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DYNAMIC BEHAVIOUR OF 2,2-DIMETHYL-3-FORMYL-4-CARBONYL-4-THIAZOLINYL VALINE ESTERS

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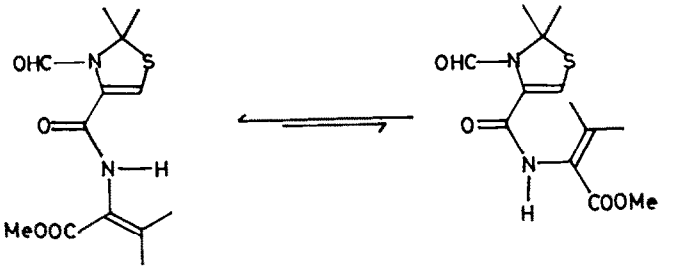
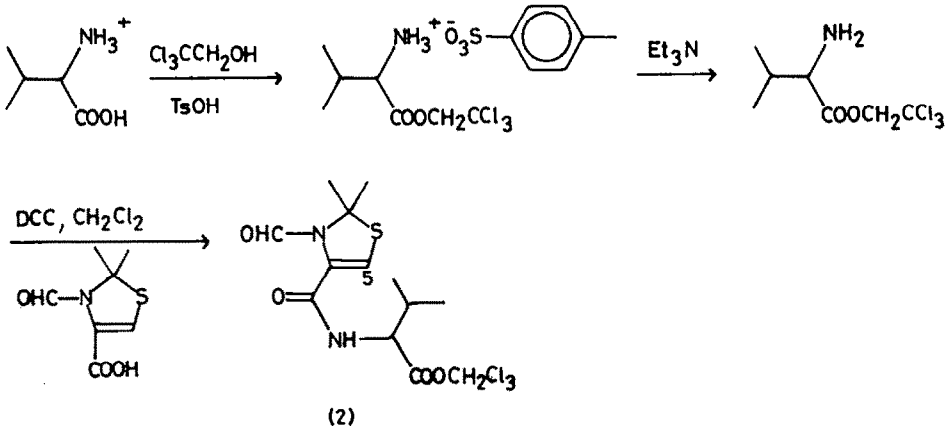
Abstract.- Thiazolinyl valine esters (1) and (2) were synthesised and their dynamic behaviour, associated with amide rotation, investigated by ^{1}H nmr spectroscopy.

In connection with synthetic studies in the β-lactam area the thiazoline derivatives (1)[1] and (2) (Scheme 1) were prepared. Our attention was drawn to possible dynamic behaviour in (2) by the observation of considerable broadening in the C-5 signal (δ 110.1 ppm) in the ^{13}C nmr spectrum and of the H-5 and formyl -H signals in the ^{1}H spectrum of this dipeptide.



(1a) (1b)



(2)

Scheme 1 Preparation of (2)

Both (1) and (2) were investigated by variable temperature ^{1}H nmr spectroscopy at 360 MHz. The upfield signals due to the methyl groups in (1) all showed changes and splittings as the

temperature was lowered, but the data were not readily analysed since the chemical shifts also change considerably with temperature. At 293 K broad singlets at δ 6.45, 7.10 and 8.72 ppm were observed respectively for the C-5 alkene hydrogen, NH and CHO. On cooling to 283 K each of these had split into two broad signals in the ratio of approximately 2:1. This ratio between major and minor species did not change appreciably on further cooling. The signals sharpened at lower temperatures (Figure 1) and limiting values are shown in Table 1. Analogous results were obtained with (2). Whilst complete line shape analyses were not undertaken, the use of coalescence data allows a value in the region of 55 kJ mol^{-1} to be estimated for $\Delta G^{\ddagger}$ for the interconversion.[2]

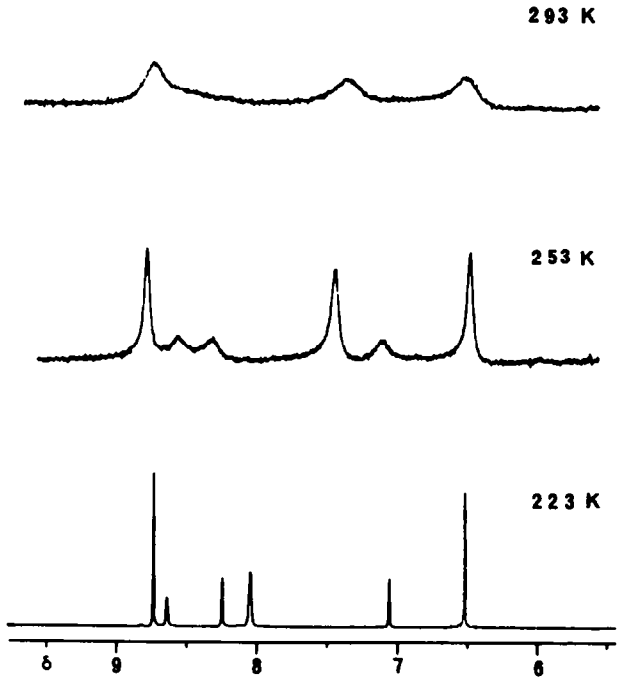


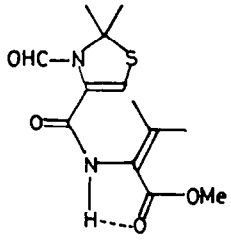
Figure 1 Low field region of variable temperature ^1H nmr of (1).

