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COMMENTS ON ASSIGNMENT OF STEREOCHEMISTRY TO 2-ACYLAMINOCROTONATES

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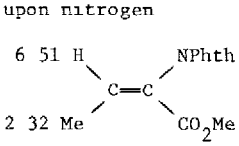
The stereochemistry of the 2-benzamido- and 2-phthalimidocrotonates was assigned by Brown and Smale[1] in 1969 using nmr spectroscopy Other reports have appeared regarding configurational assignment of 2-acylaminocrotonates, some workers[2] have used Brown's approach, while others have used different approaches involving nmr[3] or else have not assigned configuration[4] Brown and Smale's assignments[1], based on work by Morgenstern[5], were made on the basis that a vinyl proton cis to the acylamino function occurred downfield relative to the corresponding proton in the other geometrical isomer A similar assignment was made for the positions of the β-methyl groups in the crotonate system in which the downfield methyl resonance was assigned[1] to the methyl group cis to the nitrogen function. We report, herein, that the above assignment for the β-methyl group positions should be reversed, i.e., the β-methyl trans to the acylamino group, but cis to the carboxyl function, absorbs at lower field. Also, the shift positions of the β-methyl groups in the spectra of 2-acylaminocrotonates are a more reliable criteria for assignment of stereochemistry in this system. In certain cases, the chemical shifts of the vinyl protons appear to be sensitive to the nature of the acyl function attached to nitrogen and caution should be used in assigning stereochemistry based solely on the vinyl proton shift values.

The data given in Table I show that in each case the isomer with the low field β-methyl doublet also has the low field vinyl quartet, while conversely, the other isomer has these two sets of protons occurring at higher field. We assign the low field isomer as having the E configuration[6], which assignment is in accord with the previous concept[1,5] that the low field vinyl proton occupies a position cis to the acylamino function. Note that for compound 4, the shift values for the isomeric vinyl protons are almost the same, while for 2, 5, and 7, the vinyl shift differences are rather small Thus, the vinyl proton positions appear to depend upon the nature of the N-acyl function, whereas the positions of the β-methyl protons are rather uniform and adequately separated The acylamino function likely affects the vinyl protons through the olefinic bond and deshields, as previously described[1,5], the proton cis to itself The β-methyl protons are negligibly affected by the above function, but are deshielded through space by a carboxyl group when cis to that function[7].

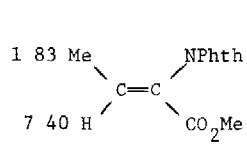
That a β-methyl group cis to an ester function in an α,β-unsaturated ester absorbs down-

field relative to the other isomer has been established by Jackman and Wiley[7]. In 1963, Galantay, et al [8], correctly assigned the β-methyl signals in methyl α-benzamido-β,β-dimethyl acrylate This assignment is confirmed by the nmr data given for compounds listed in Table II Kishi[9] established the configuration of 9 by effecting cyclization to a cephalosporin derivative, while Austel and Steglich[10] were able to convert 11 to a lactone, compound 13[11] serves as an appropriate model having fixed stereochemistry These data establish that a methyl or an alkyl group cis to the carboxyl function is downfield relative to when that group occupies a position cis to the acylamino group

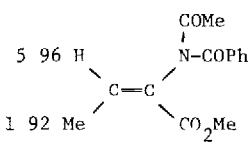
Brown and Smale[1] had in hand only the stable isomer of methyl N-benzamidocrotonate (1), which we reassign as having the Z configuration Poisel and Schmidt[4a] have reported the stable form of 2 (of unspecified configuration), to which the Z configuration also can be assigned Reassignment of stereochemistry to the 2-phthalimidocrotonates[1] (14), and also to the mold metabolite pencolide[1], on the basis of the positions of the β-methyl groups, shows the vinyl proton positions to differ markedly from the other cases listed in Table I [12] The nmr spectrum of a 2 1 mixture of the diacyl derivatives 15[13], when compared with the monoacyl derivatives 1, showed the vinyl proton of 15-E to be shifted upfield, as was also observed for 14-E, however, a corresponding downfield shift of the vinyl proton was not observed for 15-Z Molecular models indicate the two acyl groups in 15 have considerable rotational freedom compared to the rather restricted phthalimide system 14, and therefore, the acyl groups are likely oriented differently in 15 than in 14. A large upfield shift of the vinyl proton also occurs upon N-methylation of the E isomer of 7 [2c] Caution should be used, therefore, in assigning stereochemistry, based upon the position of the vinyl protons, to 2-acylaminocrotonates that have a second substituent upon nitrogen



