Synthesis of 2-(5'-Substituted Isoxazol-3'-yl)-4-oxo-3-thiazolidinylalkanoic Acids

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A series of 2-substituted 4-oxo-3-thiazolidinylalkanoic acids bearing an isoxazole nucleus in the 2-position have been prepared. None of the compounds synthesised showed antibacterial activity *in vitro*.

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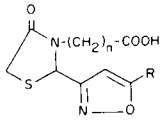
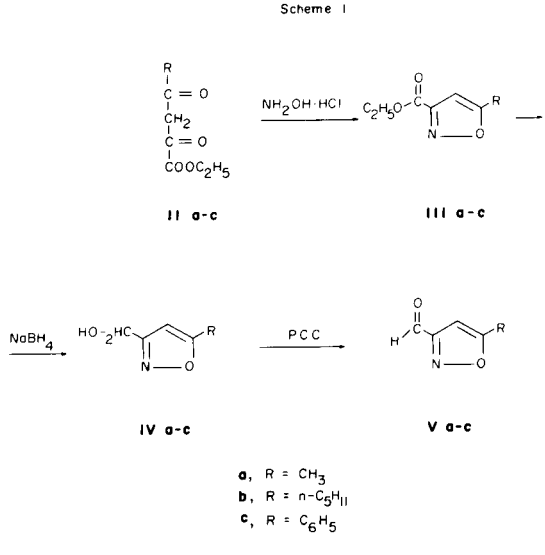
Different biological properties exhibited by substituted 4-thiazolidinones include hypnotic (1), local anaesthetic (2) and microbiological activities (3). The effectiveness of 2-(4-*p*-chlorophenyl)-3-methyl-4-thiazolidinone and 2-(2-furyl)-3-methyl-4-thiazolidinone to afford protection against pentylenetetrazol-induced seizures has also been reported (4). These observations prompted us to synthetise a new series of 2,3-disubstituted 4-thiazolidinones featured by an isoxazole moiety at the 2-position and by an alkanoic acid chain of variable length at the 3-position as shown in formula I.



I

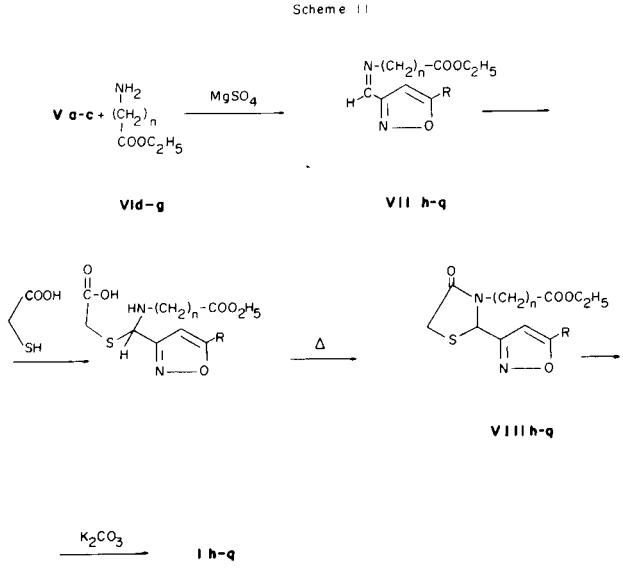
The synthetic pathway involved construction of a 3,5-disubstituted isoxazole bearing a function to be transformed into an aldehyde group. This may be readily achieved by treatment of suitable ethyl acylpyruvates (IIa-c) with hydroxylamine hydrochloride producing the desired isoxazoles (IIIa-c) in high yield (5). The ester group of IIIa-c was then transformed into an aldehyde function by a two step-procedure, namely, reduction with sodium borohydride in methanol (6) to the corresponding alcohols (IVa-c) and subsequent oxidation to the aldehydes (Va-c) by means of PCC (7).