Table 1 Limiting Chemical Shifts for downfield ^1H nmr signals at 223 K (Concentration (1) = 01 M, (2) = 0.075 M)

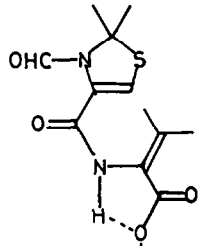
Substrate	Major Species			Minor Species		
	δCHO	δNH	δC(5)-H	δCHO	δNH	δC(5)-H
(1)	8.74	8.05	6.52	8.24	8.64	7.06
(2)	8.69	7.35	6.47	8.25	7.79	7.04

Two potential dynamic processes may be considered for (1) and (2), *viz.* rotation of the formyl group and rotation of the amide. Two experiments allowed a distinction to be made between these. At 223 K irradiation of the major NH signal of (1) gave an n.O.e. of 11% to the major alkene hydrogen. Irradiation of the major alkene hydrogen gave an 8% n.O.e. to the major NH. No significant n.O.e.'s were obtained from the NH or the alkene hydrogen in the minor conformer. Above 233 K the major effect observed on irradiation was saturation transfer.[3] We may thus propose (1a) and (1b) for the major and minor conformations of (1) respectively; rotation about the NCHO bond would not be expected to result in the n.O.e. effects observed.

A further observation confirms this explanation. δ_{NH} for the major conformer (1a, 0.1 M) was found to be quite strongly temperature dependent, shifting downfield from δ 7.42 to δ 8.05 at 223 K (Table 2). δ_{NH} of the minor conformer shifts little over the same temperature range. A more dilute sample of (1) (0.02 M) shows a substantial difference and a smaller temperature dependence in δ for the major isomer, but little difference in the minor isomer. Similar data were obtained for (2). This strongly suggests that (1a) and (2a) are involved in intermolecular H-bonding which is known to be enhanced by increased concentration or lowered temperature.[4,5] (1b), by contrast, is capable of intramolecular H-bonding, which might be expected to be relatively insensitive to temperature and concentration effects.[6,7] Present data do not allow a distinction to be made between (3a) in which the N-H is bonded to the carbonyl oxygen and (3b) in which it is asociated with the OMe group.



(3a)



(3b)

Table 2 Temperature and concentration dependence of δNH for (1) and (2).

	(1)(Major)	(1)(Minor)	(2)(Major)	(2)(Minor)
Temp(°K)	conc = 0.1 M		conc = 0.075 M	
283	7.42	8.55	6.78	7.68
253	7.50	8.56	7.02	7.79
223	8.05	8.64	7.35	7.79
	conc = 0.02 M		conc = 0.015 M	
283	a	a	6.40	7.75
252	7.17	8.69	6.41	7.75
223	7.31	8.62	6.47	7.70

a. Signals too broad for accurate assignment.

EXPERIMENTAL

Preparation of 2,3-dimethyl-3-formyl-4-carbonyl-4-thiazolinyl valine trichloroethyl ester (2)

DL-Valine (5.85 g, 0.05 mol), CCl_3CH_2OH (60 g, 0.4 mol) and p-toluene sulphonic acid monhydrate (19 g, 0.1 mol) in CCl_4 (250 ml) were heated under reflux in a Dean and Stark apparatus (48 h). The solution was concentrated to 75 ml and ether (175 ml) added. After cooling a white solid was obtained, collected by filtration and washed (Et_2O) to yield N-toluenesulphonyl trichloroethyl valinate (6.25 g, 30%). A second crop of crystals (0.85 g, 7%) was obtained by

addition of the ether washings to the mother liquor.

N-Toluenesulphonyl trichloroethyl valinate (5.02 g, 0.012 mol) was suspended in CH_2Cl_2 (60 ml) under N_2. Et_3N (1.67 ml) was added and the solution cooled in an ice-bath. N-Formyl-2,2-dimethyl-4-thiazoline-4-carboxylic acid[1] (2.15 g, 0.012 ml) was added with stirring. DCC (2.25 g) in CH_2Cl_2 (20 ml) was added dropwise to the solution. After 2 days at 25°C under N_2, CH_3COOH (0.5 ml) was added to destroy excess DCC, and the precipitate of dicyclohexylurea was removed by filtration. The solution was washed with dilute HCl (2 x 25 ml), saturated $NaHCO_3$ solution (2 x 25 ml) and water until neutral. After drying ($MgSO_4$) the solvent was removed *in vacuo* until further dicyclohexyl urea was precipitated. This was removed by filtration, and the remaining solution concentrated to a colourless oil. On cooling a white solid separated and was washed with petroleum ether and recrystallised ($CH_3COOC_2H_5$) to give (2) (2.83 g, 58.5%, m.pt. 120-2°C).

^{1}H nmr ($CDCl_3$) δ 0.93, 1.04 (d, J = 7Hz, 6H, 2 valine CH_3), 1.92 (s, 6H, 2 acetonide CH_3), 2.64 (s, 1H, valine-CH), 4.51 (m, 1H, valine-α-CH), 4.47, 4.82 (AB q, J = 12 Hz, 2H, $-OCH_2CCl_3$), 6.2 (br. s, 1H, NH) 8.44 (s, 1H, CHO)

^{13}C nmr ($CDCl_3$) δ 18.0, 19.1 (2 valine CH_3), 29.3 (2 acetonide CH_3), 30.5 (valine-CH), 57.7 (valine-α-CH), 74.3 ($-OCH_2CCl_3$), 77.7 ($(CH_3)_2CN$) 94.5 ($-CCl_3$), 110.1 (br.C-5), 129.2 (=C(CONH--N), 160.0 (amide C=O), 161.2 (CHO), 169.7 (ester C=O)

Analysis Required for $C_{14}H_{19}N_2O_4SCl_3$ C 40.25% H 4.58% N 6.70%
Found C 40.03% H 4.70% N 6.58%.

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