^{1}H NMR Long-Range Coupling in the Assignment of Stereochemistry to 4-Imidazolidinones

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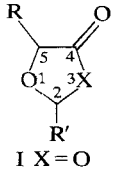
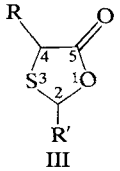
Long-range couplings were observed between protons attached to C-2 and C-5 of the 4-imidazolidinone ring. Since $^4J(25)$ has a measurable value only for a *trans* arrangement of H-2 and H-5, this coupling can be utilized as an easy method of identification of 4-imidazolidinone stereoisomers.

INTRODUCTION

Numerous examples of long-range proton–proton couplings have been shown to exist in heterocyclic systems.[1,2] Some of these interactions are small, but may be useful for structural determinations. Recently, there has been considerable interest in systems I–III derived from α-hydroxy and α-thiolo acids, which show long-range coupling between the protons at C-2 and C-5 for I–II[3–5] and, analogously, between the C-2

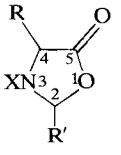


I X=O
II X=NH

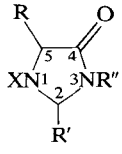


III

and C-4 protons for III.[6] However, the small differences between the magnitudes of $^4J(cis)$ and $^4J(trans)$ do not allow easy differentiation between the *cis* and *trans* diastereoisomers of these compounds. In the course of stereochemical investigations of lactones and lactams,[4] the author studied the related systems IV and V, derived from α-amino acids.



IV



V

A similar long-range interaction based on the dual-path mechanism[2,5] is expected for these compounds. Although 5-oxazolidinones (IV) do not show any measurable $^4J(24)$ couplings,[7] 4-imidazolidinones (V) exhibit large $^4J(25)$ values.

This paper reports studies on 4-imidazolidinones and the applications of $^4J(25)$ values for stereochemical assignments.

RESULTS AND DISCUSSION

Several 4-imidazolidinones were obtained by acid-catalysed reaction of the amides of *N*-acylamino acids with carbonyl compounds. The diastereoisomeric products were separated by fractional crystallization and/or column chromatography. The ^{1}H NMR data of compounds V are collected in Table 1.

Inspection of the spectra of 5-substituted imidazolidinones **1–4** and **9–11** shows that the C-2 methylene protons are non-equivalent and only one half of their AB quartets is split by coupling to the proton at C-5 (Fig. 1). In addition, the spectrum of the 2-substituted compound **5** exhibits an AB system from the C-5 methylene protons, where one of these is coupled to the C-2 proton.

4-Imidazolidinones are the heterocyclic analogues of γ-lactams and a similar geometry is expected for the five-membered ring.[8] The envelope conformation is preferred, with the amide group, C-5 and C-2 in a planar arrangement and N-1 deviating from the ring plane. The 2- and 5-substituents occupy axial positions, which diminishes unfavourable steric interaction with the bulky 1-acyl group for the 5- substituent and with the 1- and 3-groups for the 2-substituent (see Scheme 1).

This conformational behaviour is in agreement with the non-equivalence of the C-2 or C-5 methylene protons. As a result of the deshielding effect of the sulphonamide group, the signals of the equatorial hydrogens are observed at lower field. Since long-range coupling is observed only for the higher field half of the AB systems, it is clear that this effect is characteristic of a *trans* arrangement of H-2 and H-5.

