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The synthesis and antibacterial evaluation of a number of isothiazolo[5,4-*b*]pyridine isosteres of nalidixic acid are described.

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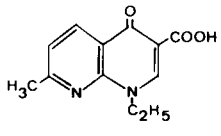
Nalidixic acid (**1**) is a chemotherapeutic agent used mainly in the treatment of urinary tract infections with gram-negative pathogens (1,2). In our laboratory during the last few years, we have synthesized nalidixic acid analogs with the thieno[2,3-*b*]pyridine structure (3). One of these compounds, 7-ethyl-4,7-dihydro-2-methyl-4-oxothieno[2,3-*b*]-pyridine-5-carboxylic acid (**2**) shows properties analogous to nalidixic acid (4). Hence, we were interested in the preparation of other sulfur containing congeners, *e.g.*, isothiazolo[5,4-*b*]pyridines. These compounds can be represented by the general formula **3**, where R_1 is alkyl or aryl and R_2 is alkyl.



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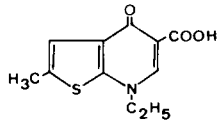

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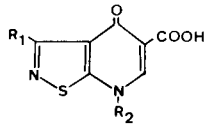
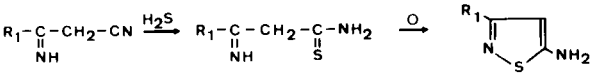


3

A general method for the synthesis of annelated 4-oxo-pyridine-3-carboxylic acids is the Gould-Jacobs synthesis (5). Starting materials for the synthesis of substituted 4,7-dihydro-4-oxoisothiazolo[5,4-*b*]pyridine-5-carboxylic acids are 3-substituted-5-aminoisothiazoles **6**. The latter compounds can be obtained by oxidative cyclisation of β-iminothioamides **5** prepared by the addition of hydrogen sulfide to a β-iminonitrile **4** (6,7).



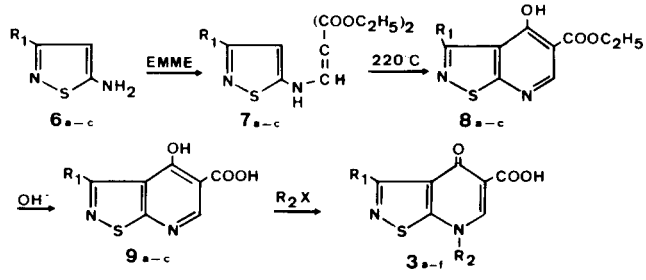
4 5 6

Unfortunately, only a few 3-substituted-5-aminoisothiazoles could be prepared by this method: namely, **6a** (R_1 = methyl), **6b** (R_1 = phenyl) and **6c** (R_1 = *p*-methoxyphenyl).

Condensation of these 5-aminoisothiazoles with diethyl ethoxymethylenemalonate (EMME) at 110° affords diethyl *N*-[5-isothiazolyl]aminomethylenemalonate (**7**), which can be converted, by thermal cyclization in boiling diphenyl ether, to the ethyl 4-hydroxyisothiazolo[5,4-*b*]pyridine-5-carboxylates **8**.

The infrared spectra of **8** show a broad absorption band between 3200 and 2500 cm^{-1}, as well as a shift to longer wavelength of the infrared absorption bands of the ester, due to intramolecular hydrogen bonding. In the ^1H-nmr spectra the proton α to the nitrogen appears as a sharp singlet, indicating also that the structure **8** exists in the enol rather than in the keto form.

Subsequent base-catalyzed hydrolysis to **9** and treatment with alkyl iodide-sodium hydride in dimethylformamide affords the desired 4,7-dihydro-4-oxoisothiazolo[5,4-*b*]pyridine-5-carboxylic acids **3**.



