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C$_6$H$_5$
C
H$_B$
H$_A$

2C

TABLE 1

Chemical Shifts (ppm.) Relative to Tetramethylsilane (internal)

Compound	Substituent				
	3	3'	4	4'	R
I	H: 3.08	H: 3.08	H: 3.42	H: 3.42	H: 7.0
II	H: 2.87	H: 2.87	H: 3.05	H: 3.05	CH_2 : 4.28 C_6H_5: 7.27
III	H: 3.08	H: 3.08	H: 3.57	H: 3.57	C_6H_5: 7.27
IV	C_6H_5: 7.27	H: 4.39	H: 3.27	H: 3.66	H: 6.83
V	H: 2.81	H: 3.63	C_6H_5: 7.26	H: 4.70	H: 6.80
VI	H: 2.69	H: 3.33	C_6H_5: 7.26	H: 4.45	CH_3: 2.70
VII	CH_3: 0.76	H: 3.48	C_6H_5: 7.23	H: 4.62	CH_3: 2.79
VIII	H: 2.96	CH_3: 1.35	C_6H_5: 7.23	H: 4.00	CH_3: 2.71
IX	C_6H_5: 7.23	H: 4.36	H: 3.18	H: 3.56	CH_2: 4.45 C_6H_5: 7.27
X	H: 2.80	H: 3.26	C_6H_5: 7.26	H: 4.35	CH_2 : 3.73 4.74 C_6H_5: 7.26
XI	CH_3: 1.27	H: 3.00	H: 2.68	H: 3.20	CH_2: 4.40 C_6H_5: 7.27
XII	H: 2.42	H: 2.94	CH_3: 1.18	H: 3.49	CH_2 : 4.04 4.46 C_6H_5: 7.25
XIII	CH_3: 0.74	H: 3.46	C_6H_5: 7.23	H: 4.59	CH_2 : 3.89 4.88 C_6H_5: 7.24
XIV	H: 3.04	CH_3: 1.24	C_6H_5: 7.25	H: 3.96	CH_2 : 3.74 4.81 C_6H_5: 7.24

TABLE 2

Coupling Constants in cycles/sec.

Compound	$J_{33'}$	$J_{44'}$	J_{34} cis	J_{34} trans	J_{gem} NCH_2	CH_3-CH
IV	-	-5.6	5.9	2.6	-	-
V	-15.0	-	5.4	2.7	-	-
VI	-14.2	-	5.0	2.4	-	-
VII	-	-	5.5	-	-	7.3
VIII	-	-	-	2.2	-	7.2
IX	-	-5.5	5.5	2.5	not obs.	-
X	-14.7	-	5.1	2.2	-14.9	-
XI	-	-5.5	5.1	2.8	not obs.	7.3
XII	-14.3	-	4.9	2.2	-15.3	5.9
XIII	-	-	5.2	-	-14.6	7.3
XIV	-	-	-	2.2	-14.8	7.3

TABLE 3

Long-range Coupling Constants in cycles/sec.

Compound	H_3	$H_{3'}$	Coupled Group
IV		1.1	NH
V	0.9	2.4	NH
VI	0.90	0.46	NCH_3
VII		0.40	NCH_3
VIII	0.70		NCH_3
IX		0.5	$NCH_2-C_6H_5$
X	0.65	0.30	$NCH_2-C_6H_5$ *
XI	not obs.	not obs.	†
XII	0.6	0.35	$NCH_2-C_6H_5$ *
XIII	0.8,0.3	-	$NCH_2-C_6H_5$ *
XIV	-	0.4	$NCH_2-C_6H_5$ *

* Major long-range coupling to the high field benzylic proton

† Long-range coupling could not be clearly distinguished.