Further confirmation for this assignment is given by the spectra of the 5-benzyl-substituted compounds **4** (Fig. 1) and **10**. The axial C-2 proton, for which a $^4J(25)$ is observed, is shifted approximately 1 ppm upfield in comparison with alkyl-substituted compounds. This effect can be attributed to the formation of a folded conformation in which the phenyl ring lies directly over the imidazolidinone ring, causing anisotropic shielding of the nearby H-2 which is *trans*-oriented to H-5 (Scheme 2). Such folding is a common

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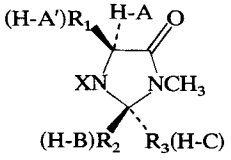
Table 1. ^{1}H NMR data for 4-imidazolidinones[a]



Compound	R_1	R_2	R_3	X	δH-A	δH-B	δH-C	J(BC)	J(AB)
1	CH_3	H	H	CH_3SO_2	4.05	4.62	4.70	6.0	1.8
2	$(CH_3)_2CH$	H	H	CH_3SO_2	3.91	4.53	4.72	7.4	1.4
3	C_6H_5	H	H	CH_3SO_2	5.13	4.82	5.04	5.9	2.3
4	$C_6H_5CH_2$	H	H	CH_3SO_2	4.36	3.66	4.54	7.0	1.8
5	H	H	C_6H_5	CH_3SO_2	4.25, 4.01[b]	5.87	—	15.2[c]	2.1
cis-**6a**	CH_3	CH_3	H	CH_3SO_2	4.03	—	4.95	—	
trans-**6b**	CH_3	H	CH_3	CH_3SO_2	4.06	5.00	—	—	2.3
cis-**7a**	C_6H_5	C_6H_5	H	CH_3SO_2	5.40	—	6.07	—	
trans-**7b**	C_6H_5	H	C_6H_5	CH_3SO_2	5.17	6.00	—	—	2.4
cis-**8a**	$(CH_3)_2CH$	C_6H_5	H	CH_3SO_2	4.20	—	5.84	—	
trans-**8b**	$(CH_3)_2CH$	H	C_6H_5	CH_3SO_2	4.06	5.77	—	—	2.6
9	CH_3	H	H	$C_6H_5CH_2OCO$	4.16	4.65	4.71	—	1.8
10	$C_6H_5CH_2$	H	H	$C_6H_5CH_2OCO$	4.36	3.55	4.50	5.6	2.0
11[d]	$C_6H_5CH_2$	H	H	H	3.49	3.80	4.06	6.2	0.9

[a] Recorded in $CDCl_3$ solution unless indicated otherwise; δ in ppm; *J* in Hz.
[b] δH-A and δH-A'.
[c] *J*(AA').
[d] In CCl_4 solution.

feature of benzyl-substituted heterocycles, such as 2,5-piperazinediones,[9] hydantoins[10] and 4-oxazolidinones,[4] and is the result of an interaction between the permanent dipole of the heterocyclic moiety and the induced dipole in the phenyl ring.

The ^4J(*trans*) value is large and varies between 1.4 and 2.6 Hz; ^4J(*cis*), however, cannot be directly observed in the spectra. Attempts were made to measure ^4J(*cis*) by decoupling experiments. In the case of *cis*-**7a** and *cis*-**8a** the irradiation of H-2 produced a significant decrease in the line width of the corresponding *cis*-H-5 signal, and ^4J(*cis*) can be approximately estimated as 0.6 Hz. This large difference between the ^4J(*cis*) and ^4J(*trans*) values can be applied as an easy means for differentiating between the *cis* and *trans* diastereoisomers of 1-acyl-4-imidazolidinones, as shown by each pair of compounds **6–8**. This is a particularly fortunate situation in view of the fact that the difference between the chemical shifts of the diastereoisomeric protons is very small and that configurational assignments based on other methods are difficult.

