Synthesis and NMR Studies of Thiazolidine-4-carboxylic Acid Derivatives Containing a Nitro Ester Function

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The preparation of thiazolidine-4-carboxylic acid derivatives containing a 2-nitrooxyethylamine group, potentially active as vasodilators, is reported. Their ^1H nmr studies carried out to establish the configuration of the C2 stereocenter and the full assignment of their ^1H and ^{13}C nmr spectra, are also reported.

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Introduction.

Organic nitrates have remained useful agents for the management of several cardiovascular diseases ever since they were introduced into clinical therapy over a hundred years ago. The major problem in the use of nitrate is that prolonged nitrate administration induces tolerance that has a decreasing effect over time.

A general consensus now exists on how vasodilatation is brought about by organic nitrates that penetrate the smooth muscle cell where metabolic activation takes place forming nitric oxide or *S*-nitrosothiol [1]. These products then interact with the intracellular enzyme guanylate cyclase, leading to the production of the second messenger cyclic GMP and, subsequently, vasodilatation. The mechanism of inaction of organic nitrates is less well characterized. One of the proposed explanations is "the sulphydryl depletion hypothesis" [2,3]. The thiol consuming transformation of organic nitrate may lead to a depletion of cysteine stores, resulting in a decreased formation of NO and consequently, a decrease in guanylate cyclase activation. Recent data have shown that the coadministration of *N*-acetylcysteine and nitroglycerine reversed the nitroglycerine tolerance [4].

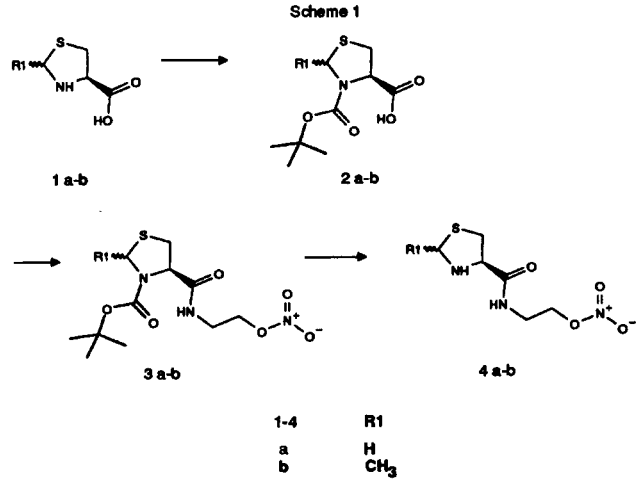
Our interest in the organic nitrates field prompted us to synthesize a series of new nitroester compounds containing the thiazolidine ring as a prodrug of cysteine [5].

Chemistry.

Scheme 1 illustrates the synthetic approach used in the preparation of derivatives **4a-b**. Known thiazolidines **2a-b** [6,7] were treated with ethyl chloroformate and triethylamine in dry chloroform in order to prepare the corresponding mixed anhydrides which were converted into desired compounds **3a-b** using 2-nitrooxyethylamine nitrate. The cleavage of *tert*-butoxycarbonyl protection using a solution of hydrochloric acid in ethyl acetate afforded thiazolidinic derivatives **4a-b**. The analytical data of compounds **3a-b** and **4a-b** are reported in the Experimental.

Shown in Scheme 2 is the synthetic route followed for obtaining derivatives **7a-d**. *N*-Acetylthiazolidines **6a-b**

