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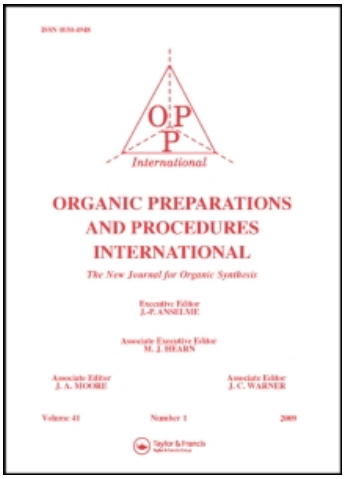

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SYNTHESIS OF 2-SUBSTITUTED THIAZOLIDINE-4-CARBOXYLIC ACIDS

Elena Pini[a]; Donatella Nava[a]; Riccardo Stradi[a]
[a] Istituto di Chimica Organica, Facoltá di Farmacia, Universitá di Milano, Milano, ITALY

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organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with water, saturated brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the crude product, which was recrystallized from methanol-ether to afford **6** (0.75 g, 84 %) as a yellow solid, mp. 194-195°C, $[\alpha]_D^{20}$ = +43°C (*c* 3, pyridine), *lit.*[4] 192°C; $[\alpha]_D^{20}$ = +43.8°C (*c* 3.08, pyridine); IR (KBr): 3364, 3061, 1598, 1515, 1350, 1215, 765 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (s, 2H, NH_2), 2.88-2.90 (t, 1H, CH), 3.07-3.33 (m, 2H, CH_2), 4.09 (s, 1H, OH), 4.69-4.70 (d, 1H, CH), 7.24-8.05 (m, 19H, ArH); ^{13}C NMR ($CDCl_3$): δ 152.63-123.24, 86.33, 73.34, 65.61, 57.61; EI-MS (m/z, %): 454.

Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.03; H, 7.06; N, 6.54. Found: C, 70.88; H, 7.14; N, 6.42

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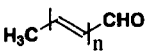
SYNTHESIS OF 2-SUBSTITUTED THIAZOLIDINE-4-CARBOXYLIC ACIDS

Submitted by (06/11/03) Elena Pini*, Donatella Nava and Riccardo Stradi

Istituto di Chimica Organica, Facoltà di Farmacia
Università di Milano, 20133 Milano, ITALY
Fax: + 39 (0)2-50314476; E-mail: elena.pini@unimi.it

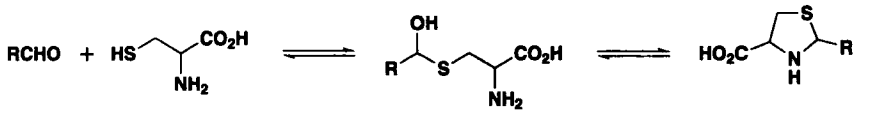
In our ongoing[1] work on chemical and pharmacological activity of polyconjugated aldehydes **1**, our attention was turned to the synthesis of 2-substituted thiazolidine-4- carboxylic acids. Preliminary *in vitro* and *in vivo* pharmacological tests carried out on polyenals **1** which are structurally related to carotenoids, have shown potential anti-proliferative and antioxidant activities. It is known that, in enzymes, the interaction between the α,β-unsaturated carbonyl compounds and the SH groups of glutathione and cysteine play an important role in the mechanism by which these molecules exert their pharmacological activity.[2-7] In fact, thiazolidine-4-carboxylic



1
n = 2-7

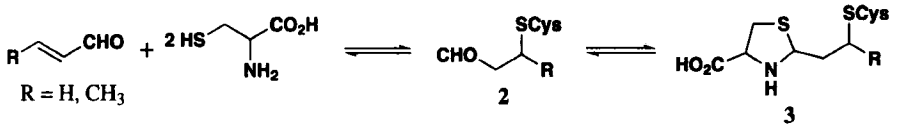
acids obtained from the reaction of cysteine with α,β-unsaturated aldehydes such as acrolein, crotonaldehyde and 4-hydroxypentenal,[8,9] exhibit increased antitumor activity and decreased toxicity in comparison with the free aldehydes, because they gradually releases the aldehydes *in situ*. The pharmacological effect is in inverse relationship to the aldehyde-cysteine bond stability.

The reaction between equimolecular amount of cysteine and saturated aldehydes or ketones,[10] aromatic aldehydes,[11] furfurals[12] and retinal[13] lead to 2-substituted thiazolidine-4-carboxylic acids through the hemimercaptal formation, followed by dehydration and cyclization *(Eq. 1)* . In the case of saturated aliphatic aldehydes or ketones, the chain length does not affect



(1)

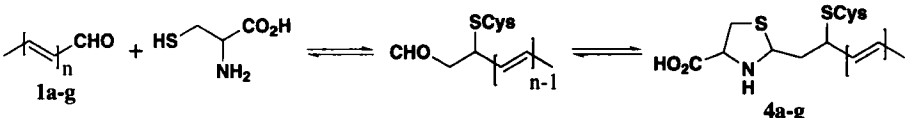
the reaction. The condensation of two equivalent of cysteine with acrolein, crotonaldehyde or 4-hydroxypentenal[14] gives the product of the Michael addition of cysteine to the double bond (**2**), followed by the addition of the second mole to form thiazolidine **3** *(Eq. 2)*.



