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STRUCTURAL REQUIREMENTS IN CHIRAL DIPHOSPHINE-RHODIUM COMPLEXES. II[1] N.M.R. DETERMINATION OF E,Z-GEOMETRY IN PROCHIRAL SUBSTRATES USED IN ASYMMETRIC HYDROGENATION REACTIONS α-ACETAMIDOCINNAMIC ACIDS, ESTERS, AND PARENT AZLACTONES

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Summary. Using n.m.r the configuration of the stable 4-benzylidene-2-methyl-2-oxazolin-5-one, substituted derivatives, and the corresponding acids and esters derived from the parent stable azlactones were all found to be of Z-stereochemistry.

Substituted and unsubstituted α-acetamidocinnamic acids have been investigated as prochiral substrates in asymmetric hydrogenation reactions. High optical yields (80-96 % ee) of N-acetyl-phenylalanine and its derivatives have been obtained utilizing homogeneous rhodium complexes containing chiral mono- or diphosphines [2-4] Yet mechanistic interpretation of these studies is hampered by lack of information regarding the olefinic bond geometry in the α-acetamidocinnamic acid and ester prochiral substrates

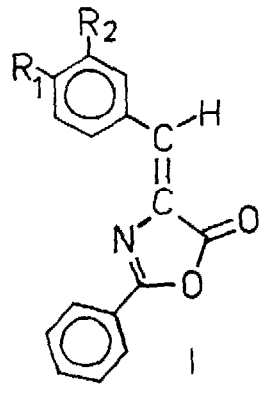
The E,Z-geometry of analogous α-benzamidocinnamic acids has been determined by n m.r. studies [5] Thus, the stable isomers of 4-benzylidene-2-phenyl-2-oxazolin-5-one (Ia) and 4-(3',4'-dimethoxybenzylidene)-2-phenyl-2-oxazolin-5-one (Ib) were assigned Z-stereochemistry while the labile azlactones are the corresponding E-isomers. Since solvolysis of the azlactones proceed with retention of configuration,[5-9] the configurational assignment of the corresponding acids and esters is that of the parent azlactones.

However, the steric and electronic nature of the 2-methyl group in the parent and aryl-substituted 4-benzylidene-2-methyl-2-oxazolin-5-ones (II) differs from that of the 2-phenyl group in analogues I. Therefore, the configurational constraints causing the stable 2-phenyl azlactones (I) to be Z, need not be the same for the 2-methyl azlactones (II)

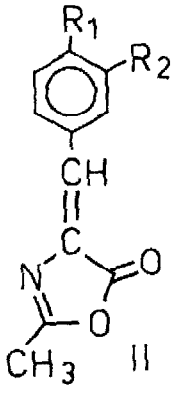
The stable isomers of the 2-methyl azlactones (II) were all synthesized by known chemical methods.[10-13] Using a modified n.m.r approach based upon the work of Nauta and coworkers,[5] we have determined that the stereochemistry of the stable isomers of the 2-methyl azlactones (II) and their solvolysis products is Z also (as in the stable 2-phenyl azlactones (I)). The n.m r spectra of the compounds II-IV are listed in tables 1 and 2.

From table 1 we can see that the stable 2-methyl azlactones (II) all have an H_β proton signal at δ 7.97±0.05 δ. If this signal can be unambiguously assigned as that of the E- or Z-proton for any one of the azlactones in this table, then it is reasonable to assume that the configuration of the other azlactones will also be known

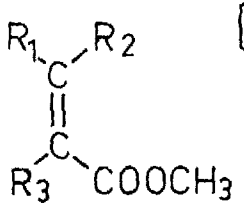
From table 2 the n.m r. spectrum of methyl α-acetamidoacrylate (IIIb) shows two olefinic protons at 6.47 δ and 5.79 δ, compared to the parent methyl acrylate (IIIa) signals of H_1 = 5.82 δ



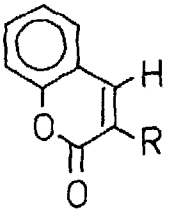
I



II



III



IV

Ia $R_1 = R_2 = H$
Ib $R_1 = R_2 = OCH_3$

IIa $R_1 = R_2 = H$
IIb R_1 = OAc, $R_2 = H$
IIc R_1 = OAc, $R_2 = OCH_3$
IId $R_1 = R_2 = OCH_3$
IIe R_1 and $R_2 = OCH_2O$