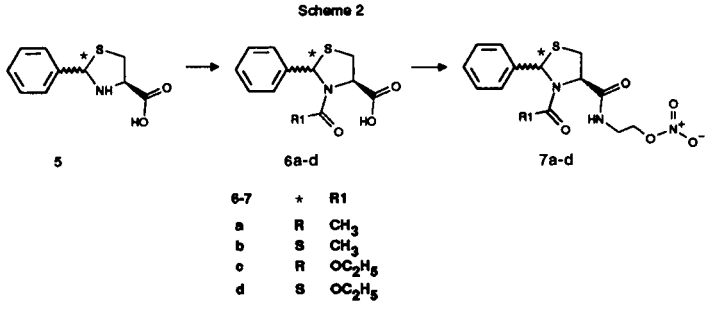
Scheme 1



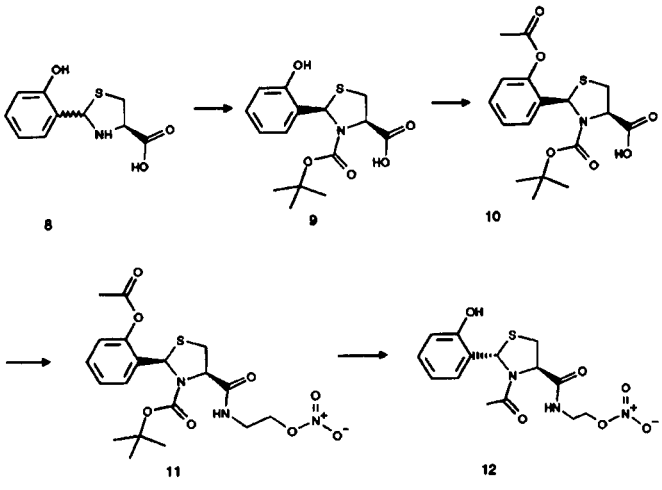
were prepared as reported [8]. Similarly we obtained new *N*-carbethoxythiazolidines **6c-d** starting from known derivative **5** [8]. The *cis* derivate **6c** was prepared by treating with ethyl chloroformate the triethylamine salt of compound **5** in tetrahydrofuran and the *trans* derivative **6d** was synthesized using ethyl chloroformate in dry pyridine. The thiazolidines **6a-d** were dissolved in dry chloroform in the presence of triethylamine and treated with ethyl chloroformate to give the corresponding mixed anhydrides. Their conversion into desired thiazolidines **7a-d**, was carried out using 2-nitrooxyethylamine nitrate. The analytical data of derivatives **7a-d** are reported in the Experimental.

The synthesis of thiazolidine **12** is reported in Scheme 3. The sodium salt of known derivatives **8** [9] was treated

Scheme 2



Scheme 3



with di-*tert*-butyl dicarbonate in tetrahydrofuran to give compound **9** which was acetylated using acetic anhydride in pyridine. Derivative **10** was dissolved in dry dichloromethane in the presence of triethylamine and treated with ethyl chloroformate to prepare the desired mixed anhydride which was transformed into compound **11** using 2-nitrooxyethylamine nitrate. The removal of *tert*-butoxycarbonyl protection under non aqueous acidic conditions with a migration of the acetyl group from the phenolic oxygen to the thiazolidine nitrogen gave compound **12**. The analytical data of derivatives **9-12** are reported in the Experimental.

NMR Studies.

Table 1 shows the fully assigned chemical shifts of the ^1H nmr spectra of compounds **4a-b**, **7a-d** and **12** and Table 2 reports the fully assigned chemical shifts of the ^{13}C nmr spectra of the same compounds. In order to identify the chemical shifts shown in these tables, the general structure of compounds **4a-b**, **7a-d** and **12** is reported in Scheme 4.

The ^1H and ^{13}C nmr spectra are in agreement with the proposed structures. The resonances of compounds **4a-b**, **7a-d** and **12** were assigned by $^{13}C/^1H$ shift correlated experiments, while the resonances of the other compounds were assigned by analogy.

The cyclization of L-cysteine to build a 2-substituted thiazolidine, gives rise to a new chiral center at C-2 position of the thiazolidine ring, affording a mixture of two diasteroisomers; a mechanism, involving the opening of the ring, the closure and the epimerization of the C-2 was previously described [8,11-14]. The protection with the acetyl, *tert*-butyloxycarbonyl and carbethoxy groups of the nitrogen of thiazolidine prevents the opening/closure of the ring and allows the isolation of a pure diastereoisomer.

