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A series of 2-substituted 4-ethyl-4,7-dihydro-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic acids were synthesized. Antibacterial activity was tested *in vitro*. None of the new compounds prepared showed any interesting antibacterial activity *in vitro* against the strains tested.

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The interesting activity of the piperazine substituted quinolone chemotherapeutics pipemidic acid [1], norfloxacine [2] and ciprofloxacine [3], analogs of nalidixic acid [4], and our interest in sulfur analogs of these chemotherapeutics [5] [6], prompted us to synthesize piperazine substituted thiazolopyridine analogs of these compounds.

In a previous paper [7], we described the preparation of a series of 7-ethyl-4,7-dihydro-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic acids substituted in 2 with a cyclic amine structure.

This paper deals with the preparation of analogous compounds with a thiazolo[4,5-*b*]pyridine structure (**14**). The 2-alkylthio derivatives were already synthesized by Hayakawa *et al.* [8]. We prepared the following series of 2-substituted-4-ethyl-4,7-dihydro-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic acids: **14.1** → **14.23**.

Chemistry.

Dipotassium cyanimidodithiocarbonate [9] is a commonly used intermediate for the synthesis of a wide variety of 2-alkylthio-4-aminothiazoles [10] [11] [12]. As we used a Gould-Jacobs reaction for the synthesis of thiazolo[5,4-*b*]-pyridine-5-carboxylic acids [7], we tried the usefulness of this reaction for the synthesis of the [4,5-*b*] series. Therefore dipotassium cyanimidodithiocarbonate (**1**) was monomethylated with an equimolar amount of methyl iodide in acetone/water at 0°, to produce potassium methylcyanimidodithiocarbonate (**2**). Next, alkylation with ethyl 2-bromoacetate in acetone gave the intermediate dithioether, which yielded ethyl 4-amino-2-methylthiothiazole-5-carboxylate (**3**) by spontaneous cyclisation. Ester hydrolysis with sodium hydroxide in water afforded the carboxylic acid **4**, which reacted with diethyl ethoxymethylenemalonate (EMME) in boiling toluene, with spontaneous decarboxylation, to yield diethyl *N*-[4-(2-methylthio)thiazolyl]aminomethylenemalonate (**5**).

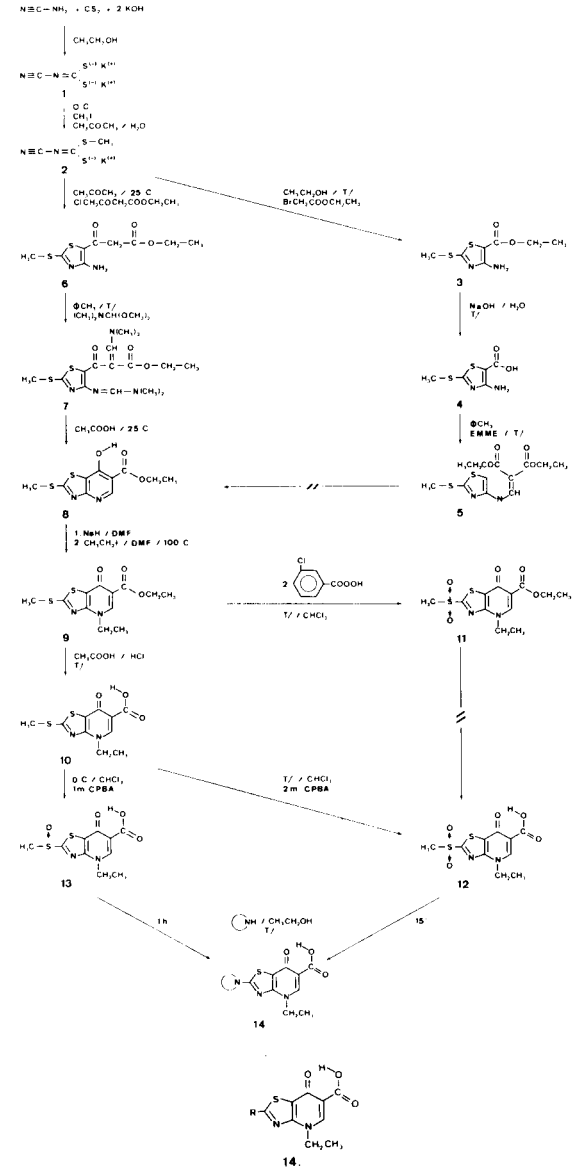
All our attempts to produce ethyl 7-hydroxy-2-methylthiothiazolo[4,5-*b*]pyridine-6-carboxylate (**8**) by thermal cyclisation at various temperatures or by oxidative ring closure with phosphorus oxychloride failed (recovery of the starting material or degradation by tar formation). Therefore an alternative way was necessary.

