Synthesis and in Solution Behaviour of New 2-Substituted-4-thiazolidinecarboxylic Acid Derivatives

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A number of 2-substituted-4-thiazolidinecarboxylic acid derivatives were synthesized by cyclocondensation of L-cysteine or its esters with various aldehydes, resulting from acids provided with antiinflammatory properties. In the cyclocondensation a new chiral center at C-2 position of thiazolidine ring is formed giving rise to a mixture of diastereoisomers which can be partially separated. These diastereoisomers show in solution a fast epimerisation at the same chiral center as evidenced by ^{1}H-nmr studies.

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Free radicals are thought to be involved in many disease processes [1]. There is good evidence that glutathione (L-glutamyl-L-cysteinylglycine) is a natural scavenger of reactive oxygen intermediates and free radicals. L-Cysteine prodrugs like *N*-acetyl-L-cysteine are known to increase intracellular glutathione levels [2].

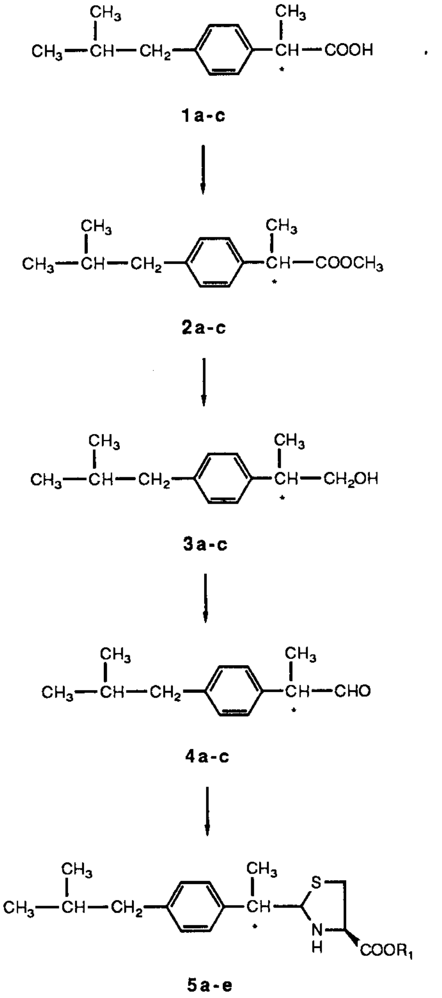
2-Methylthiazolidine-(4*R*)-carboxylic acid is reported [3,4] to deliver L-cysteine into cells by a non-enzymatic opening of the ring. Acetaldehyde is also liberated and then probably metabolically oxidized to acetic acid.

We were interested in a combined action of a L-cysteine prodrug with an antiinflammatory acid [5]. In this paper we describe the synthesis of thiazolidine derivatives of selected antiinflammatory acids. The new compounds were synthesized in order to investigate whether the non-enzimatic ring opening of 2-substituted thiazolidines might deliver not only cysteine but also, instead of acetaldehyde, and aldehyde that could be oxidized to an antiinflammatory acid.

Ibuprofen **1a** and its enantiomers **(R)** and **(S)** 2-[4-(2-methylpropyl)phenyl]propanoic acids **1b,c** were converted to respective methyl esters **2a-c** (Scheme 1). Derivatives **2a-c** were reduced with calcium borohydride to alcohols **3a-c** which were oxidized to aldehydes **4a-c** by the Swern oxidation [6]. It should be mentioned that although **4a** is an intermediate in the synthesis of ibuprofen itself, we followed the above procedure (Scheme 1) to prepare unknown optically active compounds such as **3b,c** and **4b,c** starting from resolved acids **1b,c** [7,8]. Compounds **4a-c** were condensed with L-cysteine or L-cysteine esters, in hydroalcoholic solution, to give thiazolidine derivatives **5a-e**.

Aldehydes **7a** [9] and **7b** [10] derived from naproxen **6a** and ketoprofen **6b** respectively, were condensed with L-Cysteine in water-acetone mixtures at room temperature to give thiazolidines **8a,b** (Scheme 2). Noteworthy acetone is unreactive under these conditions.