The effect of N-1-acyl substitution on the magnitude of ^4J(25) has also been considered. Compound **10** was studied which, after *N*-benzyloxycarbonyl group cleavage, yields the 4-imidazolidinone **11**. The ^{1}H NMR spectrum of **11** shows that despite the absence of a 1-acyl substituent, the C-2 methylene protons are still non-equivalent as a result of the above-mentioned shielding effect of the phenyl ring and, moreover, *both* ^4J(*cis*) and ^4J(*trans*) can be directly observed (Fig. 2). The magnitudes of these coupling constants are comparable and equal 0.7 and 0.9 Hz, respectively. This result is surprising at first sight; however, it must be remembered that the removal of the 1-acyl group causes a decrease in the electronegativity of N-1, which affects the magnitude of the coupling constants. The C-4—N-3 linkage in imidazolidinones, as in other amides, has partial double-bond character, and the observed changes in the ^4J(*cis*) and ^4J(*trans*) values can be tentatively explained on the basis of the double-path mechanism of coupling of Barfield *et al.*[2] According to this analysis, the introduction of an electron-withdrawing group should lead to less positive values of the *cis* and more positive values of the *trans* coupling constants in the studied heterocycles.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian EM-360 A (60 MHz) spectrometer, as *ca* 5% solutions, using TMS as internal reference. IR spectra were measured with a Zeiss IR-10 spectrometer. The syntheses of **1–4**, **6** and **9–11** will be published elsewhere.[7]

N-Methylsulphonyl-DL-α-phenylglycine (12)

This compound was prepared by acylation of DL-phenylglycine with methanesulphonyl chloride; m.p. 115–116 °C (chloroform). Found: C, 47.01; H, 4.88; N, 6.02; $C_9H_{11}NO_4S$ requires C, 47.17; H, 4.84; N, 6.11%.

N-Methylsulphonyl-DL-α-phenylglycine-*N*-methylamide (13)

12 (2.0 g) was dissolved in methanol (100 ml) and thionyl chloride (0.5 ml) was added. After standing

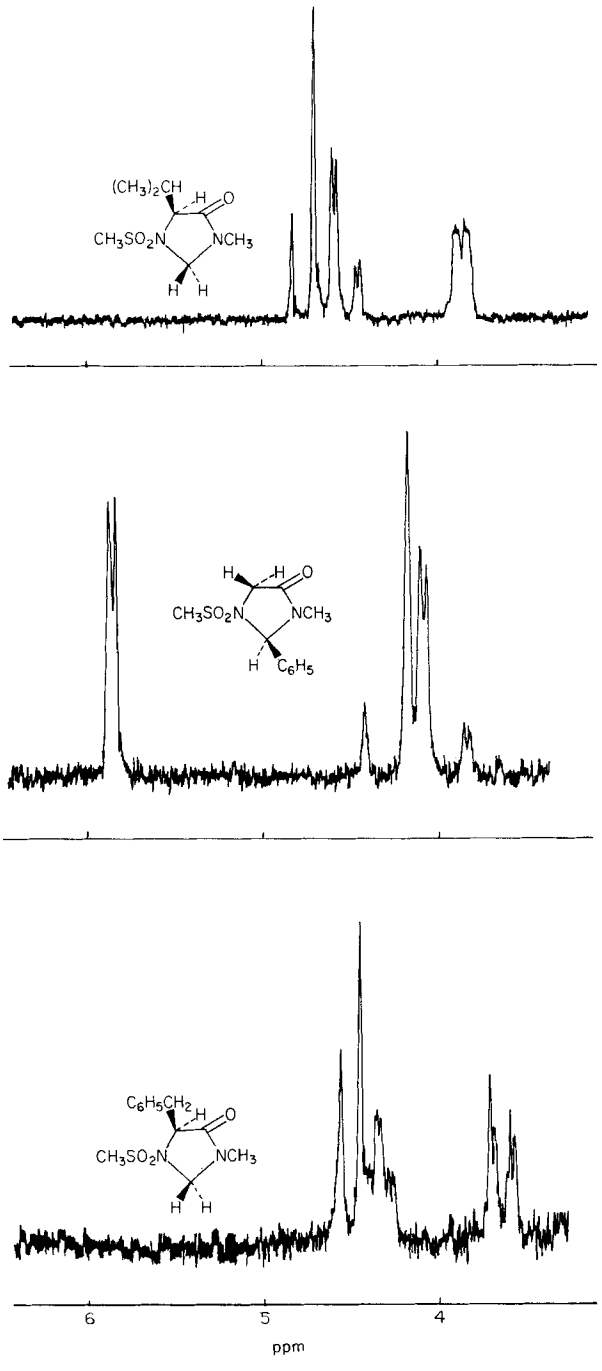
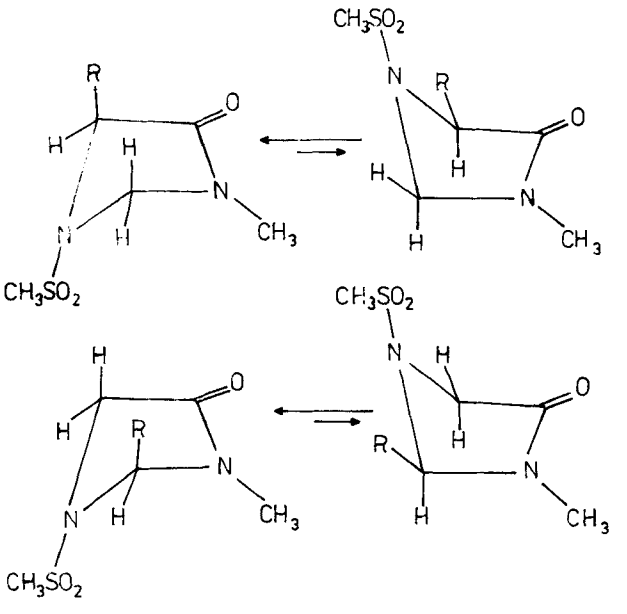
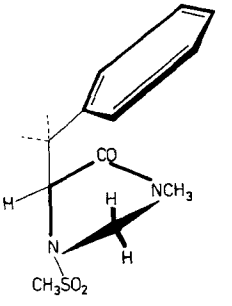