(2)

The biological activity of aldehydes **1** was investigated to evaluate their activity towards cardiovascular and proliferative pathologies or ageing alterations. Preliminary results[(1)] of *in vivo* and *in vitro* tests have shown that these molecules, like carotenoids, have potential antioxidant activity and a potential role in protection towards UV radiation damage. Since thiazolidine derivatives of α,β-unsaturated aldehydes have interesting pharmacological properties in comparison with free aldehydes[(8,9)], the aim of our work was to extend the study of the reaction between cysteine and polyconjugated aldehyde **1** and to evaluate their potential pharmacological activity.

Known aldehydes **1b-g,** obtained by literature methods,[15,16] were characterized by us *via* mono and bi-dimensional magnetic resonance; a single peak in the HPLC three-dimensional chromatograms supports the existence of only one isomer in each case. The reaction *(Eq. 3)* was



(3)

a) n = 1 b) n = 2 c) n = 3 d) n = 4 e) n = 5 f) n = 6 g) n = 7

carried out in aqueous solution using two equivalents of cysteine and one equivalent of aldehydes **1a-g**; the use of equimolecular amount of reagents lead only to lower yields of **4**. Unlike saturated aldehydes, the delocalization of the positive charge along the unsaturated chain led to

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decreased yields and it was necessary heat the reaction mixture. Compound **1g** failed to react even at 35°C; further increase in temperature led to decomposition. The thiazolidine-4-carboxylic acids **4a-f** were obtained as diasteroisomeric mixture and identified using NMR bi-dimensional techniques, IR and mass spectroscopies. The low solubility of compounds **4e** and **4f** limited analytical studies to ^{1}H-NMR, IR and mass spectroscopy.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes with a Stuart Scientific apparatus and are uncorrected. IR spectra were determined as KBr pellets with a FT-IR 16 PC Perkin-Elmer Spectrophotometer equipped with a Cambridge Instruments Microscopy for solids. ^{1}H and ^{13}C NMR spectra were recorded in D_2O/DCl on a Varian Gemini 200 operating at 200 MHz and 50 MHz respectively using TMS as internal standard or on an Avance DRX 300 Bruker operating at 300 MHz; chemical shifts (δ) in ppm, coupling constants (*J*) in Hz. Mass/HPLC analyses were performed with a Finnigan TSA 700 with thermospray MS/MS tecnique. Thin layer chromatographies were carried out on silica gel (silica gel $60F_{254}$, Merck).

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Thiazolidine-4-carboxylic Acid (4a-f). General Procedure.- To a solution of R (+)cysteine zwitterion (0.23 mmole) in distilled water, the appropriate aldehyde **1a-f** (1.15 mmol) was added at 4°C and the mixture was stirred for 6 hrs at the temperatures specified in *Table 1*; the progress of the reaction was monitored by TLC using butanol-acetic acid-water 2:1:1 and ninhydrin reagent as detector. During the reaction, the pH of the mixture decreased from 7 to 3 and the adduct began to precipitate. After the mixture was allowed to stand at 4°C overnight, the precipitate was collected and washed with water, warm ethanol and with chloroform.

Table 1. Yields, mps, Elemental Analyses and M^+ of Compounds **4 a-f**

Cmpd	Temp. (°C)	Yield (%)	mp (°C)	Elemental Analyses (Calcd) C	H	N	S	M^+
4a	4	61	165-167[a]	40.52 (40.79)	6.22 (6.16)	9.34 (9.51)	21.83 (21.78)	294
4b	4	55	175-178	45.23 (45.00)	6.15 (6.29)	8.96 (8.74)	20.22 (20.00)	320
4c	20	45	180-182	48.76 (48.53)	6.60 (6.40)	8.13 (8.08)	18.79 (18.50)	346
4d	20	35	195-198	51.38 (51.58)	6.52 (6.49)	7.32 (7.52)	17.33 (17.21)	372
4e	35	35	>200	54.51 (54.24)	6.44 (6.57)	6.90 (7.03)	16.23 (16.08)	398
4f	35	15	>200	56.48 (56.57)	6.83 (6.65)	6.44 (6.59)	14.93 (15.10)	424