Scheme 1

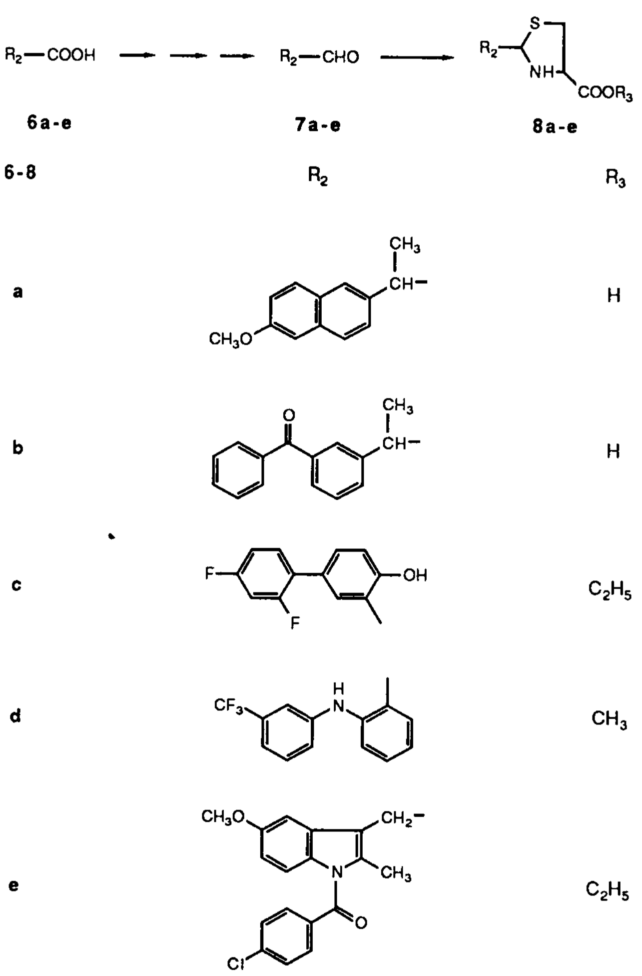


1-4	*
a	RS
b	R
c	S

5	*	R_1
a	RS	H
b	RS	CH_3
c	RS	n-C_6H_{13}
d	R	H
e	S	H

Diflunisal methyl ester **6c** [11] was reduced to 5-(2,4-difluorophenyl)salicyl alcohol with lithium aluminum

Scheme 2



hydride and then submitted to platinum catalized air oxidation in the presence of lead nitrate [12] to give aldehyde **7c** which reacted very sluggishly with L-cysteine ethyl ester in protic media. However, the reaction was over in a few hours giving desired **8c**, when we used pyridine as a solvent (Scheme 2). Similarly [2-(3-trifluoromethyl)phenylamino]benzaldehyde **7d** [12] derived from flufenamic acid **6d** and [1-(4-chlorobenzoyl)-2-methyl-5-methoxyindol-3-yl]-acetaldehyde **7e** [14] derived from indomethacin **6e**, were condensed in pyridine with L-cysteine esters giving thiazolidines **8d** and **8e** respectively (Scheme 2).

All these cyclizations give rise to a new chiral center at C-2 position of the thiazolidine ring, affording a mixture of two diastereoisomers that we tried to separate by crystallization. However, when we investigated the behaviour of these thiazolidines in solution, we found that equilibration between diastereoisomers occurs rapidly through epimerization at C-2 position. A mechanism, involving a ring seco intermediate, probably an imine, has been several times suggested [3, 15-17] to account for mutarotation and selective acetylation of C-2 substituted thiazolidines (Scheme 3). The equilibrium exhibited by our derivatives is strongly dependent on the solvent and the C-2 substituent, and, it is very fast even in neutral aprotic media. In fact, the ^{1}H-nmr spectra of these compounds show signals relevant from 2 epimers. Note that derivatives where the benzylic chiral center of the antiinflammatory moiety is not resolved show two pairs of epimers (see for example derivatives **5a-c** in Table 3).

