Thiazolidine-2,4-dicarboxylic Acid and its Esters: Synthesis, in Solution Behaviour and Regioselective Cyclocondensation

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Thiazolidine-2,4-dicarboxylic acid **2** was obtained as a diastereoisomeric mixture from the condensation of glyoxylic acid with L(-)*R*-cysteine **1**. In solution behaviour studies suggested that the reaction proceeded through an acid catalyzed epimerization mechanism. The methyl esterification of **2** was stereoselective, which can be explained by an interconversion of **2a** *via* a ring seco intermediate. Condensation of the dimethyl ester **3** or the dissymmetric diester **4** with phenyl isocyanate gave rise to the same hydantoin **5**. *N*-acylation of diesters **3** or **4** followed by the reaction with benzylamine was regioselective leading to bicyclic derivatives **8-10**.

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Thiazolidine-4-carboxylic acid and its 2-substituted derivatives have been known for some time [1-3]. Their synthesis was usually performed by the condensation of the appropriate aldehydes or ketones with the naturally occurring chiral L(-)*R*-cysteine but few mechanistic or stereochemical considerations have been reported until recently [4]. In the course of the synthesis of 2-substituted thiazolidine-4-carboxylic acids, a new chiral center is generated and a mixture of two stereoisomers was obtained. It was pointed out that in solution the equilibration between the diasteroisomers occurred rapidly through an epimerization process at the C-2 position [5] together with a ring opening [6].

Furthermore, thiazolidine-4-carboxylic acids can also be produced *in vivo* and can possess biological importance. Therefore the formation of 2,5,5-trimethylthiazolidine-4-carboxylic acid from acetaldehyde and D(-)-penicillamine appeared as a detoxication process in ethanol intoxication [7,8].

Some alkyl and aryl 2-substituted thiazolidine-4-carboxylic acids have been proposed as prodrugs of L(-)*R*-cysteine for the protection of mice against acetaminophen hepatotoxicity [9].

Thiazolidine-2,4-dicarboxylic acids and their esters have been also reported for several decades. Thus diethyl esters were obtained when ethyl glyoxylate was used instead of acetaldehyde in the reaction with L(-)*R*-cysteine ethyl ester [10]. More recently magnesium and arginine salts of thiazolidine-2,4-dicarboxylic acid were patented for their use in pharmaceutical formulations [11].

In the present paper we report the synthesis and behaviour in solution of thiazolidine-2,4-dicarboxylic acid and its 2,4-dimethyl ester or 2-methyl 4-ethyl ester. In addition the mechanism involved in the formation of two diastereoisomers of the acid and its esters is discussed. Furthermore cyclocondensations of the above esters are performed by mean of phenyl isocyanate or chloroacetyl chloride and benzylamine leading to bicyclic compounds regioselectively.

Results and Discussion.

In our experiments thiazolidine-2,4-dicarboxylic acid **2** was obtained from the condensation of glyoxylic acid with L(-)*R*-cysteine **1a** in aqueous solution. Diastereoisomers are formed while a new chiral center is created at the C-2 position, the C-4 position resulting from L(-)*R*-cysteine remaining unaffected (Scheme 1).

Scheme 1

The ^{1}H nmr analysis in dimethyl sulfoxide-d_6 reveals the presence of two diastereoisomers in the approximate ratio of 7:3, the C-4 methine proton of the two diastereoisomers appearing at 3.8 and 4.25 ppm and the C-2 methine proton at 4.85 and 5.0 ppm, respectively.

The stereochemistry of the C-2 carboxyl group with respect to the C-4 carboxyl group can be resolved by a high field nmr analysis. This analysis is based on the assignments of the high field C-5 proton of proline or the C-2 proton of thiazolidine-4-carboxylic acid as *cis* to the carboxyl group [4,12].

The assignment of 5.0 ppm and 4.25 ppm respectively for the C-2 and C-4 methine proton should fit with the structure of the *cis* isomer 2*R*,4*R*-**2a** while the assignment of 4.85 and 3.8 ppm fits with the structure of the *trans* isomer 2*S*,4*R*-**2b**.

Furthermore spectral data are in agreement with a diastereoisomeric mixture of 30% **2a** and 70% **2b** (Scheme 2).