Chemical Shifts (Table 1)

A phenyl or methyl group in positions 3- or 4- of the β-lactam ring induces marked magnetic non-equivalence in the neighbouring CH_2 group, the proton cis to the substituent being shifted to higher field and that trans to the substituent to lower field. The proton directly attached to the ring carbon bearing the substituent also shows a paramagnetic shift to lower field. For example, in compound IV, $\delta H_{3'} = 4.39$, $\delta H_4 = 3.27$ and $\delta H_{4'} = 3.66$, while in V, $\delta H_3 = 2.81$, $\delta H_{3'} = 3.63$ and $\delta H_{4'} = 4.70$; and in the parent compound I, $\delta H_3 = \delta H_{3'} = 3.08$ and $\delta H_4 = \delta H_{4'} = 3.42$. Similarly, in compounds VII, VIII, XIII, and XIV, the methyl substituent cis to the aromatic ring is found approximately 0.5 ppm. to high field of the trans methyl group. The asymmetry induced by a methyl group is unexpectedly large. The separation in compounds XI and XII of ca. 0.5 ppm. between the resonances of the protons cis and trans to the methyl group is greater than that in the corresponding phenyl compounds, IX and X.

In the phenyl compounds, this asymmetry is ascribed to a preferred conformation of the phenyl group in which the plane of the aromatic ring is approximately at right angles to the plane of the β-lactam ring in its equilibrium position. Non-bonded interactions will then be at a minimum and a proton cis to the aromatic ring will be just within the shielding region of the aromatic ring current (4) while the trans proton lies well within the deshielding region. The protons of a methyl group cis to the aromatic ring will then lie well within the shielding region, and a trans methyl group within the deshielding region. Thus a paramagnetic shift of the proton trans to a phenyl group of 0.24-0.47 ppm. is observed in the pairs of compounds I and IV, I and V, II and IX, II and X, and XIII and XIV, while the diamagnetic shift of the proton cis to the phenyl group is rather smaller and variable in the pairs II and IV, I and V, and II and X, and is apparently paramagnetic in the pairs II and IX, and XI and XIV. The anomalous behaviour of the last two pairs we ascribe to changes in conformational preferences of the

N-benzyl group in the ring-substituted compounds (see below). The shielding effect of the N-benzyl group is apparent from a comparison of the chemical shifts of the ring protons in compounds I, II, and III, and where the benzyl group is confined mainly to a position on one side of the plane of the β-lactam ring anomalous shifts are to be expected.

The proton attached directly to the carbon atom bearing the phenyl substituent shows a characteristic paramagnetic shift of 1.27-1.53 ppm.

A methyl group causes a more pronounced diamagnetic shift in a cis proton of 0.41-0.46 ppm. in the pairs of compounds VI and VIII, II and XI, II and XII, and X and XIV, and a smaller paramagnetic shift in the trans proton of 0.11-0.24 ppm. The magnitude and direction of the effect is consistent with the value of 10.0×10^{-6} cm^3 $mole^{-1}$ for the anisotropy of the carbon-carbon single bond derived by Reddy and Goldstein (5) but seems to be too large to be explained by the smaller values of the anisotropy reported by other workers (6).

Coupling Constants (Table 2)

Coupling between cis protons (4.9-5.9 cps.) and trans protons (2.2-2.8 cps.) in the β-lactam ring is similar in magnitude to values reported for the cyclobutanone system (7) and the relative magnitude of the coupling constants is in agreement with the predictions of the Karplus equation (8) although it is obvious that the same constants in the $\cos^2\varphi$ relationship do not apply to the strained β-lactam ring, where the dihedral angles should be close to 0° and 120° for the cis and trans configurations.

The variation in the gem coupling constants is striking. $J_{33'}$ (-14.3 to -15.0 cps.) is in the normal range for geminal protons α to an unsaturated centre (9) while $J_{44'}$ (-4.9 to -5.9 cps.) is considerably smaller than expected and close to values reported for substituted cyclopropanes (10). This effect cannot be explained by the presence of the electronegative nitrogen atom since the N-benzyl grouping shows a normal geminal coupling (-14.6 to -15.3 cps.), leading to the interesting speculation that ring strain in the β-lactam ring may be accommodated mainly by rehybridization of the 4-carbon atom. A smaller but similar effect is apparent in the CH_3-CH coupling constant which is 5.9 cps. at the 4-position but 7.2-7.3 cps. at the 3-position. Further work on ^{13}C-H coupling constants should clarify this matter and will be reported at a later date.

