Carbohydrate Research, 187 (1989) 223–237
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

THIAZOLIDINE-4(*R*)-CARBOXYLIC ACIDS DERIVED FROM SUGARS: PART I, C-2-EPIMERISATION IN AQUEOUS SOLUTIONS

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(Received October 22nd, 1987; accepted for publication, November 18th, 1988)

ABSTRACT

Reactions of L-cysteine (**1**) with L-xylose, D-ribose, D-lyxose, D-arabinose, D-glucose, L-rhamnose, and L-fucose in aqueous ethanol yielded crystalline 2(*S*)-(polyhydroxyalkyl)thiazolidine-4(*R*)-carboxylic acids. Likewise, glycolaldehyde and L-glyceraldehyde, D-xylose, L-arabinose, D-mannose, D-galactose, and D-fucose gave crystalline 2(*R*),4(*R*) epimers. The reaction of **1** and D-glyceraldehyde gave a syrupy mixture of 2(*S*),4(*R*) and 2(*R*),4(*R*) compounds. The same substrates, but with no ethanol present, gave the 2(*S*),4(*R*) epimers for glycolaldehyde, L-xylose, L-fucose, and L-arabinose, and the 2(*R*),4(*R*) epimers for D-lyxose, L-rhamnose, D-mannose, D-galactose, and D-fucose. The reactions of D-ribose, D-arabinose, D-xylose, and D-glucose gave syrupy mixtures of epimers. The crystalline reaction products, when dissolved in water, undergo rapid epimerisation as reflected by mutarotation and changes in the ^{1}H- and ^{13}C-n.m.r. spectra.

INTRODUCTION

The long-known[1–6] reaction between L-cysteine (**1**) and reducing sugars leads to 2-(polyhydroxyalkyl)thiazolidine-4(*R*)-carboxylic acids in which a new chiral centre is formed at C-2. The reactions of **1** and D-galactose[7] (**2**), L-arabinose[8] (**3**), or 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose[7] (**4**) were reported to give products with the 2(*R*), 4(*R*)*cis* configuration. A similar result was obtained in the reaction between **4** and L-cysteine methyl carboxylate[6,7], whereas the analogous reaction with 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-L-arabinose (**5**) was reported to give a mixture of the 2(*R*),4(*R*)*cis* and 2(*S*),4(*R*)*trans* epimers[8], and that of **1** and **5** to give only a product with the 2(*S*),4(*R*)*trans* configuration[8]. The C-2 configurations were assigned on the basis of the formation of six-membered [C-4(*R*)–C-2′] lactones that exist only for C-2,C-4*cis* epimers, but which assumed that there was no change of configuration during lactonisation. The related reactions between D-penicillamine and **4**[9] or **5**[10] produced mixtures of the 2(*R*),4(*S*)*trans* and 2(*S*),4(*S*)*cis* epimers, although condensations with the free sugars gave products with the 2(*R*),4(*S*)*trans* configuration only. Martens and Drauz[11] stated that sugar–cysteine cyclisations yield only *cis* products. On the other hand, reactions between vicinal aminothiols

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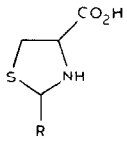
(*e.g.*, cysteine) and achiral aldehydes[12–14] have been regarded[15–18] as non-stereospecific.

Our re-examination of the condensations of **4**[18] and **5**[19] with **1** and its methyl carboxylate gave, in each reaction, a mixture of epimers, contrary to the earlier reports. Although there are many ^{13}C- and ^{1}H-n.m.r. data[7–10,16,17,20–27] for thiazolidine-4-carboxylic acid and its 2-alkyl or -aryl derivatives, little has been published on 2-polyhydroxyalkyl derivatives.

RESULTS AND DISCUSSION

Reactions were carried out in water or aqueous ethanol. Recrystallisation of the products was not attempted because of the possibility of changing their composition, since both the 2(*R*),4(*R*) and 2(*S*),4(*R*) epimers could be present.



6 R = hydroxymethyl
7 R = D-*glycero*-1,2-dihydroxyethyl
8 R = L-*glycero*-1,2-dihydroxyethyl
9 R = L-*xylo*-1,2,3,4-tetrahydroxybutyl
10 R = D-*xylo*-1,2,3,4-tetrahydroxybutyl
11 R = D-*ribo*-1,2,3,4-tetrahydroxybutyl
12 R = D-*lyxo*-1,2,3,4-tetrahydroxybutyl
13 R = D-*arabino*-1,2,3,4-tetrahydroxybutyl
14 R = L-*arabino*-1,2,3,4-tetrahydroxybutyl
15 R = D-*gluco*-1,2,3,4,5-pentahydroxypentyl
16 R = D-*manno*-1,2,3,4,5-pentahydroxypentyl
17 R = D-*galacto*-1,2,3,4,5-pentahydroxypentyl
18 R = L-*manno*-1,2,3,4-tetrahydroxypentyl
19 R = L-*galacto*-1,2,3,4-tetrahydroxypentyl
20 R = D-*galacto*-1,2,3,4-tetrahydroxypentyl

Method *A* was that of Schubert[1], slightly modified. Aqueous solutions of **1**·HCl + 1 equiv. of pyridine with glycolaldehyde, D- and L-glyceraldehyde, D-ribose, D- and L-lyxose, D- and L-arabinose, D-lyxose, D-galactose, D-glucose, D-mannose, L-rhamnose, and D- and L-fucose were kept for 20 h at room temperature, after which absolute ethanol was added. In method *B*, potassium acetate was used instead of pyridine, and no ethanol was introduced at the end of reaction; the yields were generally much lower than in method *A*. Method *B* was not applied to glyceraldehyde. All of the products were levorotatory, indicative of the *R* configuration at C-4 of the ring. Dextrorotatory 2-substituted sugar thiazolidine derivatives all have been reported[9–11] to possess the 4(*S*) configuration, regardless of the configuration of the 2-substituent.

