Thiazolopyridine Analogs of Naldixic Acid. 1. Thiazolo[5,4-*b*]pyridines

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

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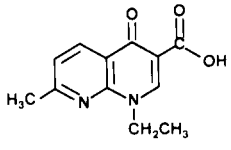
Introduction.

Since the discovery of nalidixic acid (**1**) [1] as a useful chemotherapeutic agent in the treatment of urinary tract infections with gram-negative bacteria a large number of analogs have been synthesized and some of them are in clinical use [2]. They differ from nalidixic acid as well as in the annelated heterocyclic structure (quinoline, thienopyridine, cinnoline, pyridopyrimidine, *et al*) as in ring substitution. As they all contain an annelated 1-ethyl-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid moiety (**2**), a common name has been given to these compounds, namely the quinolone chemotherapeutics.



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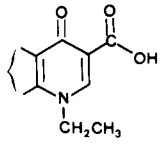

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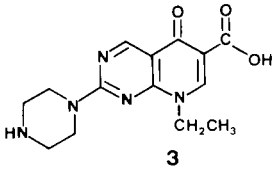
Two of the most interesting structures of the quinolone chemotherapeutics are pipemidic acid (**3**) [3] and norfloxacin (**4**) [4]. They are both substituted with a piperazine ring structure and show a high antibacterial activity against a number of gram-negative bacteria, including *Pseudomonas aeruginosa*, as well as against *Staphylococcus aureus*.



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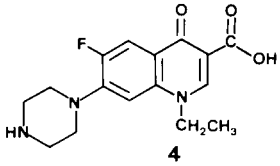

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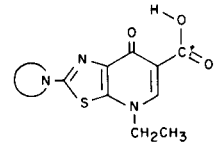
As we are interested in sulfur analogs of nalidixic acid and have already synthesized thieno[2,3-*b*]pyridine [5] and isothiazolo[5,4-*b*]pyridine [6] analogs, we wanted to combine the piperazine substitution with a thiazolopyridine ring structure. The thiazolopyridine structures are already described: the 2-hydrogen-, 2-methyl- and 2-phenylthiazolo[5,4-*b*]pyridine structure by Masui and Tamura [7] and the 2-methylthio- and 2-ethylthiothiazolo[4,5-*b*]pyridine structure by Hayakawa *et al* [8].

This paper deals with the thiazolo[5,4-*b*]pyridine structure. As the 4-oxo-3-pyridinecarboxylic acid moiety appeared to be essential for high activity and as an *N*-ethyl substitution is the most interesting, we made a series of 2-substituted-7-ethyl-4,7-dihydro-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic acids **13**.



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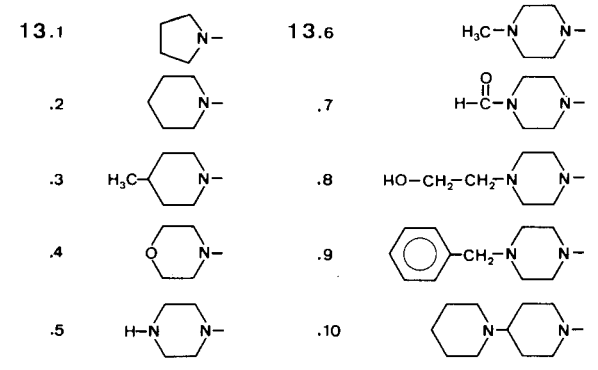


Chemistry.

As it appeared possible to displace the 2-methylthio group of 7-ethyl-4,7-dihydro-2-methylthio-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic acid (**11**) by a cyclic amine in an aprotic polar solvent, compound **11** was synthesized as a general precursor of the postulated compounds. This was performed by the Gould-Jacobs reaction [9]. As starting material, the labile 5-amino-2-mercaptothiazole (**6**) was prepared by a slightly modified method, previously described by Cook [10]. Complete water-free conditions were essential. After alkylation of the 2-thiol group with methyl iodide/sodium methoxide at -78°, the unstable 5-amino-2-methylthiothiazole (**7**) was condensed with diethyl ethoxymethylenemalonate (EMME) in ethanol without previous purification. It was clearly shown by the ^{1}H-nmr spectrum that **7** exists in two tautomeric forms, the amine structure **7a** and the imine structure **7b** (ratio **7a**/**7b** is 3:7 in deute-