Scheme 3

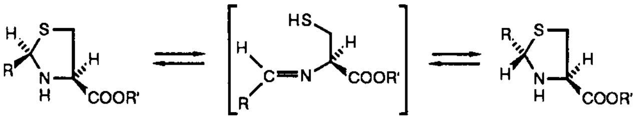


Table 1

Analytical Data of Compounds **5a-e**

Compound	Yield	Mp [a], °C (crystallization solvent)	$[\alpha]_D^{20}$ [b], °	Molecular Formula	Analysis, % Calcd./Found C	H	N	Cl	S
5a	56	160-163 (methanol)	−75.6	$C_{16}H_{23}NO_2S$	65.49 65.39	7.90 8.01	4.77 4.82		10.92 10.59
5b	40	150-152 (acetonitrile)	−42.4	$C_{17}H_{26}NO_2S$ HCl	59.37 59.46	7.62 7.80	4.07 4.11	10.31 10.40	9.32 9.40
5c	20	115-117 (*n*-pentane)	−47.2	$C_{22}H_{35}NO_2S$ HCl	63.82 63.56	8.76 9.07	3.83 3.55	8.56 8.55	7.74 7.74
5d	56	170-172 (methanol)	−36.1	$C_{16}H_{23}NO_2S$	65.49 65.21	7.90 8.05	4.77 4.78		10.93 10.73
5e	58	138-140 (methanol)	−97.0	$C_{16}H_{23}NO_2S$	65.49 65.54	7.90 8.12	4.77 4.87		10.93 10.76

[a] With decomposition. [b] Values recorded one hour after dissolution; C = 1, dimethylformamide.

Table 2

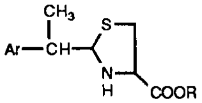
Analytical Data of Compounds **8a-e**

Compound	Yield	Mp [a], °C (crystallization solvent)	[α]	Molecular Formula	Analysis, % Calcd./Found C	H	N	Cl	S	F
8a	50	184-185	−69.8	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41		10.10	
		(acetone)			64.03	5.98	4.40		9.85	
8b	43	123-125		$C_{19}H_{19}NO_3S$	60.38	5.33	3.70	9.38	8.49	
		(ethyl acetate)		HCl	60.36	5.31	3.58	9.16	8.16	
8c [d]	31	118-120		$C_{18}H_{17}F_2NO_3S$	59.16	4.68	3.83		8.77	10.39
		(isopropyl ether)			59.11	4.68	3.71		8.65	10.24
8c [e]	11	74-76	−97.2	$C_{18}H_{17}F_2NO_3S$	59.16	4.68	3.83		8.77	10.39
		(isopropyl ether)			59.11	4.65	3.77		8.65	10.51
8d	80	70-73	+153.6	$C_{18}H_{17}F_3N_2O_2S$	51.61	4.33	6.68	8.46	7.65	13.60
		(isopropyl ether)	[c]	HCl	51.50	4.54	6.56	8.32	7.88	13.45
8e	69	100-103	−35.8	$C_{24}H_{25}ClN_2O_4S$	56.58	5.14	5.50	13.91	6.29	
		(ethyl ether)		HCl	56.31	5.32	5.30	13.64	6.35	

[a] With decomposition. [b] Values recorded one hour after dissolution; C = 1, dimethylformamide. [c] C = 1.7, dimethylformamide. [d] First crop. [e] Second crop.