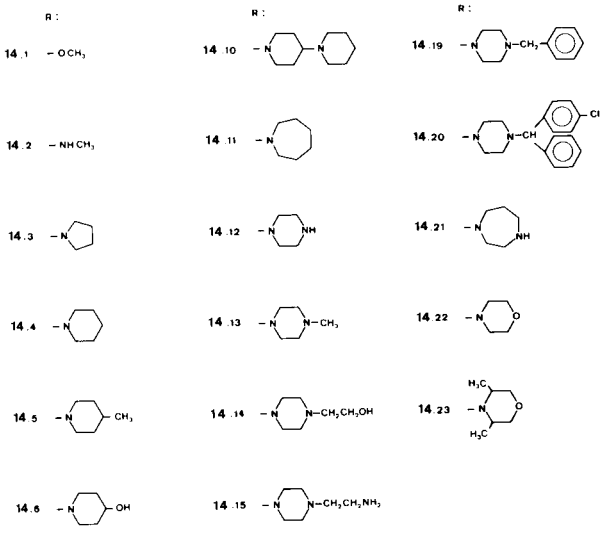
As it is possible to convert *o*-difunctional heterocycles into new cyclic systems by the use of *N,N*-dimethylformamide dimethyl acetal, as the source of the methylene group [13], we synthesized ethyl 4-amino-2-methylthio-β-oxo-5-thiazolepropionate (**6**). Therefore compound **2** was alkylated with ethyl 4-chloroacetoacetate in acetone. This synthetic sequence has already been described by Hayakawa *et al.* [8].

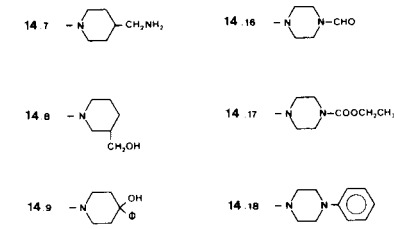
After condensation of compound **6** with *N,N*-dimethylformamide dimethylacetal, compound **7** was converted in-

Table I

Compound	Formula	MW	Elemental Analysis C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	S Calcd.	S Found
1	$C_2H_2S_2K_2$	194.36	12.36	12.43	—	—	14.42	14.38	32.99	33.10
2	$C_3H_3N_2S_2K$	170.30	21.16	21.11	1.78	1.70	16.45	16.49	37.66	37.62
3	$C_7H_{10}O_2N_2S_2$	218.29	38.52	38.41	4.62	4.59	12.83	12.78	29.37	29.43
4	$C_5H_6O_2N_2S_2$	190.23	31.57	31.46	3.18	3.20	14.73	14.69	33.71	33.63
5	$C_{12}H_{16}O_4N_2S_2$	316.39	45.56	45.51	5.10	5.09	8.85	8.90	20.27	20.33
6	$C_9H_{12}O_3N_2S_2$	260.33	41.52	41.41	4.65	4.63	10.76	10.81	24.63	24.58
7	$C_{15}H_{22}O_3N_4S_2$	370.48	48.63	48.51	5.99	6.01	15.12	15.10	17.31	17.34
8	$C_{10}H_{10}O_3N_2S_2$	270.33	44.43	44.60	3.73	3.72	10.36	10.40	23.72	23.69
9	$C_{12}H_{14}O_3N_2S_2$	298.37	48.43	48.19	4.73	4.73	9.39	9.42	21.49	21.53
10	$C_{10}H_{10}O_3N_2S_2$	270.33	44.43	44.30	3.73	3.70	10.36	10.40	23.72	23.70
11	$C_{12}H_{14}O_5N_2S_2$	330.37	43.63	43.60	4.27	4.30	8.48	8.46	19.41	19.39
12	$C_{10}H_{10}O_5N_2S_2$	302.32	39.72	39.85	3.33	3.30	9.27	9.32	21.21	21.15
13	$C_{10}H_{10}O_4N_2S_2$	286.32	41.95	42.06	3.52	3.49	9.78	9.80	22.39	22.36







to ethyl 7-hydroxy-2-methylthiothiazolo[4,5-*b*]pyridine-6-carboxylate (**8**) by cyclisation in glacial acetic acid at room temperature.

