The Absolute Stereochemistry at C-2 of Thiazolidines derived from *R*-Penicillamine and Aldehydes

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IN connection with the synthesis of some penicillin analogues we became interested in the factors which control the stereochemistry at C-2 of thiazolidines formed from *R*-penicillamine and aldehydes. Here we describe a convenient method for determining the absolute stereochemistry at C-2.

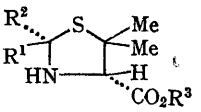
Foster and his co-workers[1] have successfully determined the absolute configuration at the acetal centre of 1,3-dioxolans by n.m.r. spectroscopy. The acetal proton was shown to be deshielded by *cis*-alkyl substituents at C-3 or C-4.[2] Consequently, it seemed likely that the chemical shift of the C-4 proton of 4-carboxythiazolidines would reflect the stereochemistry at C-2. Support for this expectation was found in the chemical shifts of the C-4 protons of 4*R*-carboxy-5,5-dimethylthiazolidine (I)[3] and 4*R*-carboxy-2,2,5,5-tetramethylthiazolidine (II)[4] which occurred at τ 6·18 and 5·78, respectively. The model compounds indicated that a methyl group at C-2 *cis* to the hydrogen at C-4 deshielded the latter by 0·40 p.p.m.

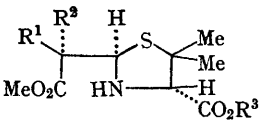
2*S*,4*R*-Dicarboxy-5,5-dimethylthiazolidine (III), m.p. 188—190° (decomp), $[\alpha]_D$ − 13° (pyridine), was synthesized from *R*-penicillamine and glyoxylic acid.[5] The stereochemistry of (III) was confirmed by conversion to its *N*-ethoxycarbonyl derivative, m.p. 148—150°, $[\alpha]_D$ − 79° (chloroform), which gave a syrupy anhydride (ν_{max} 1820, 1770, and 1715 cm.$^{-1}$; M^+ 259·0536) with dicyclohexylcarbodi-imide. Diazomethane esterification of (III) gave (IV), m.p. 63—64°, $[\alpha]_D$ + 4° (chloroform), which was equilibrated with 2*R*,4*R*-dimethoxycarbonyl-5,5-dimethylthiazolidine (V), m.p. 96°, $[\alpha]_D$ + 162° (chloroform) in methanolic hydrogen chloride. 4*R*-Methoxycarbonyl-2*S*-carboxy-5,5-dimethylthiazolidine (VI), m.p. 82—84°, $[\alpha]_D$ + 73° (chloroform) and 4*R*-methoxycarbonyl-2*R*-carboxy-5,5-dimethylthiazolidine (VII), m.p. 112—114°, $[\alpha]_D$ + 197° (chloroform), were obtained by monosaponification of (IV) and (V), respectively. 2*S*-Methoxycarbonyl-4*R*-carboxy-5,5-dimethylthiazolidine (VIII), m.p. 108—110°, $[\alpha]_D$ + 58° (chloroform) was obtained from *R*-penicillamine and methyl glyoxylate. Its stereochemistry was confirmed by conversion to (IV) with diazomethane.

The chemical shifts of the C-4 protons of these thiazolidines are shown in the Table. In all cases the C-4 proton resonated at lower field when *cis* to an alkyl substituent at C-2, compared to compounds in which the C-4 proton was *cis* to a hydrogen at C-2.

TABLE

Chemical shifts[a] *of C-4 protons in thiazolidine derivatives*





Compound	R^1	R^2	R^3	τ
(I)[3]	H	H	H	6·18
(II)[4]	Me	Me	H	5·78
(III)	H	CO_2H	H	5·89
(IV)	H	CO_2Me	Me	6·05
(V)	CO_2Me	H	Me	5·62
(VI)	H	CO_2H	Me	6·02
(VII)	CO_2H	H	Me	5·52
(VIII)	H	CO_2Me	H	6·01
(IX)[b]	CO_2H	H	H	5·26

Compound	R^1	R^2	R^3	τ
(X)[8]	$PhCH_2$·CONH	H	H	5·80
(XI)[9]	$PhCH_2$·CONH	H	Me	5·86
(XII)[10]	H	Cl	Me	5·91
(XIII)[11]	$Ph(CO)_2N$	H	H	5·73
(XIV)[11]	$Ph(CO)_2N$	H	Me	5·78

[a] N.m.r. spectra were measured in pyridine at 60 Mc./sec. with tetramethylsilane as an internal standard; [b] This compound has not been fully characterized; its presence in the mother liquor after crystallization of (III) was implied by n.m.r. spectroscopy.