Table I

Compound No.	mp (°C)	yield %	IR KBr νmax	^{1}H-N M R (CF_3COOD) δ N-CH_2-CH_3 [c]	N-CH_2-CH_3 [d]	C_6-H	C_2-R	Mass spectrum (m/e)
13.1	280	81	1580 1610	1.79	4.62	9.15	2.44 (4H) 4.00 (4H)	293 M$^+$ 249 (100%) [e]
13.2	274	74	1560 1610	1.76	4.61	9.12	1.97 (6H) 4.03 (4H)	307 M$^+$ 263 (100%) [e]
13.3	280	72	1610 1710	1.77	4.60	9.11	1.17 (3H) 2.08 (5H) 4.02 (4H)	321 M$^+$ 277 (100%) [e]
13.4	280	79	1550 1615	1.80	4.68	9.11	4.18 (8H)	309 M$^+$ 265 (100%) [e]
13.5	227	61 [a] 80 [b]	1610 1570	1.79	4.72	9.10	3.84 (4H) 4.29 (4H)	308 M$^+$ 264 (100%) [e]
13.6	> 280	65 [a] 82 [b]	1615 1560	1.79	4.73	9.11	3.98 (8H) 4.44 (3H)	322 M$^+$ 278 (100%) [e]
13.7	> 280	67 [a] 86 [b]	1665 1610	1.81	4.69	9.07	4.02 (8H) 8.41 (1H)	336 M$^+$ 292 (100%) [e]
13.8	274	69	1570 1610	1.80	4.70	9.02	3.78 (4H) 4.06 (4H) 4.41 (4H)	352 M$^+$ 308 (100%) [e]
13.9	230	62	1565 1610	1.80	4.67	9.08	3.92 (8H) 4.62 (2H) 7.58 (5H)	398 M$^+$ 354 (100%) [e]
13.10	248	79	1565 1610	1.79	4.68	9.09	2.09 (6H) 2.58 (4H) 3.70 (9H)	390 M$^+$ 346 (100%) [e]

[a] Method 13a. [b] Method 13b. [c] t, 3H, J = 7 Hz. [d] q, 2H, J = 7 Hz. [e] M-CO_2.

Table II

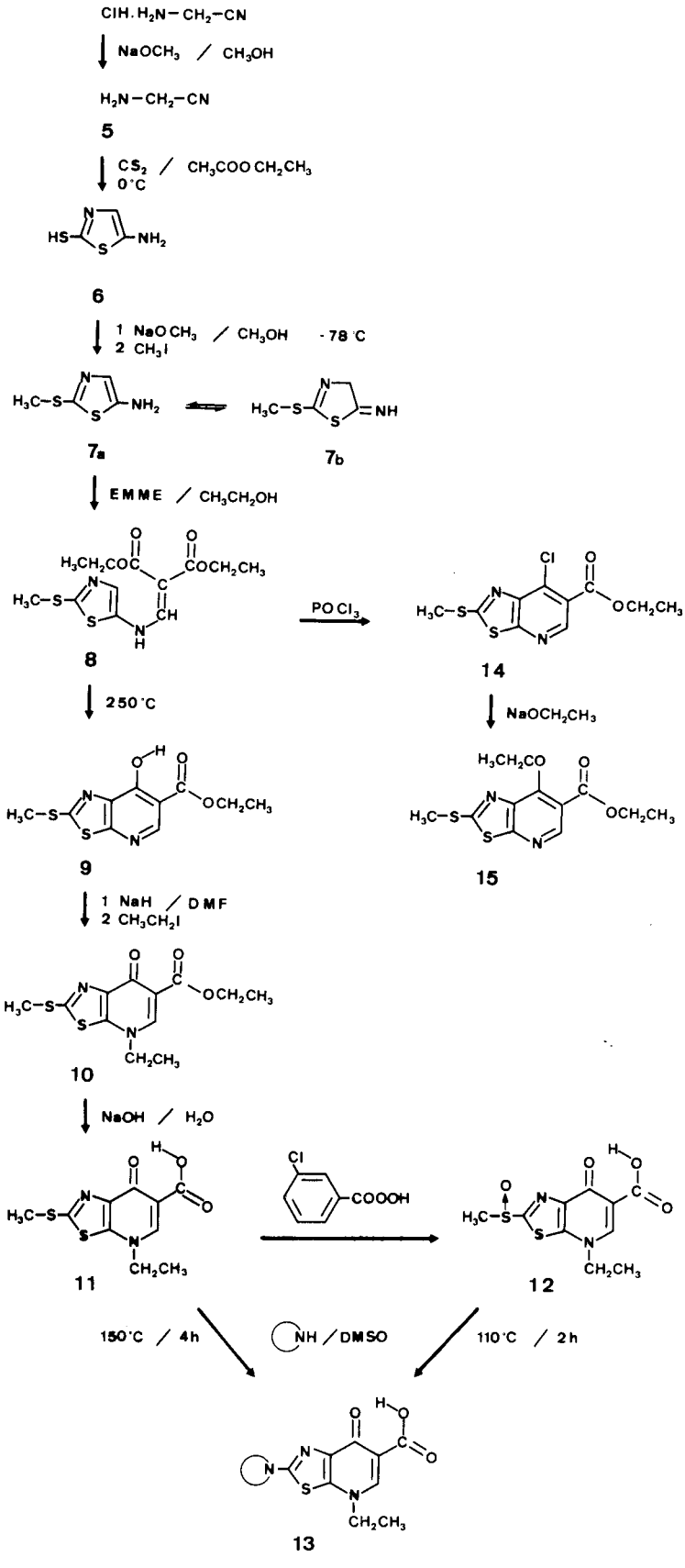
MIC μg/ml [a]	*Staph aur* (3) [b]	*Strep D* (1)	*Ps aerug* (2)	*Ser mar* (2)	*Klebs* (3)	*E. Coli* (5)	*Prot mir* (4)
Nalidixic acid	16	> 128	64	2	4	1-2	1-2
Piromidic acid	2-4	64	64-128	16	16	4-16	4-16
Pipemidic acid	16	64	16	2	2	< 1	< 1
11	128	> 128	128	4	4	4	4