The stability of the 2-substituted thiazolidine-4(*R*)-carboxylic acids in solution is crucial for the determination of the configuration at C-2. Ring-chain tautomerism of 2-substituted thiazolidines has been studied in alkaline[16,21,28] and acidic[30] solutions, by heating in protic and aprotic solvents[29], and in the molten state[29]. Mutarotation of the nearly neutral[3] solutions of the 2-(polyhydroxyalkyl)-thiazolidine-4(*R*)-carboxylic acids in water was suggested by Roberts *et al.*[31]. Györgydeák *et al.*[32] used c.d. to correlate the configuration at C-2 with the sign of the Cotton effect, which presupposes stability in solution.

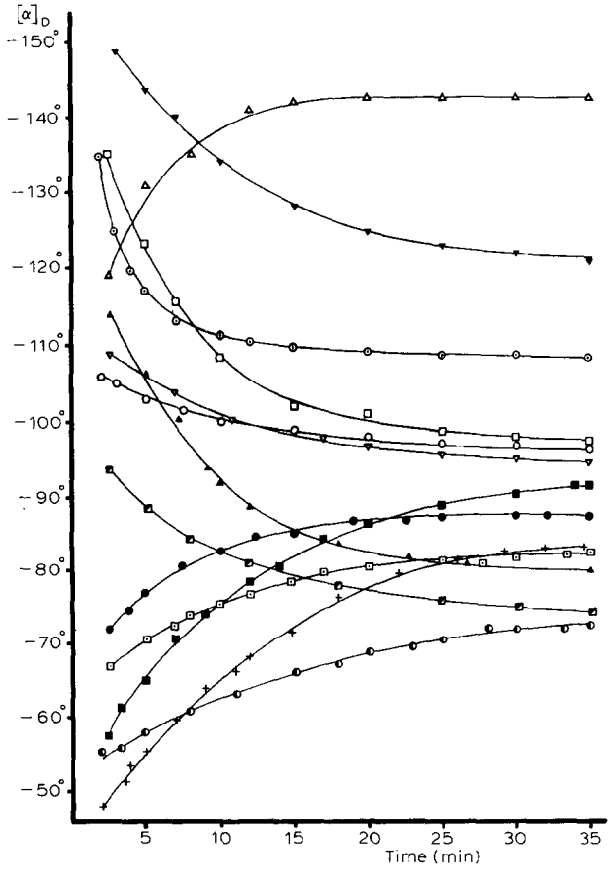


Fig. 1. Mutarotation curves of aqueous solutions (*c* 0.25–0.5) of: **6** △, **9** □, **10** ■, **11** ▼, **12** ▲, **13** ⊙, **14** ⊡, **15** ▽, **16** +, **17** ◐, **18** ◩, **19** ○, and **20** ●.

Fig. 1 shows the changes in the optical rotation of aqueous solutions of the solid products obtained by method *A*, and which were complete in <1 h. The optical rotation of **7** remained constant. Mutarotation curves for **9, 16, 17, 19,** and **20** obtained by methods *A* and *B* were the same. For **6, 12, 14,** and **18**, the direction of mutarotation was reversed, but the equilibrium values were the same as for the corresponding compounds obtained by method *A*.

The magnitude of the equilibrium rotation declined as the pH was reduced, as shown in Fig. 2 for **14**. Aqueous solutions (*c* 0.5) of **6–20** have a pH in the range 3.7–4.0 in agreement with the p*K* values reported by Weitzel *et al.*[3]. On the other hand, [H^+] reaches as high as 4M in the reaction solutions. Piriou *et al.*[33] reported complete reversal of the S puckered ring conformation (S-*exo* → S-*endo*) for thiazolidine-4-carboxylic acid on changing the pH of solution from 5 to ~8. They suggested that, at the pH equal to the p*K* of the imine group, the thiazolidine ring exists mainly in the averaged planar conformation. For the compounds studied