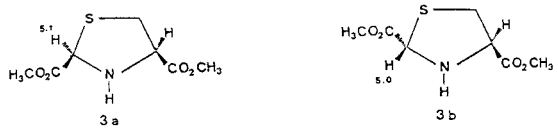
Scheme 2

The evolution of the thiazolidine-2,4-dicarboxylic acid ^{1}H nmr spectrum has been investigated in acidic, basic and neutral solution. When the thiazolidine-2,4-dicarboxylic acid is placed in a solution of dimethyl sulfoxide-d_6 containing deuteriated trifluoroacetic acid, the intensity ratios of the C-2 methine protons resonance are immediately inverted. In deuterium oxide solution without acid, the intensity ratios of the C-2 protons resonance of the individual diastereoisomers at 4.85 and 5.0 ppm are found to change with time, the equilibration occurring within 12 hours. But in solution in deuterium oxide with 2% sodium carbonate, thiazolidine-2,4-dicarboxylic acid remains stable and its ^{1}H nmr spectrum is unaffected over 24 hours.

From these results, an epimerization at the C-2 of thiazolidine-2,4-dicarboxylic acid can be postulated in neutral solution. The stability of **2** in a weak basic solution as evidenced by the ^{1}H nmr spectrum contrasted with its rapid equilibration in dilute acid solution may suggest that the epimerization is acid catalyzed.

Methyl esterification of the diastereoisomeric mixture of **2a** and **2b** by thionyl chloride in methanol solution gives rise to dimethyl thiazolidine-2,4-dicarboxylate with a 9 to 1 predominance of the 2*S*,4*R* isomer **3b** as revealed by ^{1}H nmr analysis. The C-2 methine protons of the two diastereoisomers appear at 5.1 and 5.0 ppm, respectively (Scheme 3).

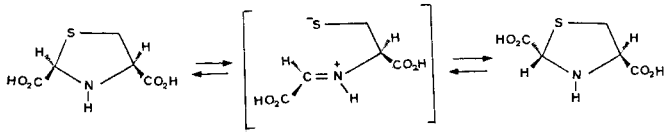
Scheme 3



This difference of stereoselectivity between the condensation reaction of glyoxylic acid with L(-)*R*-cysteine and the esterification reaction could be explained by interconversion of the two diastereoisomers *via* a ring seco intermediate according to Scheme 4.

A similar mechanism has been yet suggested [4,5] to account for mutarotation and selective acylation of C-2 substituted thiazolidines.