Previously [8,14] the sum of the coupling constant between geminal protons H-5, H-5' with H-4, that represent the ABX system of the thiazolidine ring, was related to the structure of the 2-substituted thiazolidine-4-carboxylic acid derivatives. In fact, as Szilágyi *et al.* [8] observed, the sum of these coupling constants of the *cis* isomer is greater than that of the *trans* isomer.

Because of the bond between the protective carbonyl group and the nitrogen has a double bond character, and the rotation rate of the protective group at room temperature is often sufficiently slow to give the splitting of the nmr signals, the ^1H nmr spectra of compounds **3b**, **6c-d**, **7a-d**, and **9-12** were recorded at high temperature to measure the $J_{AX} + J_{BX}$ allowing us to establish the absolute configurations of these compounds.

Table 1

Compound	t (°C) [a]	[b]	$J_{AX}+J_{BX}$	2	4	5	NH	A'	B'	A	B	C	D	E	b	c
4a	21			m 4.31	t 4.50	m 3.33	t 9.34	q 3.53	t 4.60							
4b	21	40		q 4.83	m 4.50	m 3.39	t 9.25	q 3.53	t 4.60	d 1.61						
		60		q 4.89	m 4.64	m 3.39	t 9.25	q 3.53	t 4.60	d 1.63						
7a	21	30		s 6.31			t 8.61									s 2.01
		70		s 6.40			t 8.46									s 1.84
	80		14.3 Hz	s 6.33	m 4.79	m 3.26	t 8.21	q 3.56	t 4.61		m 7.73	m 7.21-7.37				
7b	21	45		s 6.26	d 5.18		t 8.50					m 7.25-7.39				s 2.01
		55		s 6.34	d 5.04		t 8.22					m 7.25-7.39				s 1.78
	110		8.0 Hz	s 6.29	d 5.09	m 3.32	t 7.95	q 3.53	t 4.63			m 7.24-7.40				s 1.88
7c	21		14.5Hz	s 6.18	m 4.61	m 3.25	t 8.48	q 3.98	t 1.09		m 7.74	m 7.25-7.36		q 3.98	t 1.09	
7d	21	40		s 6.09	d 4.93		t 8.34		t 4.57			m 7.21-7.38				t 0.80
		60		s 6.12	d 4.93		t 8.34		t 4.57			m 7.21-7.38				t 1.13
	70		8.0 Hz	s 6.11	d 4.93	m 3.31	t 8.15	q 3.51	t 4.60			m 7.21-7.40			q 3.94	t 1.00
12	21	40		s 6.36	d 5.14		t 8.44						m 6.76-7.15			s 2.00
		60		s 6.40	d 4.99		t 8.14						m 6.76-7.15			s 1.78
	110		7.7 Hz	s 6.38	d 5.05	m 3.24	t 7.90	q 3.52	t 4.73				m 6.76-7.15			s 1.87

[a] In this column are reported the temperatures used for recording the spectra; high temperatures were necessary to obtain only one conformer. [b] In this column are reported the ratio of the epimers for compound **4b** at the equilibrium, and the ratio of the conformers for compounds **7a-b** and **12**.