Table 3

^{1}H-NMR Compounds **5b-e** [a]. Typical Signals, δ [ppm] [b]



Compound		d3H	ABX [c] system H_A	H_B	dq1H	ABX [c] System H_X	d1H
5d	A	1.29	2.98	2.80	2.81	4.00	4.76
	B	1.27	3.19	2.71	3.06	3.64	4.62
5e	A	1.33	2.63	3.01	3.05	3.73	4.76
	B	1.23	2.89	3.04	2.86	4.01	4.63
	A_1	1.40	3.09----------	----------3.54		4.72	4.90
	B_1	1.31	"	"		4.68	5.04
5b	A_2	1.41	"	"		4.83	4.96
	B_2	1.28	"	"		4.55	4.93
	A_1	1.40	3.07----------	----------3.56		4.72	4.90
	B_1	1.31	"	"		4.68	5.04
5c	A_2	1.41	"	"		4.83	4.96
	B_2	1.28	"	"		4.55	4.93

[a] The spectrum of **5a** is the sum of those of **5d** and **5e**. [b] Solvent DMSO-d$_6$. [c] The chemical shifts of the ABX system were calculated according to the method reported in "Nuclear Magnetic Resonance for Organic Chemists", D. W. Mathieson, 1962, Accademic Press. Note that for compounds **5b** and **5e** the dashed intervals indicate three undistinguishable hydrogens.

The signal intensity ratio of the two epimers changes with time in hexadeuterio-dimethylsulfoxide solution at room temperature. In the case of **5e**, for example, starting from 9:1 ratio, equilibrium is reached at 1:1 ratio in about one hour.

Interestingly, several subsequent crystallizations of thiazolidine **8c** resulted in two different crops. The first fraction shows a very rapid reversal of C-2 protons intensity ratio in deuteriochloroform solution. Indeed starting from 9:1 ratio the equilibrium is reached at 1:3 ratio in about ten minutes. The resultant spectrum is identical to that of the second crop which does not show epimerization. Spec-

Table 4

^{1}H-NMR (DMSO-d_6) of Compounds **8a-e**

Compound	δ [ppm]
8a	1.31 (d, 0.45H), 1.36 (d, 0.9H), 1.38 (d, 0.9H), 1.42 (d, 0.75H), 2.60-3.25 (m, 3H), 3.65 (dd, 0.25H), 3.78 (dd, 0.3H), 4.03 (dd, 0.15H), 4.05 (dd, 0.3H), 4.73 (d, 0.3H), 4.76 (d, 0.25H), 4.88 (d, 0.15H), 4.89 (d, 0.3H), 7.09-7.80 (m, 6H)
8b	1.31 (d, 0.51H), 1.35 (d, 0.9H), 1.44 (d, 0.9H), 1.46 (d, 0.69H), 3.05-3.54 (m, 3H), 4.43 (dd, 0.17H), 4.55 (dd, 0.3H), 4.65 (dd, 0.3H), 4.73 (dd, 0.23H), 4.96 (d, 0.17H), 4.98 (d, 0.3H), 5.05 (d, 0.23H), 5.11 (d, 0.3H), 7.48-7.82 (m, 9H)
8c	1.21 (t, 3H), 2.98-3.08 (m, 1H), 3.19-3.35 (m, 1H), 3.70-4.38 (m, 2H), 4.14 (q, 1.2H), 4.16 (q, 0.8H), 5.72 (d, 0.4H), 5.87 (d, 0.6H), 6.86-7.59 (m, 6H), 10.07 (s, 0.6H), 10.12 (s, 0.4H)
8d [a]	3.72 (m, 2H), 3.82 (s, 3H), 4.87 (m, 1H), 6.32 (d, 1H), 7.07-7.62 (m, 8H), 8.15 (t, 1H), 9.00 (broad s, 1H)
8e	1.12 (t, 1.5H), 1.25 (t, 1.5H), 2.26 (s, 1.5H), 2.27 (s, 1.5H), 3.20-3.72 (m, 5H), 3.78 (s, 1.5H), 3.79 (s, 1.5H), 4.22 (q, 1H), 4.25 (q, 1H), 4.68-5.07 (m, 2H), 6.73 (dd, 1H), 6.93 (dd, 1H), 7.25 (dd, 1H), 7.58-7.72 (m, 4H)

[a] Spectrum in deuteriochloroform.

tra of both fractions recorded in hexadeuteriodimethylsulfoxide solution were identical showing an epimeric 6:4 ratio stable with time. Unfortunately it is difficult to assess the diastereoisomeric purity of all these thiazolidines isolated by crystallization, because the time required to dissolve and analyze them is sufficient to shift the epimeric ratio from the starting status. However, we think that the analysis of the diastereoisomeric purity of these compounds does not play an important role, since these thiazolidines should be thought as the system outlined in Scheme 3 rather than single molecules. The peculiar behaviour of C-2 substituted thiazolidines is worthy of both chemical and biological considerations.