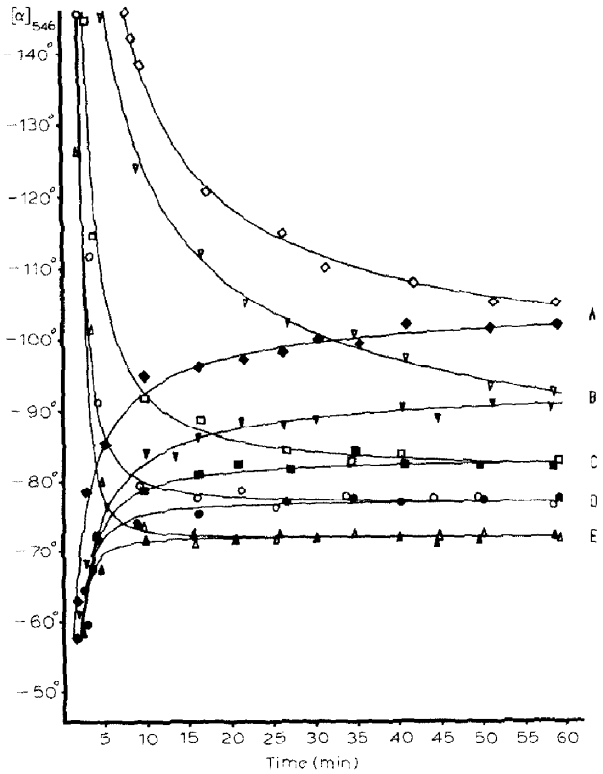


Fig. 2. Dependence of the mutarotation on the pH of aqueous solutions (*c* 0.5) of the epimers of **14**: upper curves, 2(*S*),4(*R*)*trans* (method *B*); lower curves, 2(*R*),4(*R*)*cis* (method *A*). **A**, aqueous solution (pH at equilibrium 3.80); **B**, pH 2.1 (0.5M phthalate buffer); **C**, pH 0 (M HCl); **D**, 2M HCl; **E**, 4M HCl.

here, the effect of acidity on mutarotation is due mainly to changes in composition rather than conformation, as indicated by the ^{1}H-n.m.r. spectra of solutions in D_2O.

Analysis of the ^{1}H-n.m.r. spectra was complicated by overlapping signals. Only the 90-MHz n.m.r. spectrum of **6** could be interpreted fully (Fig. 3a). The two pairs of ABC sub-spectra arise from H-4,5a,5b and H-2,1'a,1'b of the two epimers. Overlapping of the AB parts are at 2.85–3.70 and 3.70–4.15 p.p.m., respectively. The four peaks at 4.15–4.70 p.p.m. consist of two overlapping four-line resonances of H-4 (part C of the first pair). The seven-line pattern at 4.55–5.10 p.p.m. involves H-2 (part C of the second pair). This assignment was confirmed by computer-aided analysis (Fig. 3b).

The 360-MHz spectra of **7, 8,** and the major component of **17** could be interpreted fully. Partial analysis of the spectra of the minor component of **17** and of both components of **14** (Fig. 4) was also accomplished. Chemical shifts (Table I) were assigned by selective proton decoupling, and iterative analysis of the computer-simulated spectra yielded coupling constants (Table II).

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFT DATA (δ)[a,b] FOR THIAZOLIDINE-4-CARBOXYLIC ACID AND THE DERIVATIVES **6–8, 14,** AND **17**

	H-4	*H-5a*	*H-5b*	*H-2*	*H-1'*	*H-2'*	*H-3'*	*H-4'*	*H-P'a*[c]	*H-P'b*[c]
Thz[d] (90 MHz)	4.47	3.44	3.35	4.49 4.37						
Thz[d] (100 MHz)	4.46	3.43	3.34	4.47 4.36						
6(*S*)[e] (90 MHz)	4.55	3.44	3.33	5.01					3.91	3.79
6(*S*) (100 MHz)	4.57	3.48	3.37	5.03					3.94	3.81
6(*R*)[e] (90 MHz)	4.47	3.45	3.35	4.92					3.94	3.88
6(*R*) (100 MHz)	4.51	3.49	3.39	4.94					3.98	3.88
7(*S*) (360 MHz)	4.70	3.48	3.41	5.23	4.21				3.67	3.61
7(*R*) (360 MHz)	4.57	3.53	3.45	4.87	4.04				3.76	3.68
8(*S*) (360 MHz)	4.62	3.53	3.44	5.05	3.95				3.81	3.74
8(*R*) (360 MHz)	4.50	3.49	3.44	4.94	4.18				3.78	3.71
14(*S*) (360 MHz)	4.60	3.49	3.40	5.15	4.40	*f*	*f*	*f*	*f*	*f*
14(*R*) (360 MHz)	4.55	3.55	3.45	5.00	4.28	3.71	3.88	*f*	*f*	*f*
17(*S*) (360 MHz)	4.60	3.47	3.39	5.20	4.42	3.83	*f*	3.97	*f*	*f*
17(*R*) (360 MHz)	4.55	3.54	3.44	5.02	4.28	3.69	3.75	3.96	3.73	3.70

[a]Against Me_4Si. [b]Primed numbers refer to the 2-(polyhydroxyalkyl) substituent. [c]Protons of the terminal primary carbon atoms of the side chain. [d]Thiazolidine-4(*R*)-carboxylic acid. [e]*S* and *R* denote configuration at C-2. [f]Assignment precluded because of overlapping of signals.