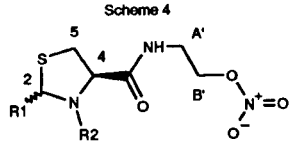
Table 2

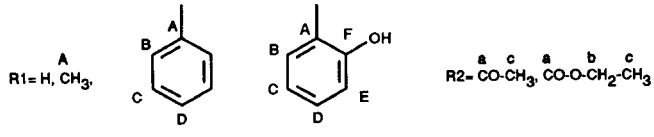
Compound	[a]	2	4	5	CO	A'	B'	A	B	C	D	E	F	a	b	c
4a		48.2	62.1	33.5	166.6	36.8	72.2									
4b	40	59.9	62.7	32.8	163.3	36.7	72.3	18.1								
	60	60.8	61.5	33.7	166.9	36.7	72.3	18.1								
7a	30	66.5	65.4	34.3	170.4	36.8	72.5	142.0	127.1	128.01	127.4			169.8		23.0
	70	65.6	65.6	32.0	170.3	36.6	72.5	142.9	126.6	128.6	127.9			169.3		22.8
7b	45	65.9	65.0	34.0	170.6	36.9	72.5	144.0	125.1	128.4	127.1			168.7		23.5
	55	65.3	64.9	31.8	170.4	36.4	72.3	143.8	125.1	129.1	127.9			168.8		23.2
7c		66.3	65.5	33.3	170.4	36.8	72.5	142.8	126.8	128.1	127.5			154.2	61.6	14.4
7d	40	64.7	64.2	32.4	170.5	36.6	72.5	144.5	125.2	128.6	127.4			153.3	61.3	14.4
	60	65.6	64.9	33.6	170.5	36.6	72.5	143.9	125.2	128.6	127.4			153.3	61.3	14.4
12	40	60.9	65.1	33.6	170.8	36.8	72.4	129.3	124.1	118.6	127.9	115.2	153.7	168.3		23.5
	60	60.3	65.1	31.7	170.7	36.6	72.2	129.6	124.5	119.4	128.8	115.5	153.6	168.6		22.8

[a] In this column are reported the ratio of the epimers for compound **4 b** at the equilibrium, and the ratio of the conformers for compounds **7a-d** and **12**.

The comparison of the sum of the coupling constant $J_{AX} + J_{BX}$ of the ABX system of the thiazolidine ring, allowed us to assign the *cis* configuration to compound **6c** ($J_{AX} + J_{BX}$ = 13.0 Hz), and the *trans* configuration to compound **6d** ($J_{AX} + J_{BX}$ = 8.1 Hz), confirming the assignments on the basis of the adopted synthetic route.

Scheme 4





By the same reasoning, we assigned the *cis* configuration to compounds **7a** and **7c** (14.3 Hz and 14.5 Hz respectively) and the *trans* configuration to compounds **7b** and **7d** (both 8.0 Hz).

For compounds **3b** and **9-11** the ^1H nmr data show the presence of a pure diastereoisomer; the *cis* configuration was deduced from the value of the sum of the coupling constants (15.0 Hz, 14.5 Hz, 13.4 Hz and 15.5 Hz respectively)

The comparison of the coupling constants of compounds **11** and **12** (7.7 Hz) shows that the removal of *tert*-butoxycarbonyl protection of compound **11** gives to the inversion of the C2 stereocenter configuration of compound **12**.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi 530 melting point apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded, respectively at 200 and 50.3 MHz on a Varian Gemini-200 spectrometer equipped with a 5 mm dual head probe and using a 0.1 *M* solution in deuterated DMSO-d_6.

The ^1H nmr spectra were recorded with a spectral width of 3000 Hz, a pulse of 20 μs (90°), acquisition time 2.7 s, 16 k data points and a 3 s relaxation delay; the chemical shifts were referenced to DMSO-d_6 (2.50 ppm). The ^{13}C nmr spectra were recorded with a spectral width of 15000 Hz, a pulse of 8.5 μs (45°), acquisition time 0.5 s, 16 k data points and a 0.5 s relaxation delay; the chemical shifts were referenced to DMSO-d_6 (39.50 ppm).

The $^{13}C/^1H$ shift correlated experiments were recorded using the Hetcor pulse sequence: 64 experiments of 512 scans each, spectral widths 6000 Hz (F1) and 1600 Hz (F2), number of data points 1 k and a 3 s relaxation delay.

All the ^1H and ^{13}C nmr spectra were recorded at room temperature (22°); for compounds **3b**, **6a**, **6b**, **9**, **10** and **11** were also recorded at 60°, 60°, 90°, 70°, 50° and 50° respectively to measure the value of the coupling constants of the ABX system of the thiazolidinic ring.

(2*R*,4*R*)-2-Phenyl-3-carbethoxythiazolidine-4-carboxylic Acid (**6c**).