Figure 1. 60 MHz ^{1}H NMR spectra (C-2 and C-5 protons) of 4-imidazolidinones **2**, **5** and **4** in $CDCl_3$ solution.



Scheme 1



Scheme 2

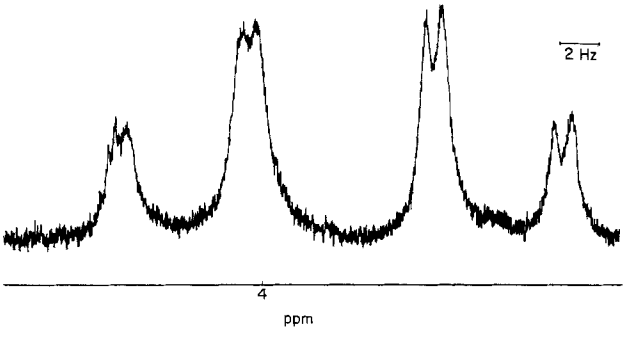


Figure 2. 60 MHz ^{1}H NMR signal of 5-benzyl-3-methyl-4-imidazolidinone (**11**) (C-2 methylene proton signals) in CCl_4 solution.

overnight the methanol was evaporated at reduced pressure, the residue was dissolved in diethyl ether, washed with saturated sodium hydrogen carbonate solution, dried and evaporated. The resulting ester was aminolized with a 33% solution of methylamine in ethanol (5 ml) for 12 h. The excess of methylamine and solvent were evaporated and the product was crystallized from ethyl acetate–hexane; yield 1.5 g; m.p. 168–169 °C. ^{1}H NMR (δ, DMSO-d_6): 8.1 (q, 1H, CONH), 7.79 (br, 1H, SO_2NH), 7.3 (m, 5H, C_6H_5), 4.91 (s, 1H, CHCO), 2.63 (s, 3H, CH_3SO_2) and 2.53 (d, 3H, $NHCH_3$). Found: N, 11.60; $C_{10}H_{14}N_2O_3S$ requires N, 11.56%.