N-Alkylation was performed with sodium hydride/ethyl iodide in *N,N*-dimethylformamide. This reaction occurred with better yields than the described alkylation in potassium carbonate/ethyl iodide by Hayakawa *et al.* [8] (85% *versus* 46%).

After ester hydrolysis with hydrochloric acid/acetic acid, the methylthio group was oxidized with *m*-chloroperoxybenzoic acid in chloroform. At 0° the methylsulfoxide **13** and at elevated temperature the methylsulfone **12** was obtained.

Nucleophilic substitution of these groups with an appropriate cyclic amine gave the desired compounds **14.1** → **14.23**. In agreement with the literature [14], the methylsulfone was displaced more easily than the methylsulfoxide group.

Prior oxidation of the ester **9** afforded compound **11**. We found (ir, ^{1}H-nmr, ms) that ester hydrolysis of compound **11** did not give compound **12** under acidic or basic conditions, but rather the 2-hydroxy derivative.

EXPÉRIMENTAL

All compounds were checked for their structure with ir spectrophotometry, ^{1}H-nmr, mass spectrometry and elemental analysis. The ir spectra were obtained with a Beckman Acculab-4 spectrophotometer. The ν max are given in cm^{-1}. All compounds were examined as potassium bromide pellets. The ^{1}H-nmr spectra were recorded on a Varian EM 360 A spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane. Mass spectral data were registered on a JEOL JMS-01SG-2 mass spectrometer. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Elemental analyses are given in Table I.

Dipotassium Cyanimidodithiocarbonate (**1**).

Compound **1** was prepared according to the method of Wittenbrook, Smith and Timmons [15], yield 73%, mp 300°; ir (potassium bromide): ν max 2150 (C≡N).

Potassium Methyl Cyanimidodithiocarbonate (**2**).

Compound **2** was prepared according to the method of Wobig [12], yield 92%, mp 199°; ir (potassium bromide): ν max 2160, 2140 (C≡N); ^{1}H-nmr (DMSO-d_6): δ 2.35 (s, S-CH_3).

Ethyl 4-Amino-2-methylthiothiazole-5-carboxylate (**3**).

To a mechanically stirred solution of 17.03 g (0.1 mole) of **2** in 200 ml of ethanol, 16.70 g (0.1 mole) of ethyl 2-bromoacetate was added. The solution was heated under reflux for 15 minutes and 2 ml of triethylamine