TABLE II

^{1}H-N.M.R. COUPLING CONSTANTS (Hz) FOR THIAZOLIDINE-4-CARBOXYLIC ACID AND THE DERIVATIVES **6–8, 14,** AND **17**

	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$	$J_{2,1'}$[a]	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	J_{Pac}[b]	J_{Pbc}[b]	J_{Pab}[b]
Thz[c] (90 MHz)	7.1	6.1	11.8	10.3[d]						
Thz (100 MHz)	7.2	5.9	12.1	10.3[d]						
6(*S*)[e] (90 MHz)	6.7	5.4	11.5					3.6	6.4	12.5
6(*S*) (100 MHz)	6.6	5.3	11.7					3.8	6.1	12.6
6(*R*)[e] (90 MHz)	7.3	7.0	11.9					3.4	7.6	12.4
6(*R*) (100 MHz)	7.5	7.2	11.7					3.7	7.8	12.4
7(*S*) (360 MHz)	4.8	4.2	12.2	2.9				5.7	6.1	11.8
7(*R*) (360 MHz)	7.5	5.5	12.1	5.2				4.7	3.6	12.2
8(*S*) (360 MHz)	6.8	4.1	12.1	7.3				3.5	4.9	12.1
8(*R*) (360 MHz)	6.6	5.3	12.0	5.0				5.2	5.5	11.0
14(*S*) (360 MHz)	7.0	5.3	11.8	3.5	*f*	*f*	*f*	*f*	*f*	*f*
14(*R*) (360 MHz)	7.4	7.0	12.1	6.8	1	11.8	*f*	2.5	*f*	*f*
17(*S*) (360 MHz)	7.0	5.7	12.2	3.7	1.5	9.4	*f*	$J_{Pac}+J_{Pbc}$ = 13.6		*f*
17(*R*) (360 MHz)	7.7	7.0	12.0	7.0	1	9.5	0.7–1	6.7	6.4	12.0

[a]Primed numbers refer to the 2-(polyhydroxyalkyl) substituent. [b]Protons of the terminal primary carbon atoms of the side chain. [c]Thiazolidine-4(*R*)-carboxylic acid. [d]Geminal coupling of H-2,2. [e]*S* and *R* denote configuration at C-2. [f]Assignment precluded because of overlapping of signals.

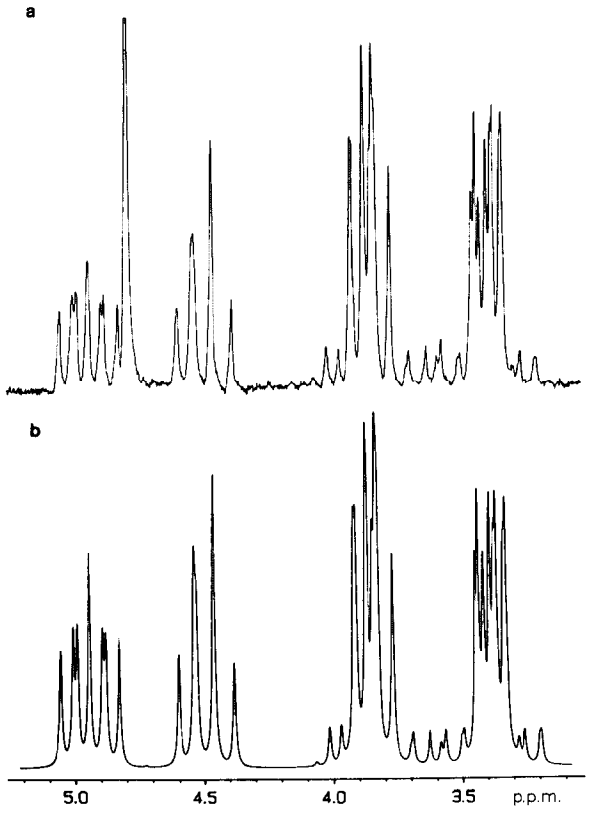


Fig. 3. 90-MHz ^{1}H-n.m.r. spectra of **6** in D_2O: (*a*) experimental (truncated peak at about 4.8 p.p.m. arises from HOD); (*b*) calculated.

For each of the compounds mentioned, although the overall appearance of the spectrum differed from that of **6**, the ranges of chemical shifts of the H-2,4,5 resonances of the ring and the protons of the primary carbon atom of the chain remained essentially the same (Table I). Except for **6**, in each of the remaining compounds, H-2, the only proton directly coupled with another one (in D_2O), gave a well defined pair of doublets from both epimers on the left of the HOD peak. McMillan and Stoodley[30] reported that H-4 resonated at lower field when *trans* to H-2, than when *cis*. Accordingly, it was possible to assign configuration at C-2 for both epimers of **6–8, 14,** and **17**. In compounds with the 2(*R*),4(*R*)*cis* configuration, H-2 resonates at higher field than in those with the 2(*S*),4(*R*)*trans* configuration.

In order to explore changes of the composition of the solutions, F.t.-^{1}H-n.m.r. spectra were recorded for each compound obtained by method *A*, using the solvent suppression pulse sequence[34]. Changes in the relative intensities of the resonances of H-2 (4.8–5.2 p.p.m.) allowed the ratio of epimers to be determined. Data thus obtained and data from polarimetry correlated well (Fig. 5), and on this basis the approximate value of the specific rotation for each epimer has been estimated (Table III).