N-Methylsulphonyl-DL-valine-*N*-methylamide (14)

This compound was obtained by a similar procedure as to that used for **13**; m.p. 171–172 °C. ^{1}H NMR (δ, DMSO-d_6): 7.93 (q, 1H, CONH), 7.0 (br, 1H, SO_2NH), 3.48 (d, 1H, CHCO), 2.78 (s, 3H, SO_2CH_3), 2.59 (d, 3H, $NHCH_3$), 1.87 [sep, 1H, $CH(CH_3)_2$] and 0.83 [d, 6H, $CH(CH_3)_2$]. Found: N, 13.51; $C_7H_{16}N_2O_3S$ requires N, 13.45%.

N-Methylsulphonylglycine-*N*-methylamide (15)

This was obtained by a similar procedure as that used for **13**; m.p. 83–85 °C. ^{1}H NMR (δ, acetone-d_6): 3.23 (s, 2H, CH_2), 2.43 (s, 3H, CH_3SO_2) and 2.23 (s, 3H, CH_3NH). Found: N, 16.72; $C_4H_{10}N_2O_3S$ requires N, 16.86%.

1-Methylsulphonyl-3-methyl-2-phenyl-4-imidazolidinone (5)

The amide **15** (1.0 g), benzaldehyde (3.0 ml) and *p*-toluenesulphonic acid (0.1 g) were refluxed in toluene (100 ml) for 3 h. Water was trapped in a Dean–Stark apparatus. After washing with saturated $NaHCO_3$, the reaction mixture was dried and evaporated at reduced pressure. The product crystallized after the addition of hexane; m.p. 159 °C. IR (KBr): 1712, 1700 and 1354. Found: C, 52.04; H, 5.49; N, 11,03; $C_{11}H_{14}N_2O_3S$ requires C, 51.97; H, 5.55; N, 11.02%.

cis- and *trans*-1-Methylsulphonyl-3-methyl-2,5-diphenyl-4-imidazolidinones, 7a and 7b, respectively

These compounds were obtained from amide **13** (2.5 g) and benzaldehyde (5 ml) in the presence of *p*-toluenesulphonic acid in a similar manner to **8a** and **8b**. After concentration at reduced pressure, *trans*-**7b** crystallized from the reaction mixture. This was filtered and recrystallized from toluene to obtain 0.55 g of **7b**; m.p. 253–254 °C. IR (KBr): 1725, 1718 and 1350. Found: C, 61.89; H, 5.56; N, 8.47; $C_{17}H_{18}N_2O_3S$ requires C, 61.81; H, 5.49; N, 8.48%. The filtrate was evaporated and after the addition of hexane *cis*-**7a** crystallized with a molecule of toluene. This was recrystallized from toluene to obtain 1.5 g of *cis*-**7a**; m.p. 150–151 °C. IR (KBr): 1715, 1700 and 1345. Found: C, 65.51; H, 5.81; N, 7.27; $C_{17}H_{18}N_2O_3S\cdot\frac{1}{2}C_6H_5CH_3$ requires C, 65.40; H, 5.89; N, 7.44%.

cis- and *trans*-5-Isopropyl-1-methylsulphonyl-3-methyl-2-phenyl-4-imidazolidinones, 8a and 8b, respectively.

Amide **14** (2.0 g), benzaldehyde (5 ml) and *p*-toluenesulphonic acid (0.1 g) were refluxed in toluene (150 ml) for 4 h. The reaction mixture was worked up as for **3**. After adding hexane, *trans*-**8b** crystallized. This was filtered and recrystallized from toluene–hexane to obtain 0.7 g of **8b**; m.p. 183–184 °C. IR (KBr): 1712, 1700, 1357 and 1335. Found: C, 56.83; H, 6.81; N, 9.55; $C_{19}H_{20}N_2O_3S$ requires C, 56.75; H, 6.80; N, 9.45%. The filtrate was evaporated at reduced pressure to remove the excess benzaldehyde, and after adding hexane *cis*-**8a** crystallized; m.p. 122 °C. IR (KBr): 1715, 1700 and 1355. Found: C, 56.77; H, 6.87; N, 9.40; $C_{14}H_{20}N_2O_3S$ requires C, 56.75; H, 6.80; N, 9.45%.

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