[a] Lowest concentration inhibiting bacterial growth after incubation overnight at 37 °C. [b] Number of strains.

riochloroform + 5% DMSO-d_6). The condensation of **7** with EMME affords the diethyl *N*-[5-(2-methylthio)thiazolyl]aminomethylenemalonate (**8**), which was converted by thermal cyclisation in boiling diphenyl ether to the ethyl 4-hydroxy-2-methylthiothiazolo[5,4-*b*]pyridine-5-carboxylate (**9**).

The infrared spectrum of **9** shows a broad absorption band between 3000 and 2500 cm^{-1} as well as a shift to longer wavelength of the ester carbonyl stretching vibration (1695 cm^{-1}) due to intramolecular hydrogen bonding. In the ^{1}H-nmr spectrum the proton α to the nitrogen appears as a sharp singlet, indicating also that the structure **9** exists in the enol-rather than in the keto tautomer.

Subsequently *N*-alkylation was performed by sodium hydride/ethyl iodide in *N,N*-dimethylformamide (DMF). In contrast with the results of Masui, *et al* [7], and Tamura *et al* [11], this reaction was carried out with good yields. The side of alkylation was clearly shown to be ring nitrogen atom (N7), not the oxygen atom at position 4. This was done by the observation of the nuclear Overhauser effect (NOE). Irradiation of the signal of the methylene protons of the 7-ethyl group in **11** resulted in an increase of C_6-H by 23%. The *O*-ethyl counterpart (**15**) was prepared by oxydative ring closure with phosphoryl chloride followed by treatment of the 4-chloro compound **14** with sodium ethoxide.


ClH. H2N−CH2−CN
NaOCH3 / CH3OH
H2N−CH2−CN
5
CS2 / CH3COOCH2CH3
0°C
6
1 NaOCH3 / CH3OH -78°C
2 CH3I
7a
7b
EMME / CH3CH2OH
8
250°C
9
1 NaH / DMF
2 CH3CH2I
10
NaOH / H2O
11
POCl3
14
NaOCH2CH3
15
COOOH
12
150°C / 4h
NH / DMSO
110°C / 2h
13

Alkaline hydrolysis of the ester group of **10** afforded the 7-ethyl-4,7-dihydro-2-methylthio-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic acid (**11**).