6a–c **7**a–c **8**a–c

9a–c **3**a–f

6,7,8,9-a: $R_1 = -CH_3$

b: R_1 = phenyl

c: R_1 = *p*-methoxyphenyl

3-a: $R_1 = -CH_3$, $R_2 = -C_2H_5$

b: R_1 = phenyl, $R_2 = -C_2H_5$

c: R_1 = *p*-methoxyphenyl, $R_2 = -C_2H_5$

d: $R_1 = -CH_3$, $R_2 = -CH(CH_3)_2$

e: $R_1 = -CH_3$, $R_2 = -CH_2-CH_2-CH_3$

f: $R_1 = -CH_3$, $R_2 = -CH_2-CH=CH_2$

These compounds were tested *in vitro* for their antibacterial activity against a series of gram-negative strains (*Escherichia coli, Proteus species, Enterobacter* species, *Providencia* species, *Klebsiella pneumoniae, Serratia marcescens* and *Pseudomonas aeruginosa*) and *Staphylococcus aureus. In vitro* bacterial susceptibility (minimal inhibitory concentration) was determined with the standard agar dilution method on Mueller-Hinton agar. None of the 4,7-dihydro-4-oxoisothiazolo[5,4-*b*]pyridine derivatives showed any antibacterial activity *in vitro* against the strains tested.

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Table I

Characteristics of Compounds **7**

Compound No.	Formula	M.p. °C	Yield %	Ir (a) (cm^{-1})	^{1}H-Nmr (Deuteriochloroform) δ	Mass Spectrum m/e
7a	$C_{12}H_{16}N_2O_4S$	77-79 (b)	91	3200 (NH) 1680 (C=O)	1.35 and 1.40 (each 3H, t, CH_3 esters, J = 7 Hz), 2.35 (3H, s, C_3-CH_3), 4.16 and 4.20 (each 2H, q, CH_2 esters, J = 7 Hz), 6.42 (1H, s, C_4-H), 7.78 (1H, d, -C*H*=, J = 12 Hz), 10.98 (1H, bd, NH, J = 12 Hz)	284 M^+ 238 (100%) M-C_2H_5OH
7b	$C_{17}H_{18}N_2O_4S$	110-112 (b)	78	3200 (NH) 1690 (C=O)	1.36 and 1.40 (each 3H, t, CH_3 esters, J = 7 Hz) 4.25 and 4.28 (each 2H, q, CH_2 esters, J = 7 Hz), 7.12 (1H, s, C_4-H), 7.40-7.76 (5H, m, C_3-C_6H_5), 8.14 (1H, d, -CH=, J = 12 Hz), 11.05 (1H, bd, NH, J = 12 Hz)	346 M^+ 300 (100%) M-C_2H_5OH
7c	$C_{18}H_{20}N_2O_5S$	128-130 (b)	72	3200 (NH) 1690 (C=O)	1.36 and 1.39 (each 3H, t, CH_3 esters, J = 7 Hz), 3.83 (3H, s, OCH_3), 4.26 and 4.30 (each 2H, q, CH_2 esters, J = 7 Hz), 6.88 (1H, s, C_4-H), 7.00 and 7.82 (each 2H, d, C_3-C_6H_4-OCH_3, J = 5 Hz), 8.10 (1H, d, -CH=, J = 12 Hz), 11.10 (1H, bd, NH, J = 12 Hz)	376 M^+ 330 (100%) M-C_2H_5OH

(a) In potassium bromide. (b) From ethanol.

Table II

Characteristics of Compounds **8** and **9**

Compound No.	Formula	M.p. (°C)	Yield (%)	Ir (a) (cm^{-1})	^{1}H-Nmr (b) (δ)			Other Signals	Mass Spectrum (m/e)
					CH_2CH_3	CH_2CH_3	C_6-H		
8a	$C_{10}H_{10}N_2O_3S$	252-254 (c)	95	1690 (C=O)	1,56 t (e)	4,68 q (e)	9,26 s	3.08 (C_3-CH_3)	238 M^+ 192 (100%) M-C_2H_5OH
8b	$C_{15}H_{12}N_2O_3S$	196-198 (c)	87	1700 (C=O)	1,52 t (e)	4,70 q (e)	9,40 s	7.38-7.68 m (C_3-C_6H_5)	300 M^+ 254 (100%) M-C_2H_5OH
8c	$C_{16}H_{14}N_2O_4S$	260-262 (c)	78	1690 (C=O)	1,54 t (e)	4,72 q (e)	9,24 s	4.08 s, (OCH_3), 7.16 (f) and 7.80 d (f) (C_3-C_6-H_4-)	330 M^+ 284 (100%) M-C_2H_5OH
9a	$C_8H_6N_2O_3S$	>275 (d)	78	1690 (C=O)	—	—	9,43 s	3.06 s (C_3-CH_3)	210 M^+ 192 (100%) M-H_2O
9b	$C_{13}H_8N_2O_3S$	>275 (c)	66	1690 (C=O)	—	—	9,44 s	7.40-7.72 m (C_3-C_6H_5)	272 M^+ 254 (100%) M-H_2O
9c	$C_{14}H_{10}N_2O_4S$	>275 (c)	59	1690 (C=O)	—	—	9,36 s	4,00 s (OCH_3), 7,13 d (f) and 7,80 d (f) (C_3-C_6H_4-)	302 M^+ 284 (100%) M-H_2O

(a) In potassium bromide. (b) In trifluoroacetic acid. (c) From ethanol. (d) From *N,N*-dimethylformamide. (e) J = 7 Hz, (f) J = 5 Hz.