[a] *lit.*[9] mp. 168-171°C

Table 2. Spectral Data of Compounds **4a-f**

Cmpd	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR
4a	3429, 2962, 2924, 1619, 1384, 1261, 1095	5.01 (m, 1H, H_2), 4.48-4.26 (m, 1H, H_4), 3.83 (m, 1H, $H_{2''}$), 3.5-3.2 (m, 2H, H_5), 3.2-2.8 (m, 3H, $H_{2'}$, $H_{3''}$), 2.3-1.9 (m, 2H, $H_{1'}$), 1.28-1.2 (d, 3H, J = 6.5, CH_3).	170, 169.4, 63, 61.9, 52.7, 39, 38.1, 31.4, 29.7, 20
4b	3413, 2924, 1630, 1504, 1384, 1344, 1047, 968	5.6-5.2 (m, 2H, $H_{4''}$, $H_{3'}$), 4.8 (m, 1H, H_2), 4.45 (m,1H, H_4), 4.05 (m, 1H, $H_{2''}$), 3.3-3 (m, 3H, H_5, $H_{2'}$), 2.8 (m, 2H, $H_{3''}$), 2.2-1.8 (m, 2H, $H_{1'}$), 1.35 (d, 3H, J = 6.7, CH_3).	170.1, 169.4, 132.3, 128.5, 62.83, 61.6, 54.2, 52.4, 37.2, 31.5, 29.6, 18.5
4c	3429, 3017, 2926, 1623, 1421, 1384, 1306, 983	6.1-6 (m, 2H, $H_{5''}$, $H_{4'}$), 5.9 (dq, 1H, J = 6.5, $H_{6'}$), 5.3 (m, 1H, $H_{3'}$), 4.8 (m, 1H, H_2), 4.6 (t, 1H, J = 5.02, H_4), 4 (dd, 1H, J = 13, 5.00), $H_{2''}$), 3.45-3.3 (m, 3H, H_5, $H_{2'}$), 2.76 (dd, 2H, J = 13.5, 22, $H_{3''}$), 2.2-2 (m, 2H, $H_{1'}$), 1.53 (d, 3H, J = 6.7, CH_3).	170.4, 169.5, 135.9, 133.1, 130, 127.5, 63.3, 62.3, 52.5, 45.3, 36.9, 31.5, 30, 17.7
4d	3419, 2927, 1625, 1384, 1302, 991	6.5-6.2 (m, 4H, $H_{7''}$, $H_{6''}$, $H_{5''}$, $H_{4'}$), 5.8 (m,1H, $H_{8'}$), 5.3 (m, 1H, $H_{6'}$), 4.9 (m, 1H, H_2), 4.6 (m, 1H, H_4), 3.8-3.5 (m, 1H, $H_{2''}$), 3.3-3. (m, 3H, H_5, $H_{2'}$), 3-2.8 (m, 2H, $H_{3''}$), 2.4-2.1 (m, 2H, $H_{1'}$), 1.6 (d, 3H, J = 6.7, CH_3).	170.25, 135, 134.3, 132.7, 131, 129.5, 128.35, 63.1, 62.2, 52.4, 45.1, 37.2, 36.3, 31.5, 29.7, 17.6
4e	3400, 3012, 2925, 1624, 1384, 1305, 1001	6-5.7 (m, 6H, $H_{9''}$, $H_{8''}$, $H_{7''}$, $H_{6''}$, $H_{5''}$, $H_{4'}$), 5.4 (m, 1H, $H_{10'}$), 5 (m, 1H, $H_{3'}$), 4.6 (m, 1H, H_2), 4.5 (m, 1H, H_4), 3.8 (m, 1H, $H_{2''}$), 3.2 (3H, m, H_5, $H_{2'}$), 2.8 (m, 2H, $H_{3''}$), 2.2-1.8 (m, 2H, $H_{1'}$), 1.35 (d, 3H, J = 7, CH_3).	
4f	3434, 2925, 1613, 1384, 1261, 1006	6.1-5.8 (m, 8H, $H_{11''}$, $H_{10''}$, $H_{9''}$, $H_{8''}$, $H_{7''}$, $H_{6''}$, $H_{5''}$, $H_{4'}$), 5.3 (m, 1H, $H_{12'}$), 5.1 (m, 1H, $H_{3'}$), 4.55 (m, 1H, H_4), 3.8 (m, 1H, $H_{2''}$), 3.1 (3H,m, H_5, $H_{2'}$), 2.8 (m, 2H, $H_{3''}$), 2.2-1.9 (m, 2H, $H_{1'}$), 1.4 (d, 3H, J = 7, CH_3).	

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FACILE ONE-POT SYNTHESIS OF FLUORESCENT BENZOTHIENO[2,3:c]QUINOLINE

Submitted by (08/20/03)

Harjinder Singh Bhatti[††] and Sambamurthy Seshadri*[†]

Dyes Research Laboratory, University Institute of Chemical Technology University of Mumbai, Matunga, Mumbai–400019, INDIA

[†] *88, Ashtalakshmi, Bhaudaji Cross Road, Matunga, Mumbai-400019, INDIA*
Email: seshgeet@vsnl.com

[††] *Ciba India Pvt Ltd, Goregaon(E), Mumbai-400063, INDIA*

Fluorescent heterocyclic compounds are of interest as functional materials for applications in tunable dye lasers,[1] molecular probes for biochemical research,[2] polymers[3] and dyes.[4] Fluorophores are also useful tools in the search for new pharmacological agents and in the development of new diagnostic methods.[5] The literature[6] abounds with examples of the use of