Nucleophilic substitution of the 2-methylthio group in **11** with an appropriate cyclic amine in dimethyl sulfoxide (DMSO) at 150° for 4 hours gave the desired compounds **13.1** → **13.10**. It was seen by tlc with ethyl acetate on silicagel that this reaction resulted in several degradation products, probably because of the high reaction temperature and the long reaction time. Therefore the methylthio group in **11** was previously oxidized with *m*-chloroperoxybenzoic acid in chloroform at room temperature to the methylsulfoxide **12**. The methylsulfoxide group can be displaced more easily by cyclic amines [12]. By this method compounds **13** could be synthesized at 110° in DMSO for 2 hours.

Table III

Compound No.	Formula		Elemental Analyses Calcd.	Found
6	$C_2H_4N_2$	56.07	C 42.85	42.76
			H 7.19	7.21
			N 49.96	49.84
7	$C_3H_4N_2S_2$	132.20	C 27.26	27.34
			H 3.05	3.05
			N 21.19	21.12
			S 48.50	48.63
8	$C_{12}H_{16}O_4N_2S_2$	316.39	C 45.56	45.49
			H 5.10	5.11
			N 8.85	8.87
			S 20.27	20.20
9	$C_{10}H_{10}O_3N_2S_2$	270.32	C 44.43	44.33
			H 3.73	3.74
			N 10.36	10.38
			S 23.72	23.81
10	$C_{12}H_{14}O_3N_2S_2$	298.37	C 48.31	48.20
			H 4.73	4.74
			N 9.39	9.36
			S 21.49	21.55
11	$C_{10}H_{10}O_3N_2S_2$	270.32	C 44.43	44.52
			H 3.73	3.72
			N 10.36	10.35
			S 23.72	23.65
12	$C_{10}H_{10}O_4N_2S_2$	286.32	C 41.95	41.85
			H 3.52	3.52
			N 9.78	9.81
			S 22.39	22.32
13.1	$C_{13}H_{15}O_3N_3S$	293.34	C 53.23	53.03
			H 5.15	5.18
			N 14.32	14.36
			S 10.93	11.00
13.2	$C_{14}H_{17}O_3N_3S$	307.37	C, 54.71	54.62
			H 5.57	5.58
			N 13.67	13.70
			S 10.43	10.48
13.3	$C_{15}H_{19}O_3N_3S$	321.39	C 56.06	56.23
			H 5.96	5.98
			N 13.07	13.05
			S 9.98	10.01
13.4	$C_{13}H_{15}O_4N_3S$	309.34	C 50.48	50.32
			H 4.89	4.88
			N 13.59	13.61
			S 10.36	10.34
13.5	$C_{13}H_{16}O_3N_4S$	308.35	C 50.64	50.49
			H 5.23	5.24
			N 18.17	18.11
			S 10.40	10.43

Table III Continued

Compound No.	Formula		Elemental Analyses Calcd.	Found
13.6	$C_{14}H_{18}O_3N_4S$	322.38	C 52.16	52.29
			H 5.63	5.66
			N 17.38	17.32
			S 9.94	9.91
13.7	$C_{14}H_{16}O_4N_4S$	336.36	C 49.99	50.11
			H 4.80	4.80
			N 16.66	16.61
			S, 9.53	9.50
13.8	$C_{15}H_{20}O_4N_4S$	352.41	C 51.13	51.02
			H 5.72	5.70
			N 15.90	15.82
			S 9.10	9.13
13.9	$C_{20}H_{22}O_3N_4S$	398.48	C 60.28	60.09
			H 5.56	5.57
			N 14.06	14.11
			S 8.05	8.08
13.10	$C_{19}H_{26}O_3N_4S$	390.50	C 58.44	58.53
			H 6.71	6.72
			N 14.35	14.40
			S 8.21	8.18
14	$C_{10}H_9O_2N_2S_2Cl$	288.77	C 41.59	41.58
			H 3.14	3.12
			N 9.70	9.73
			S 22.20	22.28
15	$C_{12}H_{14}O_3N_2S_2$	298.37	C 48.31	48.40
			H 4.73	4.73
			N 16.09	16.12
			S 21.49	21.42
16	$C_9H_8O_3N_2S_2$	256.29	C 42.18	42.23
			H 3.14	3.16
			N 10.93	10.89
			S 25.02	24.93
17	$C_{13}H_{16}O_3N_4S$	308.35	C, 50.64	50.59
			H 5.23	5.24
			N 18.17	18.20
			S 10.40	10.38

EXPERIMENTAL

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

5-Amino-2-mercaptothiazole (**6**).