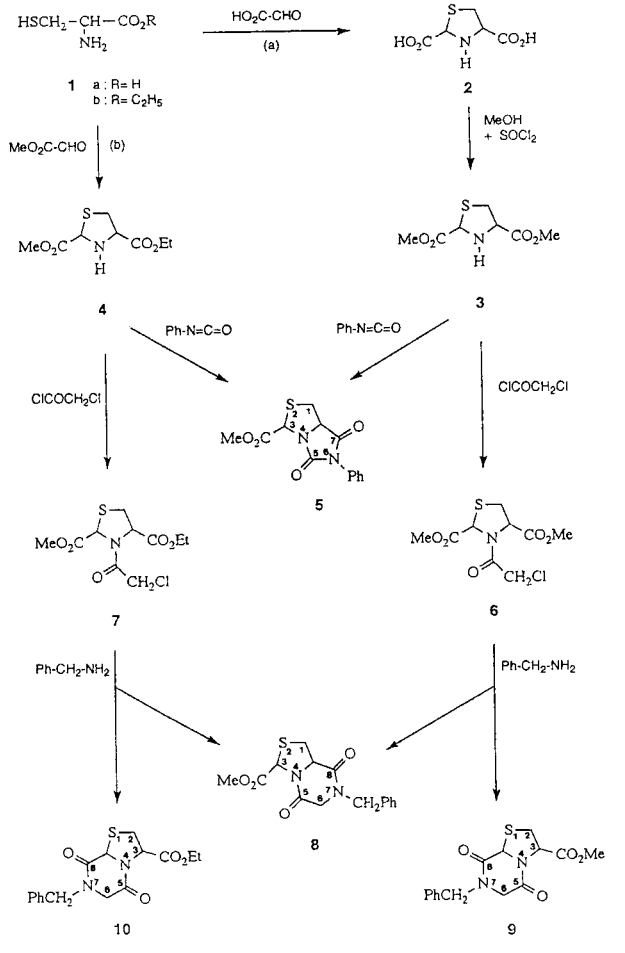
Scheme 4



From diester **3** we prepared regiospecifically hydantoin **5** by condensation with phenyl isocyanate. When diester **3** is replaced by dissymmetric diester **4**, the same hydantoin **5** was obtained. The diester **4** was prepared by condensation of methyl glyoxylate with L(-)*R*-cysteine ethyl ester hydrochloride.

The *N*-acylation of the diester **3** by chloroacetyl chloride followed by the reaction of benzylamine generated two different compounds which were separated by chromatography on a silica gel column. In order to confirm the structure of these compounds which can be expected to be regioisomers **8** and **9**, we performed the same reactions from the dissymmetric ester **4** and we obtained two bicyclic compounds which were separated by column chromatography. The ^{1}H nmr spectra allowed us to elucidate unambiguously the structure of both compounds. The major

Scheme 5



one **8** exhibited a singlet at 3.85 ppm (CO_2CH_3) while the minor one **10** exhibited a triplet at 1.25 ppm and a quadruplet at 4.15 ppm ($CO_2CH_2CH_3$). Comparing with the compounds obtained from the symmetric diester **3** it may be inferred that the major product had structure **8** while the minor one had structure **9** (Scheme 5).

EXPERIMENTAL

Melting points were determined on a Reichert apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Infrared spectra were taken in potassium bromide pellets on a Beckman 4240 spectrometer.

The ^1H nmr spectra were recorded on a Varian EM 360A spectrometer at 60 MHz and on a Bruker AC 200 spectrometer at 200 MHz for compounds **2** and **3** using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). The ^{13}C nmr spectra were recorded on a Jeol FX 60 spectrometer. Elemental analyses were carried out at the Service Central d'Analyses, Centre National de la Recherche Scientifique, 69390 Vernaison, France.

Thiazolidine-2,4-dicarboxylic Acid (**2**).

To a stirred solution of L(-)*R*-cysteine hydrochloride hydrate (15.8 g, 0.1 mole) and potassium acetate (9.8 g, 0.1 mole) in a mixture of water and ethanol (150 ml, 2:1, v/v) a solution of glyoxylic acid monohydrate (9.2 g, 0.1 mole) in 50 ml of water was added. The reaction mixture was stirred for 4 hours at room temperature then stirred for 48 hours. The precipitate obtained was collected by filtraton; the crude product (15 g) was recrystallized from hot water, yield 85%, mp 180°; $[\alpha]_D^{20}$ −75° in sodium hydroxide 0.1 *N*; ir (potassium bromide): ν (cm^{-1}) 3250 (NH), 2500-3000 (OH), 1730 (CO); ^1H nmr (dimethyl sulfoxide-d_6): δ **2a**, 3.0 (dd, 1H), 3.2 (dd, 1H), 4.25 (dd, 1H), 5.0 (s, 1H); δ **2b**, 2.75 (dd, 1H), 3.35 (dd, 1H), 3.80 (dd, 1H), 4.85 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ **2a**, 37.5 (C-5), 65.0 (C-4), 66.0 (C-2), 172.0 (C-6), 172.4 (C-7); δ **2b**, 37.2 (C-5), 65.0 (C-4), 65.7 (C-2), 172.0 (C-6), 172.4 (C-7).

Anal. Calcd. for $C_5H_7NO_4S$: C, 33.90; H, 3.95; N, 7.91; S, 18.07. Found: C, 34.03; H, 4.03; N, 7.98; S, 18.20.

Dimethyl Thiazolidine-2,4-dicarboxylate (**3**).