Table II

Compound	Mp °C	Yield % [a]	Formula	Elemental Analysis (%) Calcd.	Found	IR ν max	^{1}H-NMR (deuteriotrifluoroacetic acid δ) N CH_2 [b]	NCH_2CH_3 CH_3	[c]	C_5H	C_2-R [d]	Mass spectrum (m/e)	MW
14.1	215	92	$C_{10}H_{10}O_4N_2S$	C 47.24	47.41	1495	1.77		4.86	9.16	4.52 (3H)	254 M^+	254.26
				H 3.96	3.95	1410						210 [e]	
				N 11.02	10.99								
				S 12.61	12.62								
14.2	>290	91	$C_{10}H_{11}O_3N_3S$	C 47.42	47.52	1480	1.74		4.78	8.98	3.36 (3H)	253 M^+	253.28
				H 4.38	4.40	1610						209 [e]	
				N 16.59	16.65	1625							
				S 12.66	12.63								
14.3	>290	96	$C_{13}H_{15}O_3N_3S$	C 53.23	53.24	1495	1.72		4.79	8.99	2.33 (4H)	293 M^+	293.34
				H 5.15	5.16	1590					3.68 (2H)	249 [e]	
				N 14.32	14.38	1620					4.07 (2H)		
				S 10.93	10.90								
14.4	275	95	$C_{14}H_{17}O_3N_3S$	C 54.71	54.69	1500	1.70		4.73	8.98	2.22 (6H)	307 M^+	307.37
				H 5.57	5.57	1620					3.98 (4H)	263 [e]	
				N 13.67	13.69	1580							
				S 10.43	10.40								
14.5	232	95	$C_{14}H_{19}O_3N_3S$	C 56.06	55.90	1510	1.68		4.72	8.92	1.12 (3H)	321 M^+	321.39
				H 5.96	5.94	1620					2.00 (5H)	277 [e]	
				N 13.07	13.03	1585					3.68 (4H)		
				S 9.98	10.03								
14.6	270	84	$C_{14}H_{17}O_4N_3S$	C 52.00	51.91	1500	1.68		4.80	8.98	1.90 (5H)	323 M^+	323.37
				H 5.30	5.29	1580					4.00 (4H)	279 [e]	
				N 12.99	13.04								
				S 9.91	9.89								
14.7	205	86	$C_{15}H_{20}O_3N_4S$	C 53.56	53.50	1500	1.70		4.76	8.98	2.00 (5H)	336 M^+	336.41
				H 5.99	6.03	1620					2.50 (2H)	292 [e]	
				N 16.65	16.60						3.50 (4H)		
				S 9.53	9.55								
14.8	235	85	$C_{15}H_{19}O_4N_3S$	C 53.40	53.38	1430	1.73		4.79	8.99	2.00 (5H)	337 M^+	337.39
				H 5.68	5.67	1460					3.50 (2H)	293 [e]	
				N 12.45	12.39	1620					3.80 (4H)		
				S 9.50	9.48								
14.9	253	87	$C_{20}H_{21}O_4N_3S$	C 60.14	59.98	1500	1.73		4.78	8.98	3.00 (4H)	337 (100%):	399.46
				H 5.30	5.29	1580					4.20 (4H)	M^+-CO_2-H_2O	
				N 10.52	10.56						7.45 (5H)		
				S 8.03	8.06								
14.10	268	91	$C_{19}H_{26}O_3N_4S$	C 58.44	58.49	1490	1.75		4.81	9.03	2.25 (11H)	390 M^+	390.50
				H 6.71	6.70	1450					3.60 (8H)	349	
				N 14.35	14.30	1620							
				S 8.21	8.18								
14.11	255	90	$C_{15}H_{19}O_3N_3S$	C 56.06	55.89	1500	1.70		4.71	8.92	1.80 (8H)	321 M^+	321.39
				H 5.96	5.96	1620					3.78 (2H)	277 [e]	
				N 13.07	13.10						4.18 (2H)		
				S 9.98	10.00								
14.12	285	91	$C_{13}H_{16}O_3N_4S$	C 50.64	50.64	1500	1.72		4.78	9.01	3.82 (4H)	308 M^+	308.35
				H 5.23	5.20	1620					4.37 (4H)	264 [e]	
				N 18.17	18.20								
				S 10.40	10.38								
14.13	270	92	$C_{14}H_{18}O_3N_4S$	C 52.16	51.98	1500	1.73		4.78	9.08	3.27 (3H)	322 M^+	322.38
				H 5.63	5.62	1620					4.06 (8H)	278 [e]	
				N 17.38	17.40								
				S 9.94	9.93								
14.14	245	83	$C_{15}H_{20}O_4N_4S$	C 51.12	51.23	1500	1.71		4.76	9.03	3.74 (4H)	352 M^+	352.41
				H 5.72	5.70	1620					4.10 (4H)	308 [e]	
				N 15.90	15.89						4.32 (4H)		
				S 9.10	9.09								

was added. Reflux was continued for another 2 hours. The ethanol was removed *in vacuo*, water added to the residue and the precipitate collected. Recrystallization from the ethanol yielded 19.6 g (90%) of **3** as bright yellow crystals, mp 101°; ir (potassium bromide): ν max 1665 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.20 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 2.63 (s, 3H, S-CH_3), 4.17 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 6.01 (s, 2H, broad, Th-NH_2); ms: (m/e) 218 M^+ (100%).