A solution of sodium methoxide, prepared from 23 g (1 g-atom) of sodium and 500 ml of dry methanol, was added dropwise under ice-cooling to a mechanical stirred suspension of 100 g (1.08 moles) of aminoacetonitrile hydrochloride in 100 ml of dry methanol. Stirring was continued

for another 2 hours at room temperature. The precipitated sodium chloride was filtered off and the filtrate concentrated *in vacuo*. Ethyl acetate (20 ml) was added and evaporated under reduced pressure to remove all traces of methanol. The oily residue was dissolved in 100 ml of dry ethyl acetate (previously dried over phosphorus pentoxide) and anhydrous sodium sulfate added. After cooling, the precipitate was filtered off. Unlike the method of Cook, the solution of crude aminoacetonitrile (**5**) was used further without distillation. This solution was added dropwise during a period of 1 hour to a vigorously stirred, ice-cooled solution of 100 ml (1.66 moles) of carbon disulfide in 100 ml of dry ethyl acetate, under a nitrogen inlet. Continued mechanical stirring and complete water-free conditions were essential. The mixture was stirred at 0° for another hour. The precipitate was filtered off, washed with diethyl ether and dried, yielding 99 g of **6** (75% calculated on the amount sodium) as yellow crystals, mp 131° dec; ir (potassium bromide): ν max 1630, 1500 cm^{-1}.

5-Amino-2-methylthiothiazole (**7**).

A solution of sodium methoxide, prepared form 1.15 g (0.05 g-atom) of sodium and 100 ml of dry methanol, was cooled to -78° (carbon dioxide/acetone) and 6.6 g (0.05 mole) of **6** was added. To this red-brown solution 7.24 g (0.051 mole) of methyl iodide was added. After another hour at -78°, the mixture was allowed to reach room temperature. The methanol was removed under reduced pressure and 100 ml of water was added. This solution was extracted several times with ethyl acetate. The combined organic layers were washed with water, dried and concentrated *in vacuo*. The crude 5-amino-2-methylthiothiazole obtained was used for the preparation of **8** without further purification.

To obtain an analytical sample, the crude **7** was dissolved in ethanol and concentrated hydrochloric acid added. The precipitated salt was collected and washed with ethanol and ether. The 5-amino-2-methylthiothiazole hydrochloride obtained was dissolved in water which was extracted with chloroform after alkalinisation with 10% sodium hydroxide. After removal of the chloroform, the residue was recrystallized several times from ethanol to give **7** as colourless needles, mp 143°; ir (potassium bromide): ν max 1630 (NH_2); ^{1}H-nmr (deuteriochloroform + 5% DMSO-d_6): δ 2.6 (s, S-CH_3), 2.9 (br, C_4-H_2), 4.5 (br, -NH_2), 6.3 (s, =NH), 7.1 (s, C_4-H); ms: (m/e) 146 M^+ 47 (100%), $HSCH_3$+.

Diethyl-*N*-[5-(2-Methylthio)thiazolyl]aminomethylenemalonate (**8**).

The crude 5-amino-2-methylthiothiazole obtained under **7** was dissolved in 100 ml of ethanol and 10.8 g (0.05 mole) of diethyl ethoxymethylenemalonate added. This mixture was heated under reflux for 1 hour, treated with activated charcoal and cooled. The precipitate was filtered off and washed with cold methanol. Recrystallization from ethanol yielded 12.5 g of **8** (78% total yield **7** + **8**) as yellow needles, mp 116°; ir (potassium bromide): ν max 1240 (C=O), 1640 (C=C), 1680 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.24 (t, 3H, J = 7 Hz, -COO-$CH_2C\mathit{H}_3$), 1.30 (t, 3H, J = 7 Hz, -COO-CH_2-CH_3), 2.63 (s, 3H, S-CH_3), 4.18 (q, 2H, J = 7 Hz, -COO-CH_2-CH_3), 4.24 (q, 2H, J = 7 Hz, -COO-CH_2-CH_3), 7.28 (s, 1H, C_4-*H*), 8.03 (d, 1H, J = 13 Hz, -NH-C*H*=C), 10.95 (br d, 1H, J = 13 Hz, -N*H*-CH=C), ms: (m/e) 316 M^+, 270 (100%) M-C_2H_5OH.

Ethyl 4-Hydroxy-2-methylthiothiazolo[5,4-*b*]pyridine-5-carboxylate (**9**).