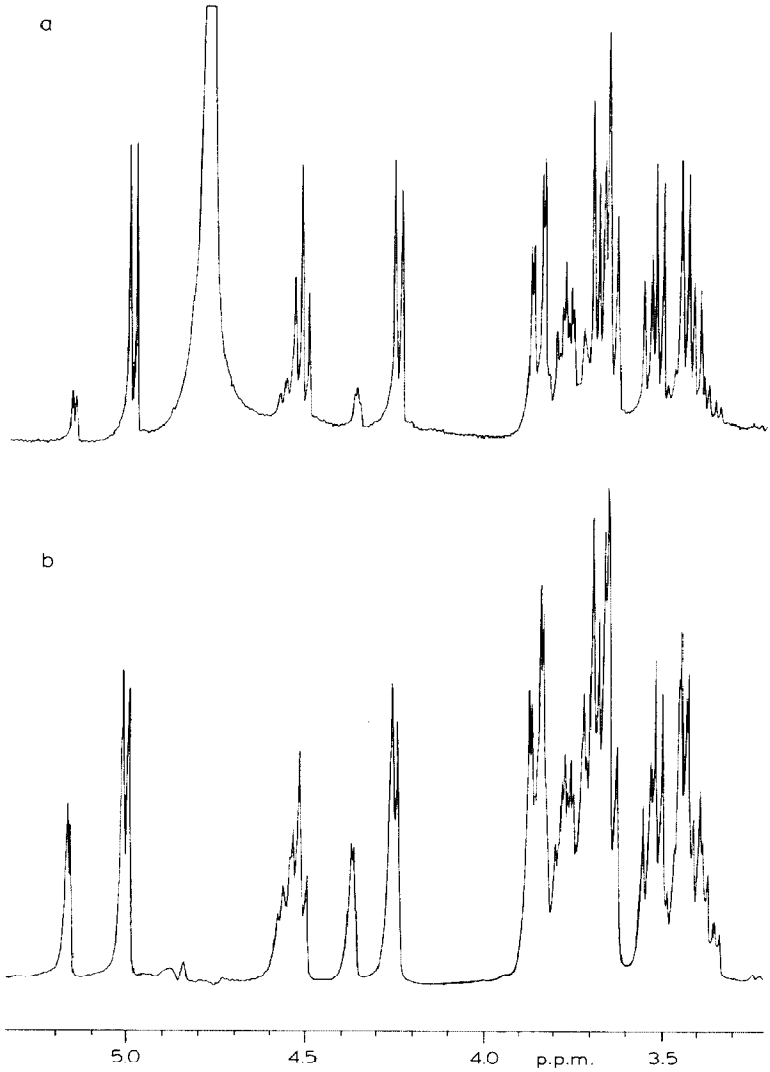


Fig. 4. 360-MHz ^{1}H-n.m.r. spectra of **14** in D_2O, recorded (*a*) 5 min, and (*b*) 30 min after dissolution. The latter spectrum was run with HOD decoupling.

For most of the compounds, the first spectra taken after the sample dissolved showed either no doublet for the minor epimer or only a small one (for the less-soluble compounds). For **9, 11–13, 15, 18,** and **19**, the values of the optical rotation diminished during mutarotation (Fig. 1) and the intensity of the H-2 doublet corresponding to the 2(*S*),4(*R*) epimer decreased. The reverse correlation was observed for **6, 8, 10, 14, 16, 17,** and **20**. Thus, where the McMillan and Stoodley rule[30] could not be applied, comparison with **14** or **17** allowed the C-2 configuration to be determined. For the majority of the compounds, 90-MHz ^{1}H-n.m.r. spectroscopy was good enough to measure the relative intensities of the H-2 doublets (Table III).

TABLE III

^{1}H-N.M.R. (90 MHz) AND POLARIMETRIC PARAMETERS FOR AQUEOUS SOLUTIONS[a] OF 2-(POLYHYDROXYALKYL)THIAZOLIDINE-4-CARBOXYLIC ACIDS

Compound	$\delta_{2(S)}$[b] *(p.p.m.)*	$\delta_{2(R)}$[b] *(p.p.m.)*	$J_{2(S)}$[b] *(Hz)*	$J_{2(R)}$[b] *(Hz)*	*Ratio*[c] *2R:2S (min)*	$[\alpha]_{eq}$[d] *(deg.)*	$[\alpha]_{lit.}$[e] *(deg.)*	$[\alpha]_{2(S)}$[f] *(deg.)*	$[\alpha]_{2(R)}$[f] *(deg.)*
6[g]	5.01	4.92	[h]	[h]	0.72 (30)	−150.3	−117.0	−178.6	−108.8
7[g]	5.15	4.91	2.90	5.40	0.96 (no changes)	−67.5		[i]	[i]
8[g]	5.05	4.97	4.83	7.25	0.54 (16)	−39.0		−127.0	123.0
9	5.07	5.01	6.47	2.69	0.58 (40)	−97.0	−107.9	−130.2	−39.8
10	5.12	4.97	3.72	5.86	4.06 (40)	−92.0	−97.8	−213.7	−62.0
11	5.30	5.16	3.12	4.33	0.77 (41)	−120.5	−103.0	−155.4	−75.5
12	5.31	5.23	3.78	4.92	1.40 (42)	−80.5	−98.9	−92.8	−71.6
13	5.03	4.98	7.86	4.12	0.59 (36)	−107.5	−128.8	−133.2	−64.2
14[g]	5.20	5.04	3.50	6.80	1.92 (35)	−82.3	−83.7	−125.3	−63.5
15	5.20	5.08	3.57	5.51	0.99 (28)	−95.5	−89.7	−117.2	−73.7
16	5.35	5.23	2.73	3.75	3.20 (45)	−83.2	−64.0	−200.5	−46.5
17[g]	5.18	5.03	3.83	6.80	2.83 (30)	−71.0	−66.9	−113.8	−55.9
18	5.28	5.08	2.67	3.36	0.25 (40)	−75.5	−95.3	[j]	[j]
19	5.07	5.05	7.69	3.08	0.41 (41)	−97.0		[j]	[j]
20	5.14	4.98	3.43	6.71	6.10 (30)	−87.0	−70.0	[j]	[j]