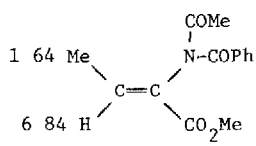
14-E



14-Z



15-E



15-Z

We have observed a correlation between configuration and change in chemical shift of the vinyl proton of an individual isomer when measured in the two solvents, $CDCl_3$ and trifluoroacetic acid (TFA) A proton trans to nitrogen (Z isomer) is shifted downfield 0 34-0 54 ppm in going from $CDCl_3$ to TFA, while a proton cis to nitrogen (E isomer) undergoes an upfield shift of 0 18-0 32 ppm. The β-methyl protons are little affected by this solvent change and in both isomers a small downfield shift is observed

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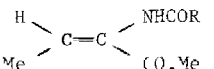
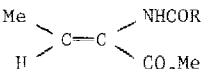
Table I - Shift Positions of β-Methyl and Vinyl Protons[a]



E

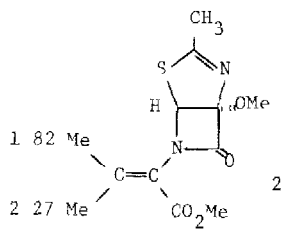


Z

Compd [b]	R	E β-Me	E vinyl	Z β-Me	Z vinyl
1	Ph	2 05	7 18	1 78	6 80
2	Me	2 02	6 90	1 71	6 72
3	$PhCH_2$	1 97	7 03	1 65	6 68
4	$PhCH_2O$	2 05	6 71	1 77	6 68
5	$Z\text{-}NHCH_2$	2 03	6 99	1 71	6 83
6	CF_3	2 07	7 15	1 73	6 92
7	Boc	2 05	6 78	1 81	6 67

[a] Shift values are reported in ppm relative to TMS. All spectra were recorded with a Varian XL-100-12 spectrometer in $CDCl_3$. [b] Compounds 1 through 6 were prepared in our laboratories by elimination reactions on O-tosyl-DL-threonine or erythro-β-chloro-α-amino-DL-butyric acid derivatives. Data for compound 7 were taken from reference 2c.

Table II - NMR Data for Appropriate Reference Compounds[a,b,c]



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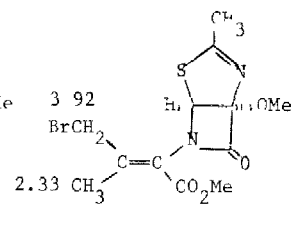

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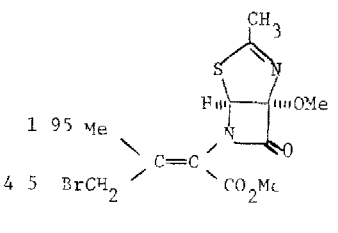

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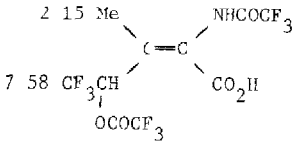

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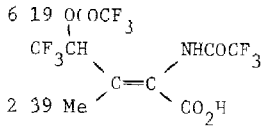

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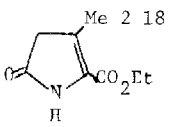

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[a] Chemical shift values are listed in ppm for the β,β-dialkyl protons. Spectra for 8, 9, 10, and 13 were recorded in $CDCl_3$, while 11 and 12 were measured in TFA. [b] For 8, 9, and 10, see reference 9, for 11 and 12, see reference 10, for 13, see reference 11. [c] Maki and Sako have recently assigned stereochemistry to isomeric β,β-dialkylacrylates, see J Amer Chem Soc, 97, 7168 (1975).

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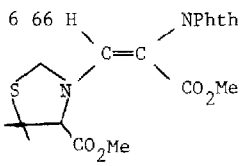

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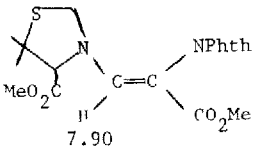

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crotonates 14 is consistent with the above data

13 Prepared by treatment of a 2 1 mixture of 1-E and 1-Z at reflux with acetyl chloride in chloroform containing an equivalent of pyridine