Table II continued

Compound	Mp °C	Yield % [a]	Formula	Elemental Analysis (%) Calcd.	Found	IR ν max	^{1}H-NMR (deuteriotrifluoroacetic acid δ) N CH_2 [b]	NCH_2CH_3 CH_3	[c]	C_5H	C_2-R [d]	Mass spectrum (m/e)	MW
14.15	160	84	$C_{15}H_{21}O_3N_5S$	C 51.27	51.20	1620	1.79		4.82	9.12	4.12 (12H)	351 M^+	351.42
				H 6.02	6.05	1500						307 [e]	
				N 19.93	19.90								
				S 9.12	9.10								
14.16	260	89	$C_{14}H_{16}O_4N_4S$	C 49.99	50.18	1500	1.73		4.80	9.04	4.17 (8H)	264 (100%):	336.36
				H 4.79	4.80	1620					8.48 (1H)	M-CO_2-CO	
				N 16.66	16.61								
				S 9.53	9.49								
14.17	272	88	$C_{16}H_{20}O_5N_4S$	C 50.52	50.41	1500	1.72		4.79	8.99	1.42 (3H)	336 (100%):	380.42
				H 5.30	5.29	1700					3.98 (8H)	M-CO_2	
				N 14.73	14.70						4.42 (2H)		
				S 8.43	8.35								
14.18	235	82	$C_{19}H_{20}O_3N_4S$	C 59.36	59.20	1500	1.75		4.81	9.10	4.30 (8H)	384 M^+	384.45
				H 5.24	5.25	1580					7.70 (5H)	340 [e]	
				N 14.57	14.57								
				S 8.34	8.30								
14.19	248	84	$C_{20}H_{22}O_3N_4S$	C 60.28	59.98	1500	1.71		4.80	9.04	4.05 (8H)	398 M^+	398.48
				H 5.56	5.55	1475					4.58 (2H)	354 [e]	
				N 14.06	14.10	1435					7.59 (5H)		
				S 8.05	8.03								
14.20	206	80	$C_{26}H_{25}O_3N_4SCl$	C 61.35	61.30	1500	1.68		4.73	9.00	4.00 (8H)	201 (100%)	509.02
				H 4.95	4.98	1445					4.47 (1H)	$C_{13}H_{10}Cl$	
				N 11.01	10.98						7.62 (9H)		
				S 6.30	6.29								
14.21	258	89	$C_{14}H_{18}O_3N_4S$	C 52.16	52.20	1500	1.68		4.72	8.98	2.62 (2H)	322 M^+	322.38
				H 5.63	5.63	1620					3.84 (8H)	278 [e]	
				N 17.83	17.45								
				S 9.94	9.91								
14.22	>290	94	$C_{13}H_{15}O_4N_3S$	C 50.48	50.53	1500	1.73		4.79	9.01	4.12 (8H)	309 M^+	309.34
				H 4.89	4.87	1620						265 [e]	
				N 13.58	13.60								
				S 10.36	10.35								
14.23	280	95	$C_{15}H_{19}O_4N_3S$	C 53.40	53.31	1500	1.72		4.78	8.99	1.52 (6H)	337 M^+	337.39
				H 5.68	5.68	1620					3.51 (2H)	293 [e]	
				N 12.47	12.48						4.13 (4H)		
				S 9.53	9.53								

[a] Method 14.a. [b] t, 3H, J = 7 Hz. [c] q, 2H, J = 7 Hz. [d] Approximative values. [e] (100%) M-CO_2.

4-Amino-2-methylthiothiazole-5-carboxylic Acid (**4**).

Compound **3** (10.9 g, 0.05 mole) was suspended in 100 ml of 10% sodium hydroxide and refluxed for 1 hour. The resulting solution was treated with charcoal and filtered hot. The filtrate was cooled in ice and acidified with acetic acid. The precipitated acid was filtered off and washed with water, ethanol and diethyl ether, yield 6.7 g (70%), mp 165°; ir (potassium bromide): ν max 1695 (C=O); ^{1}H-nmr (DMSO-d_6): δ 2.65 (s, 3H, S-CH_3), 5.30 (s, 2H, broad, Th-NH_2); ms: (m/e) 190 M^+, 146 (100%) M-CO_2.

Diethyl *N*-[4-(2-Methylthio)thiazolyl]aminomethylenemalonate (**5**).