Diphenyl ether (200 ml) was heated at 250° and 50 g (0.15 mole) of **8** was added portionwise. This solution was held at 250° for 10 minutes and treated with charcoal. After cooling the mixture was diluted with a five-fold volume of petroleum ether (40-60°). The precipitate was collected, washed with isopropyl ether and recrystallized from *N,N*-dimethylformamide/ethanol (1/1). Compound **9** was obtained as colourless crystals, mp 185°, yield, 38 g (90%); ir (potassium bromide): ν max 1700 (C=O), 1600 (C=C). ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.53 (t, 3H, J = 7 Hz, -COO-CH_2-CH_3), 2.93 (s, 3H, S-CH_3), 4.71 (q, 2H, J = 7 Hz, -COO-CH_2-CH_3), 9.20 (s, 1H, C_6-H); ms: (m/e) 270 M^+, 196 (100%) M-C_2H_5OH-CO.

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

Compound **10a**.

Compound **9** (13.5 g, 0.05 mole) was suspended in 200 ml of *N,N*-dimethylformamide and 2.4 g (0.05 mole) 50% of sodium hydride was added portionwise with stirring. The mixture was heated at 80° and 15 g (0.1 mole) of ethyl iodide was added. The brownish-red solution was kept at 80° for another 4 hours.

Compound **10b**.

After evaporation of the solvent *in vacuo*, the residue was taken up in chloroform, the chloroform layer washed with water, dried (sodium sulphate) and the chloroform distilled off. The resulting solid was recrystallized from ethyl acetate, yielding 13 g of **10** (87%) as colourless crystals, mp 230°; ir (potassium bromide): ν max 1695 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7 Hz, -COO-CH_2-CH_3), 1.49 (t, 3H, J = 7 Hz, -N-CH_2-CH_3), 2.78 (s, 3H, S-CH_3), 4.43 (q, 2H, J = 7 Hz, -COO-CH_2-CH_3), 5.02 (q, 2H, J = 7 Hz, -N-CH_2-CH_3), 8.78 (s, 1H, C_6-H); ms: (m/e) 298 M^+, 225 (100%) M-CO_2-C_2H_5.

7-Ethyl-4,7-dihydro-2-methylthio-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic Acid (**11**).

The solution obtained under **10a** was diluted with 100 ml of 10% sodium hydroxide, heated under reflux for 1.5 hour, treated with charcoal and filtered. The filtrate was cooled in ice and acidified with acetic acid. The precipitated acid was filtered of and washed with water, ethanol and diethyl ether. Recrystallization from *N,N*-dimethylformamide yielded **11** as colourless crystals, mp 230°, yield **10a** + **11** 10 g (74%); ir (potassium bromide): ν max 1700 (C=O). ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.70 (t, 3H, J = 7 Hz, N-CH_2-CH_3), 2.85 (s, 3H, S-CH_3), 4.66 (q, 2H, J = 7 Hz, N-CH_2-CH_3), 9.14 (s, 1H, C_6-H); ms: (m/e) 270 M^+, 226 (100%) M-CO_2.

7-Ethyl-4,7-dihydro-2-methylsulfinyl-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic acid (**12**).

Compound **11** (5.41 g, 20 mmoles) was suspended in 200 ml of chloroform and 8.12 g (40 mmole) of 85% *m*-chloroperoxybenzoic acid was added portionwise with stirring. After 15 minutes the yellow mixture cleared up. The solution was stirred for another 20 hours at room temperature. The precipitate was collected, washed with chloroform and recrystallized from ethanol, yielding 5.33 g (93%) of **12** as a colourless powder mp 257°; ir (potassium bromide): ν max 1080 (S=O), 1715 (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 1.96 (t, 3H, J = 7 Hz, N-CH_2-CH_3), 3.43 (s, 3H, O←S-CH_3), 4.83 (q, 2H, J = 7 Hz, N-CH_2-CH_3), 9.40 (s, 1H, C_6-H); ms: (m/e) 286 M^+, 242 (100%) M-CO_2.

2-Substituted-7-ethyl-4,7-dihydro-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic Acid (**13**).

Compound **13a**.

Compound **11** (1.35 g, 5 mmoles) was dissolved in 25 ml of dimethyl sulfoxide and 10 mmoles of an appropriate amine was added. This mixture was heated under reflux for 3.5 hours at 150°. 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.

Compound **13b**.