A more detailed analysis of C-2 epimerization of these compounds together with the pharmacological characterization is currently under investigation.

EXPERIMENTAL

Melting points and boiling points (Siwoloboff's method) were determined in open capillary tubes with a Buchi SMP 20 melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. The ^{1}H-nmr spectra were recorded on a VARIAN Gemini 200 spectrometer. Chemical shifts are referred to residual chloroform (7.24 ppm) or central peak of residual dimethylsulfoxide (2.49 ppm). In Table 3, A represents the major epimer at equilibrium, and B the minor one. The spectra of intermediates **2b,c** and **3b,c** are in agreement with literature data of the racemic compounds [18].

(2*R*)-2-[4-(2-methylpropyl)phenyl]propan-1-ol (**3b**).

Compound **2b** [8] (23.5 g, 106 mmoles) was dissolved in anhydrous ethyl alcohol (150 ml). To this solution sodium borohydride (5.2 g, 138 mmoles) and an equimolecular amount of calcium chloride were added portionwise, keeping the reaction mixture under stirring at −20° and under nitrogen atmosphere. The reaction mixture was filtered to separate the inorganic salt and the filtrate was evaporated to dryness under reduced pressure. The oily residue was dissolved in ethyl ether and this solution was washed with water until neutral. The organic phase was dried over sodium sulfate and then evaporated to dryness to give 19,5 g (96%) of alcohol **3b**; 1.5 g of this product was purified by chromatography on silica gel eluting with dichloromethane and a gradient of ethyl acetate, providing 1.3 g of pure **3b** as an oil, bp 245-247°; $[\alpha]_D^{20}$ = +14,6° (c = 1.6, chloroform).

(2*S*)-2-[4-(2-Methylpropyl)phenyl]propan-1-ol (**3c**).

This compound was similarly prepared and was obtained as an oil, bp 245-247°, yield 87%; $[\alpha]_D^{20}$ = −14.8° (c = 1.6, chloroform).

(2*R*)-2-[4-(2-Methylpropyl)phenyl]propanal (**4b**).

Dimethyl sulfoxide (1.67 ml, 23.5 mmoles) and 2 ml of methylene chloride were added dropwise to a solution of oxalyl chloride (1.4 g, 11.1 mmoles) in methylene chloride (15 ml) under stirring at −65°. After five minutes a solution of **3b** (2 g, 10.4 mmoles) in methylene chloride (8 ml) was added, maintaining the temperature at −65°. After a further five minutes, triethylamine (3 ml, 20.8 mmoles) was added dropwise while the temperature was kept at −65° and *p*H was maintained below 7. The mixture was allowed to warm to room tmeperature, water was added and the organic phase was separated. Following drying over sodium sulfate and removal of the solvent under reduced pressure, the desired aldehyde (1.9 g, 95%) was obtained as a colourless oil; $[\alpha]_D^{20}$ = +149.4° (c = 1.6, chloroform).

(2*S*)-2-[4-(2-Methypropyl)phenyl]-1-propanal (**4c**).

Compound **4c** was similarly prepared and obtained in a yield of 85% as an oil; $[\alpha]_D^{20}$ = −143.4° (c = 1.6, chloroform).

The intermediates **4b** and **4c** were used without further purification.

(4*R*)-2-[(1*RS*)-1-(4-(2-Methylpropyl)phenyl)ethyl]thiazolidine-4-carboxylic Acid (**5a**).