EXPERIMENTAL

Melting points were determined on a Büchi-capillary melting point apparatus and are uncorrected. Infrared spectra were obtained with a Beckman-Acculab-4 spectrophotometer. All compounds were examined in potassium bromide pellets. ^{1}H-Nmr spectra were recorded on a Varian EM 360-A spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane. Mass spectral data were registered on a Jeol JMS-01 SG-2 mass spectrometer.

5-Aminoisothiazoles **6** were prepared according to the literature (6,7).

General Procedure for the Preparation of Diethyl *N*-(5-Isothiazolyl)-aminomethylenemalonates (**7**).

An equimolar mixture of **6** and diethyl ethoxymethylenemalonate was heated at 110° with stirring for 1 hour. The reaction mixture crystallized upon cooling and the product was recrystallized from ethanol. The

Table III

Characteristics of Compounds **3**

Compound No.	Formula	M.p. °C	Yield %	Ir (a) (cm^{-1})	^{1}H-Nmr (b) δ	Mass Spectrum m/e
3a	$C_{10}H_{10}N_2O_3S$	200-202 (c)	76	1730 (C=O)	1.83 (3H, t, NCH_2CH_3, J = 7 Hz), 3.06 (3H, s, C_3-CH_3), 4.68 (2H, q, NCH_2CH_3, J = 7 Hz), 9.26 (1H, s, C_6-H)	238 M^+ 194 (100%) M-CO_2
3b	$C_{15}H_{12}N_2O_3S$	183-185 (c)	65	1720 (C=O)	1.92 (3H, t, NCH_2CH_3, J = 7 Hz), 4.84 (2H, q, NCH_2CH_3, J = 7 Hz), 7.40-7.72 (5H, m, C_3-C_6H_5), 9.36 (1H, s, C_6-H)	300 M^+ 256 (100%) M-CO_2
3c	$C_{16}H_{14}N_2O_4S$	202-204 (c)	58	1720 (C=O)	1.84 (3H, t, NCH_2CH_3, J = 7 Hz), 4.00 (3H, s, OCH_3), 4.72 (2H, q, NCH_2CH_3, J = 7 Hz), 7.16 and 7.76 (each 2H, d, C_3-C_6H_4-, J = 5 Hz), 9.40 (1H, s, C_6-H)	330 M^+ 286 (100%) M-CO_2
3d	$C_{11}H_{12}N_2O_3S$	236-238 (c)	56	1730 (C=O)	1.56 (6H, d, $CH(CH_3)_2$, J = 5 Hz), 2.85 (3H, s, C_3-CH_3), 5.02-5.10 (1H, m, N-C*H*), 9.10 (1H, s, C_6-H)	252 M^+ 208 (100%) M-CO_2
3e	$C_{11}H_{12}N_2O_3S$	215-217 (c)	71	1720 (C=O)	1.02 (3H, t, $NCH_2CH_2CH_3$, J = 7 Hz), 1.80-2.08 (2H, m, N-CH_2-CH_2-), 2.80 (3H, s, C_3-CH_3), 4.36 (2H, t, N-CH_2-, J = 7 Hz), 9.00 (1H, s, C_6-H)	252 M^+ 208 (100%) M-CO_2
3f	$C_{11}H_{10}N_2O_3S$	204-206 (c)	69	1715 (C=O)	2.80 (3H, s, C_3-CH_3), 4.98 (2H, d, N-CH_2-, J = 4 Hz), 5.56 (2H, d, -CH=CH_2, J = 4 Hz), 7.20-7.28 (1H, m, N-CH_2-C*H*=), 9.00 (1H, s, C_6-H)	250 M^+ 206 (100%) M-CO_2

(a) In potasstium bromide. (b) In trifluoroacetic acid, except **3d, 3e** and **3f**, which were run in DMSO-d_6. (c) From ethanol.