Compound **4** (4.75 g, 0.025 mole) was dissolved in 100 ml of toluene and 6.48 g (0.03 mole) of diethyl ethoxymethylenemalonate was added. This mixture was heated under reflux for 2 hours, treated with charcoal, filtered and the solution removed under reduced pressure. The residue was dissolved in a minimal amount of hot ethanol and cooled. The precipitated diester was filtered off and washed with cold ethanol, yielding 4.9 g (62%) of **5** as yellow crystals, mp 118°; ir (potassium bromide): ν max 1240 (C=O), 1640 (C=C), 1680 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.33 and 1.38 (each t, 3H, J = 7 Hz, COO-CH_2-CH_3), 2.70 (3H, s, S-CH_3), 4.37 and 4.54 (each q, 2H, J = 7 Hz, COO-CH_2-CH_3), 6.48 (s, 1H, C_5-*H*), 8.85 (d, 1H, J = 13 Hz, NH-C*H*=C), 11.30 (d, 1H, broad, J = 13 Hz, -N*H*-CH=C); ms: (m/e) 316 M^+, 270 (100%) M-C_2H_5OH.

Ethyl 4-Amino-2-methylthio-β-oxo-5-thiazolepropionate (**6**).

Compound **2** (40 g, 0.235 mole) was dissolved in 300 ml of acetone and 50 g (0.304 mole) of ethyl 4-chloroacetoacetate in 50 ml of acetone was added portionwise. The reaction mixture was stirred for 3 hours at room temperature and the solvent evaporated under reduced pressure. The residue was taken up in water and extracted several times with dichloromethane. The organic layer was collected, washed with water, dried over sodium sulphate and evaporated under reduced pressure. The residue was triturated with a small volume of hot ethanol and cooled for a few days. The precipitated ester was collected and washed with cold ethanol yielding 45 g (73%) of **6**. Recrystallization from methanol gave **6** as yellow needles, mp 92°; ir (potassium bromide): ν max 1620 (NH_2), 1725 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.26 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 2.65 (s, 3H, S-CH_3), 3.55 (s, 2H, CO-CH_2-COO), 4.20 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 6.80 (s, 2H, broad, Th-NH_2); ms: (m/e) 260 M^+.

Ethyl α-Dimethylaminomethylidene-4-dimethylaminomethylideneamino-2-methylthio-β-oxo-5-thiazolepropionate (**7**).

In 1 ℓ of toluene, 52 g (0.2 mole) of **6** was combined with 90 g (0.75 mole) of *N,N*-dimethylformamide dimethylacetal. The reaction mixture

Table III

No.	MIC μg/ml [a] *E. coli* (5) [b]	*Klebs. pneum.* (3)	*Morg. morg.* (1)	*Prot. mir.* (2)	*Prot. vulg.* (1)	*Ps. aerug.* (2)	*Serr. liq.* (1)	*Serr. odor.* (1)	*Staph. aur.* (3)	*Strep. D.* (1)
14.1	— [c]	—	—	—	—	—	—	—	—	—
14.2	128	128	64	64-128	64	—	16	64	16	—
14.3	64	64	64	128	64	—	16	64	16	128
14.4	—	—	—	—	—	—	16	—	16	128
14.5	—	—	—	—	—	—	16	—	16	128
14.6	128	—	64	128	64	—	16	64	16	—
14.7	—	—	—	—	—	—	—	—	—	—
14.8	—	—	—	—	—	—	128	—	16	—
14.9	—	—	—	—	—	—	—	—	16	128
14.10	16-64	64	64	64-128	64	—	16	64	128	—
14.11	—	—	128	64-128	128	—	—	—	16	64
14.12	64	64	16	64-128	16	128	4	64	16	128
14.13	128	64-128	128	128	64	—	16	128	64	—
14.14	—	—	—	—	128	—	64	—	—	—
14.15	—	—	—	—	—	—	—	—	—	—
14.16	64	64	16	64-128	16	128	16	64	16	128
14.17	128	128	64	128	64	—	64	128	64	—
14.18	—	—	—	—	—	—	—	—	16	—
14.19	—	—	—	—	—	—	16	—	16	—
14.20	—	—	—	—	—	—	—	—	64	—
14.21	—	—	64	—	64	128	64	128	64	128
14.22	—	—	—	—	128	—	64	128	64	—
14.23	—	—	—	—	—	—	—	—	—	—
Nal A	2-4	2	2	2-4	2	64	1	2	16	—