Scheme I



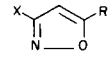
Exposure of Va-c to ψ-aminoacid ethyl esters VId-g at room temperature in benzene solution in the presence of anhydrous magnesium sulfate, generated the Schiff bases (VIIh-q) which were used as crude materials. Addition of mercaptoacetic acid to the C=N linkage proceeded smoothly to afford the corresponding adducts, which were heated in a Dean Stark aparatus to promote ring closure, thus completing the construction of the 4-thiazolidine nucleus of VIIIh-q (4).

Scheme II



The title compounds Ih-q were finally secured by mild hydrolysis of the esters by treatment with aqueous methanolic potassium carbonate. All derivatives (VIIIh-q and Ih-q) synthesized were tested *in vitro* for their anti-

Table I



Compound No.	X	R	Yield %	Mp°C (a) Bp°C/mm Hg	Molecular Formula	Analyses % Calcd./Found C	H	N
IIIa	$CO_2C_2H_5$	CH_3	82	111-113/18 (b)	$C_7H_9NO_3$	54.19	5.85	9.03
						53.97	5.82	8.94
IIIb	$CO_2C_2H_5$	n-C_5H_{11}	91	85/0.1 (c)	$C_{11}H_{17}NO_3$	62.54	8.11	6.63
						62.38	8.02	6.55
IIIc	$CO_2C_2H_5$	C_6H_5	85	52-53 (d) (AE)	$C_{12}H_{11}NO_3$	66.35	5.10	6.45
						66.17	5.01	6.37
IVa	CH_2OH	CH_3	80	120-22/18 (e)	$C_5H_7NO_2$	53.09	6.24	12.38
						53.25	6.18	12.18
IVb	CH_2OH	n-C_5H_{11}	93	90/0.1	$C_9H_{15}NO_2$	63.88	8.94	8.28
						63.62	8.85	8.11
IVc	CH_2OH	n-C_6H_5	82	91-92 (f) (E)	$C_{10}H_9NO_2$	68.56	5.18	8.00
						68.32	5.01	7.91
Va	CHO	CH_3	52	31-33 (e)	$C_5H_5NO_2$	54.05	4.54	12.61
						54.21	4.61	12.57
Vb	CHO	n-C_5H_{11}	65	95-97/18	$C_9H_{13}NO_2$	64.65	7.84	8.38
						64.51	7.72	8.27
Vc	CHO	C_6H_5	57	59-61 (g) (PE)	$C_{10}H_7NO_2$	69.36	4.07	8.09
						69.25	3.98	7.97

(a) AE: 95% ethanol; E: diethyl ether; PE: petroleum ether 40-70°. (b) Lit (5). (c) Lit (8) reported bp, 136-140°/2 mm Hg. (d) Lit 10 reported 52° (ethanol). (e) Lit (11) reported for IVa bp, 134.5-135.5°/30 mm Hg and for Va bp, 65-75°/30 mm Hg. (f) Lit (12). (g) Lit (13) reported 52-55°.

IR and NMR Spectral Data for III-V (a-c)

	IR (chloroform) cm^{-1}	NMR (deuteriochloroform)
IIIa	1740, 1600	1.4 (t, J = 7, OCH_2CH_3), 2.5 (s, CH_3-5), 4.45 (q, J = 7, OCH_2CH_3), 6.64 (s, H-4)
IIIb	1740, 1600	0.9 (t, J = 6, CH_3 final), 1.4 (t, J = 7, OCH_2CH_3), 2.85 (t, J = 7, -CH_2-5), 6.45 (s, H-4)
IIIc	1720, 1610, 1590, 1570	1.4 (t, J = 7, OCH_2CH_3), 4.45 (q, J = 7, OCH_2CH_3), 6.9 (s, H-4), 7.45 (m, arom), 7.75 (m, arom)
IVa	3350 (b), 1600	2.4 (s, CH_3-5), 4.4 (s, CH_2-3), 4.9 (sb, OH), 6.1 (s, H-4)
IVb	3370 (br), 1600	0.9 (t, J = 7, final CH_3), 4.5 (s, CH_2-3), 4.9 (sb, OH), 6.1 (s, H-4)
IVc	3340 (br), 1600	3.2 (sb, OH), 4.75 (s, CH_2-3), 6.6 (s, H-4), 7.5 (m, arom), 7.8 (m, arom)
Va	1710, 1600	2.9 (s, CH_3-5), 6.0 (s, H-4), 10.1 (s, CHO)
Vb	1710, 1600	0.9 (t, J = 7, final CH_3), 2.85 (t, J = 7, CH_2-5), 6.4 (s, H-4), 10.1 (s, CHO)
Vc	1710, 1610, 1590, 1570	6.9 (s, H-4), 7.5 (m, arom), 7.8 (m, arom), 10.2 (s, CHO)