Table IV

Elemental Analysis

Compound No.	Formula	% (Calculated) C	H	N	S	% (Found) C	H	N	S
7a	$C_{12}H_{16}N_2O_4S$	50.69	5.67	9.85	11.28	50.80	5.61	9.85	11.21
7b	$C_{17}H_{18}N_2O_4S$	58.94	5.24	8.09	9.26	58.79	5.20	8.14	9.30
7c	$C_{18}H_{20}N_2O_5S$	57.43	5.36	7.44	8.52	57.72	5.31	7.39	8.40
8a	$C_{10}H_{10}N_2O_3S$	50.41	4.23	11.76	13.46	50.68	4.15	11.70	13.35
8b	$C_{15}H_{12}N_2O_3S$	59.99	4.08	9.33	10.68	60.23	4.13	9.41	10.65
8c	$C_{16}H_{14}N_2O_4S$	58.17	4.27	8.48	9.71	58.37	4.36	8.43	9.70
9a	$C_8H_6N_2O_3S$	45.71	2.88	13.33	15.25	45.79	2.97	13.21	15.11
9b	$C_{13}H_8N_2O_3S$	57.35	2.96	10.29	11.78	57.62	3.04	9.98	11.55
9c	$C_{14}H_{10}N_2O_4S$	55.62	3.33	9.27	10.61	55.75	3.39	9.12	10.42
3a	$C_{10}H_{10}N_2O_3S$	50.41	4.23	11.76	13.46	50.65	4.20	11.72	13.54
3b	$C_{15}H_{12}N_2O_3S$	59.99	4.08	9.33	10.68	60.14	4.15	9.23	10.62
3c	$C_{16}H_{14}N_2O_4S$	58.17	4.27	8.48	9.71	58.26	4.19	8.58	9.90
3d	$C_{11}H_{12}N_2O_3S$	52.37	4.79	11.10	12.71	52.59	4.85	11.00	12.58
3e	$C_{11}H_{12}N_2O_3S$	52.37	4.79	11.10	12.71	52.43	4.83	9.97	12.54
3f	$C_{11}H_{10}N_2O_3S$	52.79	4.03	11.19	12.81	52.90	3.98	11.02	12.67

physical data of the diethyl *N*-(5-isothiazolyl)aminomethylenemalonates **7** are summarized in Table I.

Preparation of Ethyl 4-Hydroxyisothiazolo[5,4-*b*]pyridine-5-carboxylates (**8**).

Compound **7** was added to a five-fold volume of boiling diphenyl ether and heated under reflux for 45 minutes. After cooling, the mixture was diluted with a five-to ten-fold volume of *n*-hexane. The precipitate formed was collected, washed with isopropyl ether and recrystallized from ethanol. The physical data of the ethyl 4-hydroxyisothiazolo[5,4-*b*]-pyridine-5-carboxylates **8** are summarized in Table II.

Preparation of 4-Hydroxyisothiazolo[5,4-*b*]pyridine-5-carboxylic Acids (**9**).

A mixture of 10 mmoles of **8**, 5 ml. of ethanol and 20 ml. of a 10% sodium hydroxide solution was heated under reflux for 1 hour. The cooled solution was poured into 100 ml. of water and acidified with a 10% sulfuric acid solution. The precipitated acid was filtered, washed with water, ethanol and ether, and recrystallized from an appropriate solvent (**9a** = *N,N*-dimethylformamide, **9b, 9c** = ethanol). The physical data of the 4-hydroxyisothiazolo[5,4-*b*]pyridine-5-carboxylic acids **9** are summarized in Table II.

Preparation of 7-Alkyl-4,7-dihydro-4-oxoisothiazolo[5,4-*b*]pyridine-5-carboxylic Acids (**3**).

Compound **9** (10 mmoles) was suspended in 50 ml. of *N,N*-dimethylformamide. Potassiumcarbonate (15 mmoles) was added with stirring and the stirred mixture was heated at 70°-80°. The alkylhalide (30 mmoles) was added and the mixture was kept at 70°-80° for 4 hours. After cooling the mixture was diluted with ice water. The solid that separated was filtered, washed with water, ethanol and ether, dried and recrystallized from ethanol. The physical data of the 7-alkyl-4,7-dihydro-4-oxoisothiazolo[5,4-*b*]pyridine-5-carboxylic acids **3** are summarized in Table III.

The elemental analyses of the compounds synthesized are summarized in Table IV.

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