4*R*-Carboxy-2,5,5-trimethylthiazolidine, m.p. 149—150°, $[\alpha]_D$ + 133° (pyridine), was prepared from *R*-penicillamine and acetaldehyde and was shown to be a mixture of stereoisomers by n.m.r. spectroscopy. The tertiary protons, which appeared at τ 6·07 and 5·88 in the ratio of 4 : 1, suggested that the predominant stereoisomer was 4*R*-carboxy-2*S*-5,5-trimethylthiazolidine. Similarly 4*R*-carboxy-5,5-dimethyl-2-phenylthiazolidine[6] was found to be a mixture of stereoisomers. The tertiary protons, which resonated at τ 5·93 and 5·87, were present in the ratio of 3 : 1 implying that the major isomer was 4*R*-carboxy-5,5-dimethyl-2*S*-phenylthiazolidine.

A number of penicilloic acid derivatives and related compounds were also examined and the results are shown in the Table. In these cases, in which the substituent at C-2 of the thiazolidine is known to possess the *R*-configuration, the chemical shift of the C-4 protons fell between τ 5·73 and 5·91. Consequently, it was expected that if a penicilloate possessed the 2*S*-stereochemistry then the C-4 proton would resonate at higher field. The γ-isomer of methyl 4*R*-carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidine acetate, m.p. 180—182°, $[\alpha]_D$ − 8° (dioxan), was prepared by Sheehan's method.[7] The C-4 proton resonated at τ 6·12 suggesting that this isomer possessed the 2*S*-configuration.

The results described indicate that, in the case of the 4-carboxythiazolidine derivatives, the chemical shift of the C-4 proton is a valuable guide to the relative stereochemistry at C-2. In particular if both stereoisomers at C-2 are available the isomer in which the C-4 proton appears at lowest field possessed the *trans*-configuration.

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[1] N. Baggett, K. W. Buck, A. B. Foster, and J. M. Webber, *J. Chem. Soc.*, 1965, 3401; N. Baggett, K. W. Buck, A. B. Foster, M. H. Randall, and J. M. Webber, *ibid.*, 1965, 3394; N. Baggett, J. M. Duxbury, A. B. Foster, and J. M. Webber, *J. Chem. Soc. (C)*, 1966, 208.

[2] M. Anteunis and F. Alderweireldt (*Bull. Soc. chim. belg.*, 1964, **73**, 889) have reached the opposite conclusion but their interpretation is based upon a misassignment of stereochemistry. We thank Dr. J. G. Buchanan for pointing out this paper to us.

[3] H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin", Princeton University Press, Princeton, 1949, p. 958.

[4] Ref. 3, p. 26.

[5] A similar condensation utilizing the methyl ester of penicillamine has been described (R. Bentley, A. H. Cook, J. A. Elvidge, and G. Shaw, *J. Chem. Soc.*, 1949, 2351; see also ref. 3, p. 964). No stereochemical assignments were made.

[6] Ref. 3, p. 946.

[7] J. C. Sheehan and D. A. Johnson, *J. Amer. Chem. Soc.*, 1954, **76**, 158.

[8] Ref. 3, p. 582.

[9] Ref. 3, p. 613.

[10] I. Mcmillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205. The absolute stereochemistry at C-2 and the β-position has now been established by a chemical method.

[11] J. C. Sheehan and P. A. Cruickshank, *J. Amer. Chem. Soc.*, 1956, **78**, 3677.