bacterial activity against a series of gram-negative and gram-positive organisms. None of the compounds showed any antibacterial activity.

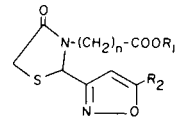
EXPERIMENTAL

All compounds were checked for structural consistency by ir and nmr spectroscopy. Melting points were determined on a Büchi apparatus and are uncorrected. The ir spectra were measured with a Perkin-Elmer model 257 spectrometer. The ^{1}H-nmr spectra were determined in deuteriochloroform with TMS as the internal standard on a Perkin-Elmer R32 spectrometer. Elemental analyses for C, H, N, and S of all the compounds synthesized were determined within ±0.3% of the theoretical values and these data were determined in the microanalytical laboratory of the Pharmaceutical Chemistry Institute at Padova. These data are recorded in the Tables. Organic layers were dried over anhydrous sodium sulfate before concentration. The acylpyruvates (8) and the amino acid ethyl ester hydrochlorides (9) were prepared according to literature procedures.

General Procedure for the Preparation of 5-Substituted Isoxazole-3-carboxethyl Esters IIIa-c.

A mixture of hydroxylamine hydrochloride (20 g, 0.28 mole) and the appropriate ethyl acylpyruvate (0.080 mole) in ethanol (200 ml) was heated under reflux for 3 hours. The mixture was partially concentrated *in vacuo*, diluted with water (200 ml) and extracted with diethyl ether (3 × 100 ml). The ethereal extracts were washed with brine, then the 1*N* sodium hydroxide solution (50 ml) and finally with brine. Evaporation of the solvent and distillation afforded the isoxazole esters IIIa-c. The yields, physical constants and spectral data of the products are summarized in Table I.