To a stirred solution of compound **5** (4 g, 19 mmoles) in tetrahydrofuran (40 ml), triethylamine (6.6 ml, 47.8 mmoles) was added dropwise at -10°. After 15 minutes at room temperature the solution was evaporated. The triethylamine salt was dissolved in tetrahydrofuran (60 ml), cooled at -10° and treated with ethyl chloroformate (4.4 ml, 46 mmoles). After stirring at room temperature for 1 hour, the solvent was evaporated under reduced pressure. The residue was treated with water (100 ml) and then with 37% hydrochloric acid to *p*H 3 and extracted with ethyl acetate. The organic layer was washed with water, separated and dried over sodium sulfate. After the evaporation of the solvent under reduced pressure, 3.7 g (70%) of compound **6c** was obtained as a thick oil; ^1H nmr (DMSO): δ 0.94 (t, 1.5 H, CH_3), 1.14 (t, 1.5 H, CH_3), 3.33 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 13.0 Hz), 3.98 (q, 2 H, CH_2), 4.74 (m, 1 H, H4, X region of ABX system), 6.12 (s, 1 H, H2), 7.25-7.38 (m, 3 H, H *meta* and *para* aromatics), 7.63 (d, 2 H, H *ortho* aromatic).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.48; H, 5.44; N, 4.85.

(2*S*,4*R*)-2-Phenyl-3-carbethoxythiazolidine-4-carboxylic Acid (**6d**).

To a stirred solution of compound **5** (5 g, 24 mmoles) in dry pyridine (60 ml), ethyl chloroformate (3.6 ml, 38 mmoles) was added dropwise at -40°. The cooled mixture was stirred for 2 hours, treated with water (100 ml) at room temperature and then with 37% hydrochloric acid to *p*H 3 and extracted with ethyl acetate. The organic layer was washed with water, separated and dried over sodium sulfate. After the evaporation of the solvent under reduced pressure the residue was chromatographed on silica gel eluting with dichloromethane/ethyl acetate/acetic acid 3/7/0.05 to give 3.7 g (55%) of compound **6d** as a thick oil; ^{1}H nmr (DMSO): δ 0.82 (t, 1.35 H, CH_3), 1.13 (t, 1.65 H, CH_3), 3.42 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 8.1 Hz), 3.87 (q, 0.9 H, CH_2), 3.99 (q, 1.1 H, CH_2), 5.05 (m, 1 H, H4, X region of ABX system), 6.03 (s, 1 H, H2), 7.18-7.37 (m, 5 H, H aromatics).

Anal. Calcd. for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.66; H, 5.48; N, 4.79.

(2*R*,4*R*)-2-(2-Hydroxyphenyl)-3-(*tert*-butoxycarbonyl)thiazolidine-4-carboxylic Acid (**9**).

Aqueous 1 *N* sodium hydroxide (783 ml) was added at room temperature to a solution of compound **8** (160 g, 710 mmoles) in tetrahydrofuran (1200 ml). After 10 minutes a solution of di-*tert*-butyl dicarbonate (156 g, 715 mmoles) in tetrahydrofuran (600 ml) was dropwise at room temperature. After stirring for 18 hours the solution was washed with diethyl ether, acidified with 18% hydrochloric acid to Congo red and extracted with ethyl ether. The ethereal extract was washed with water, dried over sodium sulfate and evaporated to dryness under reduced pressure to give a solid white residue which was crystallized from *n*-hexane/diethyl ether (84%, mp 143-145°); ^{1}H nmr (DMSO): δ 1.16 (s, 3.6 H, *tert*-butyl), 1.38 (s, 5.4 H, *tert*-butyl), 3.23 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 14.5 Hz), 4.49 (m, 0.6 H, H4, X region of ABX system), 4.60 (m, 0.4 H, H4, X region of ABX system), 6.16 (s, 1 H, H2), 6.77 (m, 2 H, H aromatics), 7.08 (m, 1 H, H aromatic), 7.87 (d, 1 H, H aromatic), 9.65 (s, 0.4 H, Ph-OH), 9.75 (s, 0.6 H, Ph-OH).

Anal. Calcd. for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30. Found: C, 55.62; H, 6.14; N, 4.07.