To a stirred and ice cooled suspension of thiazolidine-2,4-dicarboxylic acid **2** (17.7 g, 0.10 mole) in anhydrous methanol (250 ml) was added dropwise thionyl chloride (23.8 g, 0.2 mole). The mixture was stirred further for 10 hours at room temperature, heated at reflux for 1 hour, then evaporated under vacuum. The resulting residue was the crude diester as the hydrochloride. This product was dissolved in water (100 ml) and ethyl ether was added (100 ml). The aqueous solution was made basic by addition of sodium carbonate and the mixture was stirred. The organic phase was separated, dried over sodium sulfate and then evaporated. After cooling the 2,4-di(methoxycarbonyl)thiazolidine crystallized (19.7 g), yield 95%, mp 70°; $[\alpha]_D^{20}$ −83° in chloroform; ir (potassium bromide): ν (cm^{-1}) 3290 (NH), 2990 (CH), 1740 (CO); ^1H nmr (deuteriochloroform): δ **3a**, 3.0 (dd, 1H), 3.1 (s, NH), 3.2 (dd, 1H), 3.85 (s, 6H, $2CH_3$), 4.0 (m, 1H), 5.1 (s, 1H); **3b**, 2.8 (dd, 1H), 3.1 (s, NH), 3.3 (dd, 1H), 3.85 (s, 6H, $2CH_3$), 3.95 (m, 1H), 5.0 (s, 1H).

Anal. Calcd. for $C_7H_{11}NO_4S$: C, 40.98; H, 5.37; N, 6.83; S, 15.61. Found: C, 40.98; H, 5.36; N, 6.82; S, 15.66.

2-Methoxycarbonyl-4-ethoxycarbonylthiazolidine (**4**).

To a suspension of L(-)*R*-cysteine ethyl ester hydrochloride (5.60 g, 0.03 mole) in ethanol (500 ml) was added methyl glyoxylate (2.65 g, 0.03 mole). The mixture was stirred for 30 minutes at room temperature then at 60° for 1 hour.

The reaction mixture was cooled and evaporated; the residue was dissolved in water (50 ml) and the aqueous layer was washed with ether (2 x 20 ml). The aqueous layer was separated, neutralized with sodium carbonate then extracted with chloroform (2 x 50 ml) and the combined organic layers were dried over sodium sulfate, filtered and evaporated. The residue was purified by trituration with ether to give pale yellow crystals, yield 70%, mp 60°; ir (potassium bromide): ν (cm^{-1}) 1760 (CO); ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H), 3.1 (s, NH), 3.2 (m, 2H), 3.7 (m, 1H), 3.85 (m, 3H), 4.15 (q, 2H), 5.0 (s, 1H).

Anal. Calcd. for $C_8H_{13}NO_4S$: C, 43.83; H, 5.94; N, 6.39; S, 14.61. Found: C, 43.78; H, 5.95; N, 6.36; S, 14.70.

Methyl 5,7-Dioxo-6-phenyl-5,6,7,7a-tetrahydro-1*H*,3*H*-imidazo-[1,5-*c*]thiazole-3-carboxylate (**5**).

A mixture of **3** (6.15 g, 0.03 mole) or **4** (6.57 g, 0.03 mole) and phenyl isocyanate (3.57 g, 0.035 mole) in pyridine (50 ml) was stirred at room temperature for 24 hours. The crude product contained some amount of 1,3-diphenylurea. It was extracted with 25 ml of dichloromethane at room temperature. After evaporation of the solvent the residue was recrystallized from ethanol to give white needles, yield 75%, mp 110°; ir (potassium bromide): ν (cm^{-1}) 1710, 1735, 1770; ^1H nmr (deuteriochloroform): δ 3.3 (m, 2H), 3.85 (s, 3H), 4.7 (dd, 1H), 5.1 (s, 1H), 7.5 (s, 5H).

Anal. Calcd. for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.11; N, 9.59; S, 10.96. Found: C, 53.54; H, 4.16; N, 9.50; S, 11.01.

3-Chloroacetyl-2,4-di(methoxycarbonyl)thiazolidine (**6**).

To a suspension of **3** (6.15 g, 0.03 mole) in benzene (100 ml) was added chloroacetyl chloride (3.4 g, 0.03 mole). The mixture was stirred for 15 minutes at room temperature then at 80° for 1.5 hours. The reaction mixture was cooled and evaporated. The residue obtained was recrystallized from ether to give pale yellow crystals, yield 70%, mp 121°; ir (potassium bromide): ν (cm^{-1}) 1735, 1740, 1660; ^1H nmr (deuteriochloroform): δ 3.4 (m, 2H), 3.85 (s, 6H), 4.3 (s, 2H), 5.2 (m, 1H), 5.6 (s, 1H).