Table II



Compound No.	R_1	R_2	n	Yield %	Mp °C (a)	Molecular Formula	Analyses % Calcd./Found C	H	N	S
VIIIh	$CO_2C_2H_5$	CH_3	2	82	-	$C_{12}H_{16}N_2O_4S$	50.70	5.67	9.86	11.26
							50.55	5.54	9.83	11.13
VIIIi	$CO_2C_2H_5$	CH_3	5	79	54 (E-EP)	$C_{15}H_{22}N_2O_4S$	55.20	6.80	8.58	9.81
							55.35	6.91	8.49	9.76
VIIIl	$CO_2C_2H_5$	n-C_5H_{11}	2	75	-	$C_{16}H_{24}N_2O_4S$	56.46	7.11	8.23	9.40
							56.23	7.01	8.23	9.32
VIIIm	$CO_2C_2H_5$	n-C_5H_{11}	6	68	-	$C_{20}H_{32}N_2O_4S$	60.58	8.11	7.07	8.07
							60.32	8.02	6.97	8.17
VIIIn	$CO_2C_2H_5$	n-C_5H_{11}	1	58	-	$C_{15}H_{22}N_2O_4S$	55.20	6.80	8.58	9.80
							54.97	6.75	8.47	9.71
VIIIo	$CO_2C_2H_5$	C_6H_5	2	88	104-105 (E-EP)	$C_{17}H_{18}N_2O_4S$	58.95	5.24	8.09	9.24
							58.69	5.18	7.99	9.17
VIIIp	$CO_2C_2H_5$	C_6H_5	5	85	68-69 (E-EP)	$C_{20}H_{24}N_2O_4S$	61.84	6.23	7.21	8.24
							61.58	6.34	7.34	8.35
VIIIq	$CO_2C_2H_5$	C_6H_5	1	61	-	$C_{16}H_{16}N_2O_4S$	57.83	4.85	8.43	9.63
							57.62	4.73	8.21	9.40
Ih	H	CH_3	2	90	113-114 (T-H)	$C_{10}H_{12}N_2O_4S$	46.88	4.72	10.93	12.49
							46.67	4.56	10.78	12.34
Ii	H	CH_3	5	85	116-117 (T-H)	$C_{13}H_{18}N_2O_4S$	52.34	6.08	9.39	10.73
							52.56	6.23	9.45	10.65
Il	H	n-C_5H_{11}	2	88	107-108 (E-EP)	$C_{14}H_{20}N_2O_4S$	53.84	6.45	8.97	10.25
							53.67	6.56	9.06	10.23
Im	H	n-C_5H_{11}	6	93	73-74 (E-EP)	$C_{18}H_{28}N_2O_4S$	58.68	7.66	7.60	8.69
							58.58	7.63	7.65	8.62
In	H	n-C_5H_{11}	1	75	91-93 (E-EP)	$C_{13}H_{18}N_2O_4S$	52.34	6.08	9.39	10.73
							52.11	5.97	9.28	10.52
Io	H	C_6H_5	2	82	136-138 (T-H)	$C_{15}H_{14}N_2O_4S$	56.60	4.43	8.80	10.05
							56.45	4.23	8.89	10.32
Ip	H	C_6H_5	5	87	81-83 (T-H)	$C_{18}H_{20}N_2O_4S$	59.99	5.59	7.79	8.88
							59.78	5.56	7.56	8.98
Iq	H	C_6H_5	1	70	188-190 (T-H)	$C_{14}H_{12}N_2O_4S$	55.26	3.98	9.21	10.51
							55.17	3.85	9.14	10.37

(a) E-EP: ethyl ether-petroleum ether 40-70 (1:1); T-H: THF-Hexane (1:1).

	IR (chloroform) cm^{-1}	IR and NMR Spectral Data for Ih-q NMR (deuteriochloroform)
Ih	1710, 1670, 1600	2.45 (s, CH_3-5'), 2.6 (t, J = 7, CH_2COOH), 3.7 (m, N-CH_2-, S-CH_2-), 5.9 (s, H-2), 6.1 (s, H-4'), 8.5 (sb, COOH)
Ii	1710, 1680, 1600	2.3 (t, J = 7 Hz, CH_2-COOH), 2.45 (s, CH_3-5'), 3.7 (m, N-CH_2, S-CH_2), 5.8 (s, H-2), 6.05 (s, H-4'), 9.2 (sb, COOH)
Il	1710, 1670, 1600	0.9 (t, J = 6 Hz, CH_3 final), 2.7 (m, CH_2-COOH, CH_2-5'), 3.75 (m, N-CH_2, S-CH_2), 5.9 (s, H-2), 6.05 (s, H-4'), 10 (sb, COOH)
Im	1715, 1670, 1600	0.9 (t, J = 6 Hz, CH_3 final), 2.3 (t, J = 7 Hz, CH_2-COOH), 2.8 (t, J = 7 Hz, CH_2-5'), 3.7 (m, N-CH_2, S-CH_2), 5.8 (s, H-2), 6 (s, H-4'), 9.4 (sb, COOH)
In	1720, 1680, 1600	0.9 (t, J = 6 Hz, CH_3 final), 2.8 (t, J = 7 Hz, CH_2-5'), 3.8 (m, S-CH_2), 4.05 (dd, J = 17 Hz, N-CH_2), 6.0 (s, H-2), 6.15 (s, H-4'), 10.1 (sb, COOH)
Io	1710, 1670, 1610, 1590, 1570	2.7 (m, CH_2-COOH), 3.7 (m, N-CH_2, S-CH_2), 6.0 (s, H-2), 6.7 (s, H-4'), 7.5 (m, arom), 7.8 (m, arom), 10.1 (sb, COOH)
Ip	1710, 1680, 1610, 1590, 1570	2.35 (t, J = 7 Hz, CH_2-COOH), 3.8 (m, N-CH_2, S-CH_2), 5.85 (s, H-2), 6.6 (s, H-4'), 7.5 (m, arom), 7.8 (m, arom), 10.1 (sb, COOH)
Iq	1720, 1670, 1610, 1590, 1570	3.8 (m, S-CH_2), 4.05 (dd, J = 17 Hz, N-CH_2), 6.05 (s, H-2), 6.7 (s, H-4'), 7.5 (m, arom), 7.8 (m, arom), 9.8 (sb, COOH)