[a]Saturated solutions at 37°. [b]Chemical shifts and coupling constants of H-2 ring protons; 2(*R*) and 2(*S*) denote the configuration of the corresponding carbon atom. [c]From the relative intensities of 2(*R*) and 2(*S*) protons, after given time. [d]Equilibrium value after the time noted in the previous column. [e]Lit.[6]. [f]Values of 2(*R*) and 2(*S*) epimers calculated from n.m.r. and polarimetric data after 5 min and at the equilibrium time. [g]See also Tables I and II, and discussion for other n.m.r. data. [h]See Tables I and II, and Fig. 3. [i]Syrup. [j]Solubility too low for good S/N ratio in the 90-MHz F.t. spectrum.

Neither the ^{13}C- (see below) nor the ^{1}H-n.m.r. spectra indicated any deuterium exchange for H-2, which excluded[17] epimerisation *via* a C-2 carbanion. Moreover, no evidence[21,29] was obtained for the presence of an acyclic tautomer, the only other possible route of ring conversion. This finding, and the good correlation with polarimetry, indicate that the acyclic form, if present, must be short lived on the n.m.r. time-scale.

The ^{13}C-n.m.r. data are given in Table IV. There are four groups of resonances

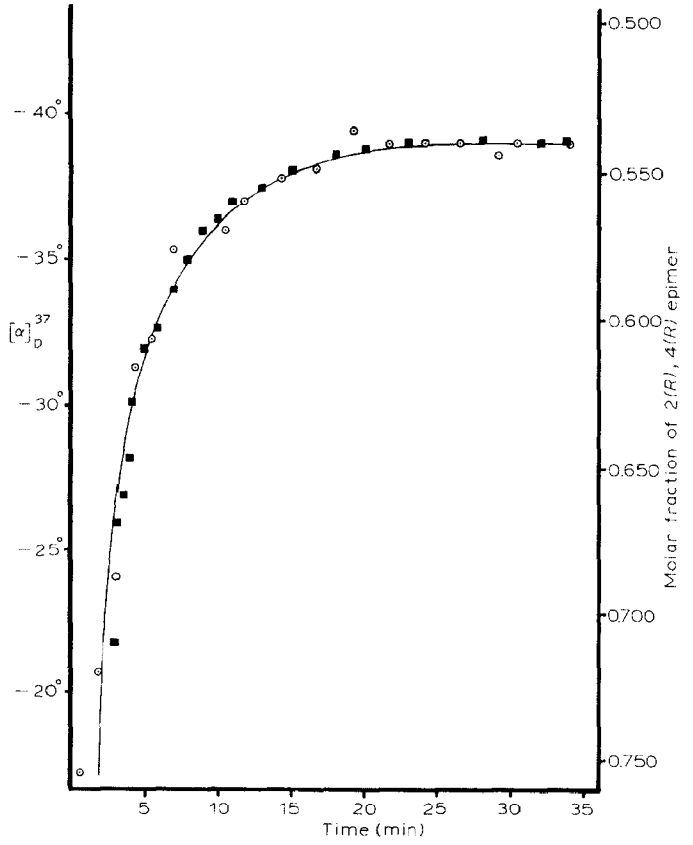


Fig. 5. The molar fraction of the 2(*R*),4(*R*)-epimer of **8** on dissolution in water as shown by the polarimetric (■) and ^{1}H-n.m.r. spectroscopic (⊙) data.

for carbon atoms, namely, for (*a*) the ring, (*b*) the side chain (secondary), and (*c*) the side chain (primary), and (*d*) resonances of carbonyl groups. Since there is no clear-cut division between groups (*a*) and (*b*) in most of the compounds, the assignments are not completely unequivocal. The assignment of resonances at 33–34 p.p.m. to C-5 of the ring was based on a comparison with data for thiazolidine-4-carboxylic acid[25–27]. Likewise, the resonance of C-4 was assigned at 64–65 p.p.m. The primary carbon atom of the 2-substituent resonates at 61–62 p.p.m. It was inferred that the resonance of C-4 was slightly upfield of that for C-2 since, for the pairs of epimers, the $\Delta\delta$ values were greater for C-2 (maximum of 2.2 p.p.m. for **9**) than for C-4 (maximum of 0.9 p.p.m. for **20**). Such an upfield location of the C-4 signals has been reported for 2-alkyl[24] and 2-aryl thiazolidines, although spectra of the latter were recorded for solutions of their *N*-acetyl derivatives in methyl sulfoxide[19,23]. On the other hand, for the products of reaction of **1** and pyridoxal and its derivatives[16,22], the resonances of C-2 are further upfield than those of C-4. Due to overlapping of the ^{1}H resonances (see above), few of the resonances were separated