IIIa $R_1 = R_2 = R_3 = H$
IIIb $R_1 = R_2 = H$, $R_3 = NHCOCH_3$
IIIc $R_1 = p\text{-}AcOC_6H_4$, $R_2 = H$, $R_3 = NHCOCH_3$
IIId $R_1 = H$, $R_2 = p\text{-}AcOC_6H_4$, $R_3 = NHCOCH_3$
IIIe $R_1 = C_6H_5$, $R_2 = R_3 = H$
IIIf $R_1 = R_3 = H$, $R_2 = C_6H_5$

IVa R = H
IVb R = NHCOCH$_3$

(trans to $COOCH_3$ group) and H_2 = 6.38 δ (cis to $COOCH_3$ group). There are two ways to estimate the effect of an α-acetamido group upon the chemical shift of the H_β protons, H_1 and H_2

METHOD 1 Arbitrarily assign the 6.47 δ and 5 79 δ signals to H_1 and H_2, respectively Thus, when compared to the parent compound IIIa, the α-acetamido group has caused a downfield shift of +0.65 δ to proton H_1 and an upfield shift of -0.59 δ to proton H_2

METHOD 2 Reverse the assignment of the 6 47 δ and 5 79 δ signals so that they are now those of H_2 and H_1, respectively Thus, when compared to the parent compound IIIa, the α-acetamido group has caused an upfield shift of -0.03 δ to proton H_1 and a downfield shift of +0.09 δ to proton H_2.

Comparison of the H(4) signal in coumarin (IVa) and 3-acetamidocoumarin (IVb) shows that the 3-acetamido group causes a downfield shift of +0.88 δ to the cis-proton H(4). Therefore, method 1 seems to provide a more reasonable assessment of the effect of the α-acetamido group upon the cis-proton H_1 and the trans-proton H_2 (cis and trans designation relative to the α-acetamido group in IIIb)

Comparison of the Z- and E-methyl cinnamates (IIIe and IIIf) with that of the parent compound IIIa, shows that the substitution of a phenyl group has resulted in a downfield shift of +1.33 δ and +1.09 δ to the H_β protons in IIIe and IIIf, respectively. Assuming the substituent effects of the p-acetoxyphenyl group to be similar to that of the phenyl group itself, the chemical shifts of the H_β proton in the Z-methyl α-acetamido-p-acetoxycinnamate (IIIc) and in the E-isomer, IIId, can now be estimated.

Table 1 N.M.R. CHEMICAL SHIFTS OF THE STABLE 2-METHYL AZLACTONES (II)[a]

Compd.	mp[b]	H_β	H(2)	H(5)	H(6)	$CH_3C=N$	other
IIa	147-148[c]	7 02(S)	7 94±0.06(M)	7.31±0 05(M)	7.94±0.06(M)	2.36(S)	-
IIb	136-138[d]	6.98(S)	7 98(D) (J = 8 5)	7 05(D) (J = 8 5)	7 98(D) (J = 8 5)	2.34(S)	2.26(S) (CH_3CO)
IIc	143-145[e]	6 95(S)	7.72(D) ($J_{2,6}$ = 2)	6 95(D) ($J_{5,6}$ = 8)	7 38(D of D) ($J_{2,6}$ = 2) ($J_{5,6}$ = 8)	2 33(S)	2.27(S) (CH_3CO) 3 82(S) (CH_3OPh)
IId	165-166[f]	6.96(S)	7 77(D) ($J_{2,6}$ = 2)	6 79(D) ($J_{5,6}$ = 8)	7 38(D of D) ($J_{2,6}$ = 2) ($J_{5,6}$ = 8)	2.33(S)	3 87(S) (CH_3OPh)
IIe	178-180[g]	6 93(S)	7 79(D) ($J_{2,6}$ = 2)	6 74(D) ($J_{5,6}$ = 8)	7.29(D of D) ($J_{2,6}$ = 2) ($J_{5,6}$ = 8)	2.33(S)	5.95(S) (OCH_2O)

Table 2 N M R. CHEMICAL SHIFTS OF COMPOUNDS III-IV[a]