To a stirred suspension of L-cysteine hydrochloride (7.88 g, 50 mmoles) and potassium acetate (4.9 g, 50 mmoles) in a mixture of water and ethanol (150 ml, 1:1 v/v), previously deoxygenated by a stream of nitrogen, a solution of **4a** [18] (10 g, 52 mmoles) in 10 ml of ethanol was added dropwise at room temperature. In a short time the almost complete dissolution of cysteine was observed, meanwhile a precipitate begins to form. After twenty minutes, the precipitate is filtered, washed with plenty of water and dried. The crude product (13.3 g) was crystallized from hot methanol (250 ml) to give pure **5a** (9g).

Compounds **5b-e** (Table 1) were similarly prepared.

5-(2,4-Difluorophenyl)-2-hydroxybenzaldehyde (**7c**).

To a suspension of 7.9 g (0.2 mole) of lithium aluminum hydride in 750 ml of tetrahydrofuran at 0°, 47 g (0.18 mole) of methyl 5-(2,4-difluorophenyl)2-hydroxybenzoate [10] was added portionwise under stirring. The ice bath was removed after complete addition and 200 ml of ethyl acetate, 200 ml of a saturated sodium sulfate aqueous solution and 400 ml of 5% sulfuric acid were added. The organic phase was separated, dried over sodium sulfate, filtered and concentrated *in vacuo* to give 36.9 g (88%) of 5-(2,4-difluorophenyl)salicyl alcohol, mp 143-145°; ^{1}H-nmr (DMSO-d$_6$): δ 8.00-6.80 (m, 6H, aromatic), 4.65 (s, 2H, CH$_2$-O)].

This crude alcohol (2.4 g, 0.01 mole) was dissolved at room temperature in 10 ml of 1N sodium hydroxide and 5 ml of tetrahydrofuran. To this solution lead nitrate (0.5 g dissolved in 5 ml of water) and then 10% platinum on charcoal (0.24 g) were added. This mixture was kept at 45° for 30 hours. Subsequently, the reaction mixture was cooled at room temperature, filtered, acidified with 10% hydrochloric acid to Congo red and extracted with ethyl ether. The ethereal extracts were dried over sodium sulfate and evaporated to dryness under reduced pressure obtaining 1.9 g (81%) of **7c** as a white solid, mp 98-100°; ^{1}H-nmr (DMSO-d$_6$): δ 10.50 (s, 1H, CHO), 8.10-7.00 (m, 6H, aromatic). This intermediate was used without further purification.

(4*R*)-2-[1-(6-Methoxy-2-naphtyl)ethyl]thiazolidine-4-carboxylic Acid (**8a**).

To a stirred solution of L-cysteine hydrochloride (5.94 g, 37.6 mmoles) and potassium acetate (3.69 g, 37.6 mmoles) in a mixture of water and acetone (100 ml; 1:1 v/v) a solution of **7a** [9] (8.2 g, 38.3 mmoles) in 50 ml of acetone was added dropwise at room temperature. The precipitate obtained was collected after 1 hour at room temperature and washed with a mixture of water and acetone (1:1, v/v) and then with acetone to give 6 g of **8a**.

Compound **8b** was similarly prepared.

Methyl (4*R*)-2-[(2-(3-Trifluoromethyl)phenylamino)phenyl]thiazolidine-4-carboxylate Hydrochloride (**8d**).

To a solution of L-cysteine methyl ester hydrochloride (8.3 g, 48 mmoles) in pyridine (100 ml), deoxygenated by a stream of nitrogen and kept under stirring at room temperature, **7d** [14] (11.7 g, 44 mmoles) was added. After stirring for 4 hours at room temperature, the reaction mixture was poured into water (1000 ml) and extracted with ethyl ether. The combined ethereal extracts were dried over sodium sulfate and the solvent was removed by evaporation under reduced pressure. The oily residue was purified by chromatography on silica gel (eluent, dichloromethane: ethyl acetate, 97:3) obtaining an oil (16 g) which was dissolved in isopropyl ether and treated with a 4N hydrochloric acid solution in ethyl ether. Compound **8d** was collected and washed with ligroin to give a pure solid (16.1 g).

Compounds **8c,e** (Tables 2 and 4) were similarly prepared.

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