TABLE IV

^{13}C-N.M.R. DATA (δ)[a] FOR THE 2-(POLYHYDROXYALKYL)THIAZOLIDINE-4-CARBOXYLIC ACIDS **6–20**[b]

	Ring			*Chain*					*COOH*
	C-2	*C-4*	*C-5*	*Secondary*				*Primary*	
Thz[c]	49.47	64.75	33.75						172.45
6	65.46	65.23	33.35					61.95	172.31
	66.54	65.60	33.52					60.87	
7	67.00	64.83	33.40	70.55				63.89	171.64
	66.86	64.88	33.51	71.37				63.97	
8	65.81	64.96	33.39	72.19				63.70	172.11
	68.71	64.81	33.90	69.56				63.96	172.31
9	66.53	65.13	33.21	73.09	71.84	71.84		62.96	172.40
	68.76	64.69	34.13	72.28	72.17	69.57		63.12	172.57
10	67.83	65.56	33.65	73.14	72.48	70.98		62.90	172.35
	66.97	65.13		72.50	72.00	70.65		63.07	172.42
11	67.13	65.40	33.38	74.17	73.25	70.81		63.34	172.45
	66.98	65.13	33.97	73.52	72.44	70.11		62.69	
12	67.40	65.45	33.65	73.25	70.98	69.62		63.45	172.45
	66.43		33.48	72.06	70.44	68.59			
13	66.64	65.02	33.21		71.35[d]	70.71		63.61	172.40
	67.67	64.26	34.24			69.51		63.39	172.67
14	67.83	65.68	33.57	72.11	71.25	69.84		63.55	172.34
	68.11	64.91		71.82	71.46	69.24		63.44	172.57
15	67.72	65.56	33.81	72.44	71.84	71.63	71.09	63.61	172.51
	66.64	65.23		73.04	72.11	71.41	70.92	62.23	173.10
16	68.48	65.56	33.65	72.94	71.25	69.79	69.62	63.93	172.73
	66.53		33.54	71.41	71.03	70.87	70.06		172.51
17	68.00	65.56	33.48	71.46	70.54	69.95	69.84	63.88	172.18
	66.48	64.75		70.81	70.14	69.08	68.27		172.20
18	67.56	65.72	33.27	73.63	72.11	69.57		19.83	173.00
	68.00	64.85	34.08	74.12	71.46	69.95		19.72	172.40
19	66.81	65.02	33.15	73.49	71.16	70.96		19.43	172.51
	66.44	64.58		72.21	69.79	68.21			
20	66.37	65.61	33.54	73.30	71.84	70.06	68.00	19.45	172.35
	67.40	64.85		73.58	71.30	69.41	68.23		172.40

[a]Internal 1,4-dioxane. [b]When appropriate, data for major and minor epimers are given in the upper and lower rows, respectively. [c]Thiazolidine-4(*R*)-carboxylic acid. [d]Broad signal of triple (or greater) intensity.

sufficiently from their nearest neighbours to allow the use of the selective carbon–proton decoupling technique. For **10**, chosen for its excellent solubility, selective irradiation of H-2 of the major component enhanced only the ^{13}C resonance at 67.8 p.p.m., which must therefore belong to C-2*.

In alkaline media (at pH $\geq$8.5), although the mutarotation seems to be slower, decomposition occurs. After 5 min at pH 9, considerable amounts of un-

*Since this paper was submitted, the ^{13}C-n.m.r. spectrum of the ^{14}C-2-enriched derivative of D-glucose [in $(CD_3)_2SO$] was reported[31], which correlates well with our assignments.

TABLE V

YIELDS AND MELTING POINTS OF THE 2-(POLYHYDROXYALKYL)THIAZOLIDINE-4-CARBOXYLIC ACIDS **6–20**

Compound	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Yield (%)															
Method *A*	83	[a]	53	72	82	57	83	84	88	43	71	93	58	83	78
Method *B*	20	[a]			[a]	[a]	49	[a]	38	[a]	34	24	34	54	49
M.p.(°)															
Method *A*	149		120	162	152	157	157–158	160–162	161–162	174	174–177	154–156	174–175	160–161	147
Method *B*	153–155			158			115–120		137–138			156	154–156	160–162	144
Lit.[6]	149–151			158–159	152	152–155	150–151	162–163	161–162	169	173–175	148–149	174		147

[a]Syrup.

identified hydrolysis products were detected by t.l.c.[18]. At pH 12, only ~50% of the starting compounds remained after 10 min. To determine the role of the base, reactions of **3** and **1**·HCl were carried out using various bases, namely, potassium and ammonium hydroxide, piperidine, and morpholine, in the presence and absence of ethanol. Pyridine was used only in aqueous solutions. The products were as described for methods *A* and *B*, respectively, irrespective of the base and determined only by the presence [2(*R*),4(*R*) product] or absence of ethanol [2(*S*),4(*R*) product]. Reaction in aqueous ethanol containing potassium acetate yielded the 2(*S*),4(*R*) epimer. Reactions of the free base **1** with **3**, in the presence and absence of ethanol, gave the 2(*S*),4(*R*) isomer. Moreover, when base was added to a solution of the 2(*R*),4(*R*) epimer of **14** in 4M hydrochloric acid, the 2(*S*),4(*R*) isomer was obtained. However, on reversal of the procedure, the configuration at C-2 was retained. On storage of the 2(*R*) epimer of **14** in its solid state, the 2(*S*) isomer was formed.