Compd.	mp[b]	H_β	H(2,6)	H(3,5)	NH	CH_3CON	other
IIIa		5 82[h] (R_1 = H) 6 38[h] (R_2 = H)	-	-	-	-	-
IIIb[i]	36-38	6 47(S) 5 79(D) (J = 1)	-	-	7.71 (broad S)	2.11(S)	3.79(S) (CH_3O)
IIIcd[j]	128-129	7.21(S)	7 36(D) (J = 8.5)	6.96(D) (J = 8.5)	-[k]	2 00(S)	3.75(S) (CH_3O) 2 25(S) (CH_3COO)
IIIe[l]		7.71(D) (J = 16)	-	-	-	-	-
IIIf[l]		6 91(D) (J = 13)	-	-	-	-	-
IVa[m]		7.80	-	-	-	-	-
IVb[n]		8 68	-	-	8 1	2.25	-

[a]the spectra were measured with a Varian XL-100 ($CDCl_3$, ca 38°C), and the chemical shifts are expressed in δ values (p.p.m) relative to internal Me_4Si, J values are in Hz [b]Melting points (°C) are uncorrected. [c]lit [10] 148-150°. [d]lit [11] 138-139° [e]lit.[12] 144-148°. [f]lit [13] 167°. [g]lit.[13] 181°. [h]Varian spectra catalogue, spectrum No 64 [i]synthesised by reaction of CH_2N_2 and α-acetamidoacrylic acid [j]data for the stable ester (synthesized by reaction of CH_2N_2 with α-acetamido-p-acetoxycinnamic acid (mp 233-235 dec) obtained by neutral hydrolysis of the stable azlactone IIb [k]signal buried under those of aromatic protons [l]ref. 8 [m]ref. 14. [n]ref 15

The chemical shifts of the H_1 (6 47 δ) and H_2 (5 79 δ) protons in methyl α-acetamidoacrylate (IIIb) can be added to the substituent effects of the p-acetoxyphenyl group upon H_1 (+1.09 δ) and H_2 (+1 33 δ), respectively Therefore, the chemical shift of the H_β proton in the Z-isomer IIIc is estimated to be 7.12 δ, while that in the E-isomer IIId is estimated to be 7 56 δ The value of 7 21 δ found for the stable methyl α-acetamido-p-acetoxycinnamate (mp 128-129°C) is close (Δδ = 0 09) to the estimated value of the H_β proton (7.12 δ) expected in the Z-isomer IIIc

A singlet at 7 21 δ is also found in the n m r spectrum of the stable methyl α-acetamido-3'-methoxy-4'-acetoxycinnamate (mp 173 5-175°C), but it cannot be unequivocally assigned due to multiplets for the H(2) and H(6) protons

Method 1 shows the α-acetamido group to cause an upfield shift of -0.59 δ upon the trans (H_2) proton in methyl α-acetamidoacrylate (IIIb). This is consistent with the n m.r data of Z-methyl cinnamate (IIIe) The H_β proton in the Z-isomer IIIc is moved by the α-acetamido group upfield (-0 50 δ) relative to the H_β proton in Z-methyl cinnamate (IIIe)

Moreover, the larger downfield effect of +0 98 δ of an α-benzamido group upon the proton cis to it in methyl α-benzamidoacrylate,[5] relative to that of +0 65 δ for an α-acetamido group, is is also consistent with the assignment Furthermore, use of this method predicts the H_β protons to be at 7 34 δ and 7.89 δ and Z- and E-methyl α-benzamido-3',4'-dimethoxycinnamates, respectively, compared to the experimentally determined values of 7 44 δ and 8 00 δ [5]

Since the stereochemistry of the stable IIIc ester is now assigned as Z, the configuration of the parent azlactone IIb and the others (IIa-e) may also be considered to be Z

Finally, the n.m.r assignment of Z-stereochemistry to the stable azlactone isomer IIb is further strengthened by the x-ray analysis of the 199°C mp isomer of α-benzamidocinnamic acid [9] This isomer (obtained by hydrolysis of the stable 2-phenyl azlactone Ia, mp 165-166°C) was assigned the Z-configuration by n m r.,[5] and this subsequently was confirmed by x-ray analysis.[9]

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