Anal. Calcd. for $C_9H_{12}NO_5SCl$: C, 38.36; H, 4.26; N, 4.97; S, 11.37; Cl, 12.61. Found: C, 38.16; H, 4.19; N, 4.89; S, 11.17; Cl, 12.70.

3-Chloroacetyl-4-ethoxycarbonyl-2-methoxycarbonylthiazolidine (**7**).

Acylation of **4** using the above procedure gave **7**, yield 70%, mp 110°; ir (potassium bromide): ν (cm^{-1}) 1660, 1740; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H), 3.4 (m, 2H), 3.85 (s, 3H), 4.15 (q, 2H), 4.3 (s, 2H), 5.2 (m, 1H), 5.6 (s, 1H).

Anal. Calcd. for $C_{10}H_{14}NO_5SCl$: C, 40.61; H, 4.74; N, 4.74; S, 10.83; Cl, 12.01. Found: C, 40.42; H, 4.70; N, 4.80; S, 10.75; Cl, 12.07.

Methyl 7-Benzyl-5,8-dioxo-2,3,6,7,8,8a-hexahydro-5*H*-thiazolo-[3,4-*a*]pyrazine-3-carboxylate (**8**) and Methyl 7-Benzyl-5,8-dioxo-

2,3,6,7,8,8a-hexahydro-5*H*-thiazolo[3,2-*a*]pyrazine-3-carboxylate (**9**).

A mixture of **6** (2.82 g, 0.01 mole), triethylamine (1.01 g, 0.01 mole) and benzylamine (1.07 g, 0.01 mole) in 2-ethoxyethanol (50 ml) was heated overnight at 130°. After cooling the reaction mixture was evaporated, the residue obtained was dissolved in 25 ml of chloroform and washed with 5% hydrochloric acid and then with water. The chloroform was dried over sodium sulfate and the solvent was removed by evaporation under reduced pressure. The oily residue was purified by chromatography on silica gel with ethyl acetate-hexane (5:5) as eluent to give two regioisomers **8** and **9**.

Compound **8** was obtained in 52% yield, mp 101°; ir (potassium bromide): ν (cm^{-1}) 1640, 1660, 1740 (CO); ^1H nmr (deuteriochloroform): δ 3.4 (m, 2H), 3.85 (s, 3H), 3.95 (m, 2H), 4.4 (dd, 1H), 4.6 (m, 2H), 5.35 (s, 1H), 7.3 (s, 5H).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.25; H, 5.0; N, 8.75; S, 10.0. Found: C, 56.18; H, 5.01; N, 8.78; S, 9.96.

Compound **9** was obtained in 24% yield, bp (0.01 mm Hg) 145°; ir (potassium bromide): ν (cm^{-1}) 1650, 1740 (CO); ^1H nmr (deuteriochloroform): δ 3.4 (m, 2H), 3.85 (s, 3H), 3.9 (m, 2H), 4.6 (m, 2H), 4.9 (dd, 1H), 5.6 (s, 1H), 7.3 (s, 5H).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.25; H, 5.0; N, 8.75; S, 10.0. Found: C, 56.16; H, 5.05; N, 8.68; S, 9.97.

Ethyl 7-Benzyl-5,8-dioxo-2,3,6,7,8,8a-hexahydro-5*H*-thiazolo-[3,2-*a*]pyrazine-3-carboxylate (**10**).

Compound **10** was obtained from **7** using the above procedure, yield 25% bp (0.01 mm Hg) 138°; ir (potassium bromide): ν (cm^{-1}) 1650, 1740 (CO); ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H), 3.4 (m, 2H), 3.9 (m, 2H), 4.15 (q, 2H), 4.6 (m, 2H), 4.9 (dd, 1H), 5.6 (s, 1H), 7.3 (s, 5H).

Anal. Calcd. for $C_{16}H_{18}N_2O_4S$: C, 57.48; H, 5.39; N, 8.38; S, 9.58. Found: C, 57.28; H, 5.34; N, 8.45; S, 9.70.

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