(2*R*,4*R*)-2-(2-Acetoxyphenyl)-3-(*tert*-butoxycarbonyl)thiazolidine-4-carboxylic Acid (**10**).

To a stirred solution of compound **9** (194.3 g, 596 mmoles) in dry pyridine (212 ml), acetic anhydride (79.2 ml, 837 mmoles) was added dropwise at 15°. After 24 hours at room temperature, the reaction mixture was poured into ice, acidified with 37% hydrochloric acid and extracted with diethyl ether. The organic layer was washed with 1 *N* hydrochloric acid and with water, dried over sodium sulfate and evaporated under reduced pressure to dryness. The residue was crystallized from ethyl acetate to give pure compound **10** (78%, mp 149-150°); ^{1}H nmr (DMSO): δ 1.14 (s, 5 H, *tert*-butyl), 1.38 (s, 4 H, *tert*-butyl), 2.32 (s, 3 H, CH_3), 3.29 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 13.4 Hz), 4.57 (m, 0.45 H, H4, X region of ABX system), 4.70 (m, 0.55 H, H4, X region of ABX system), 6.07 (s, 0.55 H, H2), 6.15 (s, 0.45 H, H2), 7.09-7.38 (m, 3 H, H aromatics), 8.07 (d, 0.45 H, H aromatic), 8.13 (d, 0.55 H, H aromatic).

Anal. Calcd. for $C_{17}H_{21}NO_6S$: C, 55.57; H, 5.76; N, 3.81. Found: C, 55.31; H, 5.92; N, 3.70.

(2*R*,4*R*)-2-(2-Acetoxyphenyl)-3-(*tert*-butoxycarbonyl)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**11**).

To a stirred solution of compound **10** (65.2 g, 177 mmoles) and triethylamine (24.6 ml, 177 mmoles) in dichloromethane (260 ml) at 0°, ethyl chloroformate (17.0 ml, 177 mmoles) in dichloromethane (30 ml) was added dropwise. After 1 hour at 0°, triethylamine (24.6 ml, 177 mmoles) was added. The reaction mixture kept at 15° was treated portionwise with 2-nitrooxyethylamine nitrate (30.0 g, 177 mmoles), stirred for 1 hour and washed with water and aqueous 5% solution of sodium bicarbonate and water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to dryness. The residue was crystallized from acetone/diethyl ether to give pure compound **11** as a white solid (61%, mp 133-134°); ^{1}H nmr (DMSO): δ 1.18 (s, 3.2 H, *tert*-butyl), 1.34 (s, 5.8 H, *tert*-butyl), 2.32 (s, 3 H, CH_3), 3.16 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 15.5 Hz), 3.53 (m, 2H, NH-CH_2), 4.49 (m, 1 H, H4, X region of ABX system), 4.61 (m, 2 H, CH_2-ONO_2), 6.14 (s, 1 H, H2), 7.11-7.37 (m, 3 H, H aromatics), 8.42 (d, 0.45 H, H aromatic), 8.53 (t, 1 H, CO-NH).

Anal. Calcd. for $C_{19}H_{25}N_3O_8S$: C, 50.10; H, 5.53; N, 9.23. Found: C, 50.32; H, 5.61; N, 9.16.

Compounds **3a-b** and **7a-d** were similarly prepared and crystallized from acetone/diethyl ether; the ^{1}H nmr data of compounds **7a-d** are reported in Table 1.

(4*R*)-3-(*tert*-Butoxycarbonyl)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**3a**).

This compound was obtained in 87% yield, mp 97-98°; ^{1}H nmr (DMSO): δ 1.40 (s, 9 H, *tert*-butyl), 3.17 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 12.1 Hz), 3.47 (m, 2H, NH-CH_2), 4.48 (m, 2 H, H2, AB system), 4.54 (m, 2 H, CH_2-ONO_2), 4.57 (m, 1 H, H4, X region of ABX system), 8.24 (t, 1 H, CO-NH).

Anal. Calcd. for $C_{11}H_{19}N_3O_6S$: C, 41.11; H, 5.96; N, 13.08. Found: C, 40.93; H, 6.02; N, 12.92.