The vicinal coupling constants have been shows to be of the same sign (assumed positive) and opposite in sign to the two geminal coupling constants by field-sweep double resonance experiments.

Magnetic Non-equivalence of Benzylic Protons

From Tables 1 and 2 it may be seen that a 4-substituent is required for observable magnetic non-equivalence of the N-benzylic protons. A phenyl group in this position results in a difference in chemical shift of about 1 ppm. in the benzylic protons, while the methyl group in XII causes a difference of 0.61 ppm. If we assume that the N-benzyl group lies on the opposite side of the β-lactam ring to the 4-substituent it is apparent that conformations 2A and 2B will be preferred to 2C where there is strong interaction between the aromatic ring of the benzyl group and the 4-substituent. The proton H_A in conformation 2A will then be strongly deshielded by the carbonyl group relative to proton H_B while both protons would probably be slightly deshielded by the ring-current of the aromatic ring in the 4-position. In conformation 2B, H_B and H_A should be approximately equally deshielded by the carbonyl group and by the aromatic ring in the 4-position. Further evidence for these two conformations comes from a consideration of stereospecific coupling of the 3-protons to the high-field benzylic proton H_B discussed in the following section.

Long-range Coupling and Conformation (Table 3)

Long-range coupling between the N-substituent (H, CH_3, $CH_2C_6H_5$) and protons in the 3 and 3' positions has been established by double resonance experiments. The coupling is largest in compounds IV and V (coupling over 4 bonds) but resolvable 5-bond coupling was observed as first-order splittings of the ring proton multiplets in all cases cited. A NH substituent split each peak into a doublet, a N-CH_3 substituent gave a quartet, and a N-benzyl substituent gave either a triplet or a doublet of doublets. In no case was coupling to the 4 and 4' protons observed, suggesting that the coupling is transmitted *via* the sp^2 carbon of the carbonyl group, or possibly by direct orbital overlap.

The coupling is highly stereospecific. The greatest coupling is to the proton *cis* to the ring substituent in the 4-position except in compound V and there is a smaller, resolvable coupling to the *trans* proton. This implies that the N-substituent cannot lie in the plane of the β-lactam ring, but that the hybridization of the ring nitrogen atom must be somewhere between sp^3 and sp^2 with the N-substituent lying out of the ring plane. The magnitude of the 4-bond coupling in N-H compounds is remarkably similar to the cis and trans four-bond coupling observed in cyclobutanones (7). With the N-substituent trans to the 4-substituent, or to the 3-substituent in 4-unsubstituted compounds, the pathway of greatest long-range coupling is transoid. Similarly in the N-benzyl compounds, stereospecific coupling to H_B, the high field benzylic proton, follows an extended transoid arrangement in conformation 2B. In conformation 2A, H_A and H_B should be equally coupled to the 3 and 3' protons. Compound V shows anomalous behaviour with the greatest coupling to the proton trans to the ring substituent. We suggest that the steric requirements of the solvated nitrogen lone pair are greater than those of the hydrogen atom and that the lone pair is trans to the 4-substituent in the preferred conformation leading to the transoid pathway for the larger long-range coupling.

P.M.R. Spectra

All P.M.R. spectra were determined in 10% $CDCl_3$ solution on a Varian D.P. 60 spectrometer and calibrated by the side-band technique using a Muirhead-Wigan D 890 A audio-oscillator. Double resonance experiments were made by operating in the lower side-band mode of the V 3521 integrator. Chemical shifts and coupling constants were obtained by analysis of the AB and ABX systems and are accurate to 0.005 ppm. and 0.1 cps. respectively. Long-range coupling constants were obtained by first-order analysis. Compounds I, II, and III gave A_2B_2 or AA'BB' spectra and unequivocal values of the coupling constants have not yet been obtained. Chemical shifts for these compounds are accurate to 0.01 ppm.

All compounds were prepared by established literature methods.

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