[a] Lowest concentration inhibiting bacterial growth after incubation overnight at 37°C. [b] Number of strains. [c] MIC > 128 μg/ml.

was heated under reflux for 2 hours, concentrated to 500 ml under reduced pressure and cooled. The precipitate was collected and washed with cold diethyl ether yielding 71 g (96%) of **7** as a yellow amorphous powder, mp 169°; ir (potassium bromide): ν max 1610 (C=O), 1635 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.05 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 2.65 (s, 3H, S-CH_3), 2.95 (s, 6H, N(CH_3)$_2$), 3.05 (s, 6H, N(CH_3)$_2$), 4.05 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 7.42 (s, 1H, =C*H*-N), 8.42 (s, 1H, =C*H*-N); ms: (m/e) 370 M$^+$.

Ethyl 7-Hydroxy-2-methylthiothiazolo[4,5-*b*]pyridine-6-carboxylate (**8**).

Compound **7** (37 g, 0.1 mole) was dissolved in 200 ml of acetic acid. The solution was stirred for 4 hours at room temperature. The precipitate was collected and washed with water, ethanol and diethyl ether. Recrystallization from *N,N*-dimethylformamide/ethanol (1/1) yielded 26 g (96%) of **8** as colourless crystals, mp 199°; ir (potassium bromide): ν max 1700 (C=O), 1605 (C=C); ^{1}H-nmr (deuteriochloroform + 10% DMSO-d_6): δ 1.40 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 2.80 (s, 3H, S-CH_3), 4.43 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 8.70 (s, 1H, C_5-*H*); ms: (m/e) 270 M$^+$, 196 (100%) M-C_2H_5OH-CO.

Ethyl 4-Ethyl-4,7-dihydro-2-methylthio-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylate (**9**).

To a stirred suspension of 1.0 g (0.0208 mole) of benzene washed 50% sodium hydride in 20 ml of dry *N,N*-dimethylformamide, was added 5.4 g (0.02 mole) of **8** in 100 ml of dry *N,N*-dimethylformamide. The mixture was heated at 80° and 7.5 g (0.05 mole) of ethyl iodide added. The brown-red solution was kept at 100° for another 3 hours. After evaporation of the solvent *in vacuo*, the residue was taken up in chloroform, washed with water, dried over sodium sulphate and the chloroform distilled off *in vacuo*. The resulting solid was recrystallized from ethyl acetate, yielding 5.1 g (85%) of **9** as colourless crystals, mp 160°; ir (potassium bromide): ν max 1675 (C=O), 1625 (C=C); ^{1}H-nmr (deuteriochloroform): δ 1.45 and 1.52 (each t, 3H, J = 7 Hz, COO-CH_2-CH_3 and N-CH_2-CH_3), 2.80 (s, 3H, S-CH_3), 4.43 and 4.45 (each q, 2H, J = 7 Hz, COO-CH_2-CH_3 and N-CH_2-CH_3), 8.34 (s, 1H, C_5-*H*); ms: (m/e) 298 M$^+$, 225 (100%) M-C_2H_5-CO_2.

4-Ethyl-4,7-dihydro-2-methylthio-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic Acid (**10**).

Compound **9** (3 g, 0.01 mole) was dissolved in 100 ml of a mixture of 1*N* hydrochloric acid/90% acetic acid and refluxed for 3 hours. The solution obtained was diluted with ice. The precipitated acid was collected and washed with water, ethanol and diethyl ether. Recrystallization from *N,N*-dimethylformamide/ethanol (1:1) yielded 2.3 g (85%) of **10** as colourless crystals, mp 221°; ir (potassium bromide): ν max 1620 (C=C), 1725 (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.73 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 3.00 (s, 3H, S-CH_3), 4.98 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 9.18 (s, 1H, C_5-*H*); ms: (m/e) 270 M$^+$ 226 (100%) M-CO_2.

Ethyl 4-Ethyl-4,7-dihydro-2-methylsulfonyl-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylate (**11**).