(2*R*,4*R*)-2-Methyl-3-(*tert*-butoxycarbonyl)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**3b**).

This compound was obtained in 77% yield, mp 99-101°; ^{1}H nmr (DMSO): δ 1.39 (s, 9 H, *tert*-butyl), 1.50 (d, 3 H, CH_3), 3.22 (m, 2 H, H5, AB region of ABX system, $J_{AX} + J_{BX}$ = 15.0 Hz), 3.47 (m, 2H, NH-CH_2), 4.46 (m, 1 H, H4, X region of ABX system), 4.56 (m, 2 H, CH_2-ONO_2), 5.14 (q, 1 H, H2), 8.25 (t, 1 H, CO-NH).

Anal. Calcd. for $C_{12}H_{21}N_3O_6S$: C, 42.98; H, 6.31; N, 12.53. Found: C, 43.07; H, 6.37; N, 12.36.

(2*R*,4*R*)-2-Phenyl-3-(acetyl)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**7a**).

This compound was obtained in 53% yield, mp 101 -103°.

Anal. Calcd. for $C_{14}H_{17}N_3O_5S$: C, 49.55; H, 5.05; N, 12.38. Found: C, 49.87; H, 5.18; N, 12.53.

(2*S*,4*R*)-2-Phenyl-3-(acetyl)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**7b**).

This compound was obtained in 64% yield, mp 102-103°.

Anal. Calcd. for $C_{14}H_{17}N_3O_5S$: C, 49.55; H, 5.05; N, 12.38. Found: C, 49.64; H, 5.08; N, 12.51.

(2*R*,4*R*)-2-Phenyl-3-(carbethoxy)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**7c**).

This compound was obtained in 89% yield, mp 89-90°.

Anal. Calcd. for $C_{15}H_{19}N_3O_6S$: C, 48.77; H, 5.18; N, 11.38. Found: C, 48.57; H, 5.09; N, 11.43.

(2*S*,4*R*)-2-Phenyl-3-(carbethoxy)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**7d**).

This compound was obtained in 78% yield, mp 94-95°.

Anal. Calcd. for $C_{15}H_{19}N_3O_6S$: C, 48.77; H, 5.18; N, 11.38. Found: C, 48.90; H, 5.07; N, 11.25.

(2*S*,4*R*)-2-(2-Hydroxyphenyl)-3-(acetyl)thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide (**12**).

To a solution of compound **11** (37.0 g, 81 mmoles) in dichloromethane (185 ml) at 20° a 3 *M* solution of hydrochloric acid in ethyl acetate (270 ml, 810 mmoles) was added dropwise. After 1 hour at room temperature, the solvent was evaporated under reduced pressure to dryness and the residue crystallized from 95% ethanol to give pure compound **12** as a white solid (70%, mp 187-189°); the ^1H nmr data are reported in Table 1.

Anal. Calcd. for $C_{14}H_{17}N_3O_6S$: C, 47.32; H, 4.82; N, 11.82. Found: C, 47.12; H, 4.86; N, 11.85.

Compounds **4a-b** were similarly prepared and crystallized from ethanol/diethyl ether as hydrochloric acid salts; the ^1H nmr data are reported in Table 1.

(4*R*)-Thiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide Hydrochloric Acid Salt (**4a**).

This compound was obtained in 72% yield, mp 132-134°.

Anal. Calcd. for $C_6H_{12}ClN_3O_4S$: C, 27.97; H, 4.69; Cl, 13.76; N, 16.31. Found: C, 28.04; H, 4.72; Cl, 13.46; N, 16.30.

(4*R*)-2-Methylthiazolidine-4-[*N*-(2-nitrooxyethyl)]carboxamide Hydrochloric Acid Salt (**4b**).

This compound was obtained in 90% yield, mp 132-133°.

Anal. Calcd. for $C_7H_{14}ClN_3O_4S$: C, 30.94; H, 5.19; Cl, 13.05; N, 15.46. Found: C, 30.90; H, 5.17; Cl, 13.19; N, 15.47.

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