General Procedure for the Preparation of 5-Substituted-3-methanols IVa-c.

To an ice-cooled and stirred solution of the isoxazole ester (IIIa-c) (10 g, 0.048 mole) in dry ethanol (100 ml) was added portion-wise sodium borohydride (4 g, 0.131 mole). The resulting solution was stirred at room temperature for 3 hours, carefully acidified with 1*N* hydrochloric acid and concentrated *in vacuo*. The aqueous solution was extracted with diethyl ether (3 × 100 ml) and concentrated *in vacuo* to give an oil which was distilled affording compounds IVa-c. The yields, physical constants and spectral data of the products are reported in Table I.

General Procedure for the Preparation of 5-Substituted Isoxazole-3-carboxaldehydes Va-c.

To a well-stirred suspension of pyridinium chlorochromate (32.3 g, 0.15 mole) in dry methylene chloride (200 ml) a solution of the appropriate alcohols IVa-c (0.1 mole) in methylene chloride (30 ml) was added drop-wise. The resulting slurry was stirred at room temperature for 3 hours. Addition of diethyl ether (300 ml) followed by filtration through a pad of Celite and concentration *in vacuo* afforded the isoxazole aldehydes Va-c. The yields, physical constants and spectral data of the products are reported in Table I.

General Procedure for the Preparation of 2-(5'-Substituted Isoxazol-3'-yl)-4-oxo-3-thiazolidinylalkanoic Acid Ethyl Esters VIIIh-q.

To an ice-cooled and stirred solution of the appropriate aldehyde Va-c (0.0135 mole) and of the appropriate amino acid ethyl ester hydrochloride VId-g (0.0135 mole) in dry methylene chloride (20 ml) was added triethylamine (3.1 ml) and anhydrous magnesium sulfate (1 g). The suspension was stirred at room temperature overnight, concentrated *in vacuo*, diluted with diethyl ether (100 ml) and washed with brine (2 × 50 ml). Evaporation of the solvent gave the crude requisite Schiff base as a pale yellow oil. The ir spectra of the crude imine showed two peaks at 1740 (ester CO) and 1660 cm^{-1} (C=N) and the lack of a carbonyl absorption of the aldehyde at 1710 cm^{-1}. A solution of the oily imine and mercaptoacetic acid (0.018 mole) in benzene (30 ml) was refluxed in a Dean Stark apparatus for 15 hours. Removal of the solvent afforded an oil which was chromatographed on silica gel (100 g), using as eluent a mixture of diethyl ether-petroleum ether 40-70° (1:1). The yields, physical constants and spectral data of the products are summarized in Table II.

General Procedure for the Preparation of 2-(5'-Substituted Isoxazol-3'-yl)-4-oxo-3-thiazolidinylalkanoic Acids Ih-q.

A mixture of the appropriate ester VIIIh-q (0.0024 mole), methanol (15 ml) and potassium carbonate (10 ml) was refluxed for 1 hour. After removal of the solvent *in vacuo* the residue was diluted with water (10 ml) and acidified with 2*N* hydrochloric acid. The requisite precipitated acid was collected and crystallized as specified in Table II.

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