To a solution of 2 g (7.4 mmoles) of **9** in 100 ml of chloroform, was added portionwise with stirring 3.2 g (16 mmoles) of 85% *m*-chloroperoxybenzoic acid. The reaction mixture was heated under reflux for 1 hour. The solvent was removed *in vacuo* and the residue diluted with ethanol/diethyl ether and cooled. Recrystallization from ethyl acetate/hexane yielded 2.2 g (90%) of **11** as colourless crystals, mp 229°; ir (potassium bromide): ν max 1675 (C=O), 1625 (C=C); ^{1}H-nmr (deuteriochloroform + 10% DMSO-d_6): d 1.40 and 1.58 (each t, 3H, J = 7 Hz, COO-CH_2-CH_3 and N-CH_2-CH_3), 3.47 (s, 3H, SO_2-CH_3), 4.37 and 4.55 (each q, 2H, J = 7 Hz, COO-CH_2-CH_3 and N-CH_2-CH_3), 8.68 (s, 1H, C_5-*H*); ms: (m/e) 330 M$^+$, 257 M-C_2H_5-CO_2.

4-Ethyl-4,7-dihydro-2-methylsulfonyl-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic Acid (**12**).

Compound **10** (2 g, 7.4 mmoles) was suspended in 100 ml of chloroform and 3.2 g (16 mmoles) of 85% *m*-chloroperoxybenzoic acid was added portionwise with stirring. The reaction mixture was heated under reflux for 1 hour. Diethyl ether was added and the mixture cooled. The precipitated acid was collected and washed with diethyl ether. Recrystallization from ethyl acetate/hexane yielded 2.1 g (94%) of **12** as colourless crystals, mp 230°; ir (potassium bromide): ν max 1610 (C=C), 1720 (C=O), ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.84 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 3.70 (s, 3H, SO_2-CH_3), 5.14 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 9.50 (s, 1H, C_5-*H*); ms: (m/e) 258 (100%) M-CO_2.

4-Ethyl-4,7-dihydro-2-methylsulfinyl-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic Acid (**13**).

Compound **10** (2 g, 7.4 mmoles) was suspended in 50 ml of chloroform and cooled at 0°. Then 1.5 g (7.4 mmoles) of 85% *m*-chloroperoxybenzoic acid was added portionwise with stirring. After 1 hour at 0°, diethyl ether was added and the mixture cooled. The precipitate was collected and washed with diethyl ether. Recrystallization from ethanol yielded 1.9 (90%) of **13** as colourless crystals, mp 235°; ir (potassium bromide): ν max 1720 (C=O), 1610 (C=C); ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.80 (t, 3H, J = 7 Hz, COO-CH_2-CH_3), 3.40 (s, 3H, SO-CH_3), 5.08 (q, 2H, J = 7 Hz, COO-CH_2-CH_3), 9.25 (s, 1H, C_5-*H*); ms: (m/e) 286 (100%) M-CO_2.

2-Substituted-4-ethyl-4,7-dihydro-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic Acid (**14**).

Method 14.a.

To as suspension of 3 g (0.01 mole) of **12** in 50 ml of ethanol 0.03 mole of an appropriate amine was added. This mixture was heated under reflux for 15 minutes. The solids were obtained after cooling or after concentration *in vacuo*, followed by trituration of the residue with water. The precipitate was collected and recrystallized from *N,N*-dimethylformamide/ethanol.

Method 14.b.

To a suspension of 2.9 g (0.01 mole) of **13** in 50 ml of *N,N*-dimethylformamide/ethanol (1/1) 0.03 mole of an appropriate amine was added. This mixture was heated under reflux for 1 hour. The results are summarized in Table II.

Microbiology.

The 2-substituted-4-ethyl-4,7-dihydro-7-oxothiazolo[4,5-*b*]pyridine-6-carboxylic acids **14.1** → **14.23** were tested *in vitro* for their antibacterial activity against a series of gram-negative strains (*Escherichia coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Serratia liquefaciens* and *Serratia odorifera*) and gram-positive strains (*Staphylococcus aureus* and *Streptococcus D.*). *In vitro* bacterial susceptibility (minimal inhibitory concentration) was determined with the agar dilution method on T.S.A. agar. Some of the derivatives **14** showed slight antibacterial activity *in vitro* against the strains tested. The results are summarized in Table III.

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