Compound **12** (1.43 g, 5 mmoles) was dissolved in 25 ml of dimethyl sulfoxide and 10 mmoles of an appropriate amine added. The mixture was heated at 110° for 2 hours.

The results are summarized in Table I.

Ethyl 4-Chloro-2-methylthiothiazolo[5,4-*b*]pyridine-5-carboxylate (**14**).

A solution of 3.16 g of **8** in 50 ml of phosphoryl chloride was refluxed for 3 hours. The excess phorphoryl chloride was removed *in vacuo*, the residue poured on ice, neutralized with aqueous 5% sodium hydroxide and extracted with chloroform. The chloroform extract was washed with water, dried and concentrated to give 1.52 g of **14** (53%). Recrystallization from acetonitrile gave **14** as colourless needles mp 79°; ir (potassium bromide): ν max 1180 (C-O), 1435 (C=C), 1730 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.47 (t, 3H, J = 7 Hz, -COO-CH_2-CH_3), 2.87 (s, 3H, -S-CH_3), 4.54 (q, 2H, J = 7 Hz, -COO-CH_2-CH_3), 8.90 (s, 1H, C_6-H).

Ethyl 4-Ethoxy-2-methylthiothiazolo[5,4-*b*]pyridine-5-carboxylate (**15**).

A solution of sodium ethoxide in dry ethanol, prepared from 0.062 g of sodium (2.7 mg-atoms) and 10 ml of dry ethanol, was added to a suspension of 0.710 g of **14** (2.5 mmoles) in 10 ml of dry ethanol. The mixture was refluxed for 30 minutes and the solvent evaporated under reduced pressure. The residue was taken up in chloroform. This solution was washed with water, dried and concentrated to give 0.58 g (78%) of **15**. Recrystallization from *n*-hexane gave **15** as colourless crystals, mp 88°; ir (potassium bromide): ν max 1180 (C-O), 1260 (C-O), 1710 (C=O), 1560 (C=C); ^{1}H-nmr (deuteriochloroform): δ 1.43 (t, 3H, J = 7 Hz, -COO-CH$_2$-C*H*$_3$), 1.53 (t, 3H, J = 7 Hz, Ar-O-CH$_2$-C*H*$_3$), 2.90 (s, 3H, -S-C*H*$_3$), 4.45 (q, 2H, J = 7 Hz, -COO-C*H*$_2$-CH$_3$), 4.68 (q, 2H, J = 7 Hz, Ar-O-C*H*$_2$-CH$_3$), 8.71 (s, 1H, C$_6$-H).

4,7-Dihydro-7-methyl-2-methylthio-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic Acid (**16**).

Compound **16** was obtained from 0.05 mole of **9** and 0.1 mole of methyl iodide in the same manner as described for the preparation of **10** and **11**. Recrystallization from *N,N*-dimethylformamide yielded **16** as colourless crystals, mp 246°, yield 12.5 g (88%); ir (potassium bromide): ν max 1710 (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 2.93 (2, 3H, S-C*H*$_3$), 3.28 (s, 3H, N-C*H*$_3$), 9.18 (s, 1H, C$_6$-H); ms: (m/e) 256 M$^+$, 212 (100%) M-CO$_2$.

4,7-Dihydro-7-methyl-2-(4-methyl-1-piperazinyl-oxothiazolo[5,4-*b*]pyridine-5-carboxylic Acid (**17**).

Compound **17** was obtained from **16** in the same manner as described for the preparation of **13a**, yielding 1.10 g (71%) as cream-coloured crystals, mp 280°; ir (potassium bromide): ν max 1550 (C=C), 1610 (C=O); ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 3.23 (s, 3H, N-C*H*$_3$), 9.09 (s, 1H, C$_6$-H); ms: (m/e) 308 M$^+$, 238 (100%).

Microbiology.

The 2-substituted-7-ethyl-4,7-dihydro-4-oxothiazolo[5,4-*b*]pyridine-5-carboxylic acids were tested *in vitro* for their antibacterial activity against a series of gram-negative strains (*Serratia marcescens, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Proteus mirabilis*) and gram-positive strains (*Staphylococcus aureus* and *Streptococcus D.*). *In vitro* bacterial susceptibility (minimal inhibitory concentration) was determined with the standard agar dilution method on T.S.A. agar. None of the derivatives **13** showed any antibacterial acitivity *in vitro* against the strains tested, only **11** was slightly active. The results are summarized in Table II.

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