The question arises as to the role of epimerisation in the aqueous solutions during the synthesis of **6–20**. ^{1}H-N.m.r. spectroscopy could not to be used to study the changes in composition. Moreover, the ^{13}C-n.m.r. spectra revealed no traces of product after 20 h and, after 2 weeks, only relatively weak signals were detected. No crystallisation occurred before the addition of base to the reaction mixtures. On the other hand, in reactions of the free base **1**, the products crystallised shortly after dissolution of substrates. The speed of cyclisation is a maximum[35] when the pH of the medium equals the p*K* of the imine group. It is possible that, when sufficient base is added, crystallisation occurs so quickly that epimerisation is negligible. The role of the ethanol is not easy to understand. Added to a reaction mixture, even when some crystallisation has already occurred, it causes configuration reversal of crystalline reaction products for **6, 12, 14,** and **18**.

The data in Table V show the yields of crystalline products obtained by methods *A* and *B*. Comparison of the ^{13}C-n.m.r. spectra of the solid and syrupy residues for each reaction proved their identity. Only small amounts of substrates were detected in the spectra of syrups and this was confirmed by g.l.c. analysis[18].

EXPERIMENTAL

D-Glyceraldehyde and L-glyceraldehyde were obtained according to Perlin[36]. Optical rotations were determined with Perkin–Elmer 241 (589 nm) and Polamat A (Carl Zeiss) (546 nm) polarimeters. Melting points were measured on the Böetius (Carl Zeiss) apparatus, and are uncorrected. Water used for all syntheses and for polarimetry was triple quartz-distilled and thoroughly washed with nitrogen.

*2-(Polyhydroxyalkyl)thiazolidine-4-(*R*)-carboxylic acids* (**6–20**). — A solution of **1**·HCl·H_2O (3.61 g, 20 mmol) and the aldehyde (20 mmol) in water (2–5 mL) was kept at room temperature for 20 h and then neutralised with a base (20 mmol; in method *A*, the addition of pyridine was followed, after ~20 h, by 200 mL of ethanol). The mixture was stored for 20 h, the precipitate was then collected, but recrystallisation was not attempted. Solids were dried to constant weight in a

vacuum desiccator over P_2O_5. Filtrates were concentrated *in vacuo* at 25–30° and the residues were stored in a vacuum desiccator over P_2O_5.

Compound **7** (syrup) was not analysed, since g.l.c.[18] indicated the presence of ~10% of unreacted substrates and unidentified impurities.

Compound **8**: Calc. for $C_6H_{11}NO_4S$: C, 37.30; H, 5.73; N, 7.25; S, 16.59. Found: C, 37.15; H, 5.66; N, 7.33; S, 16.66.

Compound **19**: Calc. for $C_9H_{17}NO_6S$: C, 40.44; H, 6.41; N, 5.24; S, 12.00. Found: C, 40.28; H, 6.21; N, 5.34; S, 12.34.

N.m.r. spectroscopy. — For ^{13}C-n.m.r. measurements, the samples were prepared as saturated solutions in D_2O just prior to recording. Spectra were recorded with a Jeol FX 90Q (22.53 MHz) instrument, using an 8-μs (30°) pulse with 1-s repetition, 5-kHz spectral width, and 8k data points. 1,4-Dioxane was used as the internal standard. ^1H-N.m.r. experiments were performed on Jeol FX 90Q (90 MHz), Bruker WP 100 SY (100 MHz), and AM 360 (360 MHz) instruments. A simple program (IBM PC-XT, 640 kB operating memory, 8087 coprocessor), based on well established principles[37–40] using the LAOCOON method[38], was written in Turbo Pascal to allow interpretation of the proton spectra. Iterative simultations of up to seven-spin systems, comprised of side-chain, backbone, and H-2 ring protons, employing a Lorentzian line-shapes plotting routine, were used to fit spectral parameters. For measurement of the ratio of epimers, the HOD peak was eliminated by applying, in the F.t. mode, a 90° pulse followed, after a short delay (usually 7–8 s, depending on the sugar substituent and concentration of the solute), by a 180° pulse. The FID was acquired directly, and, after a delay for relaxation (60–70 s), the sequence was repeated until no changes were detectable (usually after 30–40 cycles).

ACKNOWLEDGMENTS

We thank Dr. Anna Dąmbska (Warsaw University) for measurements of ^{13}C-n.m.r. and low-resolution ^1H-n.m.r. spectra, and Mrs. Joan Street (Southampton University) for recording the high-resolution ^1H-n.m.r. spectra.

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