THIENOPYRIDONE ANTIBACTERIALS. PART I. A SYNTHESIS OF SOME 7-ALKYL-2-CHLORO-1,4-DIHYDRO-4-OXOTHIENO[2,3-*b*]PYRIDINE-5-CARBOXYLIC ACIDS

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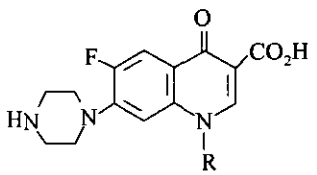
Abstract — A selected set of 7-alkyl-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids (**7**) and their methyl esters (**6**) were prepared by cyclization of the respective 3-*N*-alkylamino-2-(2,5-dichloro-3-thienoyl)acrylates (**5**) which, in turn, are accessible *via* methyl 3-(2,5-dichlorothien-3-yl)-3-oxopropanoate (**3**). Of the present series, the *N*-cyclopropyl derivative **(7b)** exhibited the highest potency against *Escherichia coli* (*MIC* = 0.5 μg/ml).

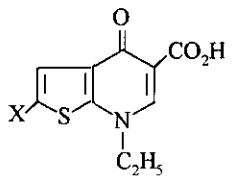
INTRODUCTION

The second generation "fluoroquinolones" **(1)** constitute an important class of clinically useful antibacterial agents.[2,3] Here, quinolones that have *N*-1-cyclopropyl group (ciprofloxacin **1b**)[4] are generally more potent than those with an ethyl group (norfloxacin **1a**),[5] especially against Gram-negative bacteria.[6] Recently, series of 7-ethyl-4-oxothieno [2,3-*b*]pyridine-5-carboxylic acids **(2)**, bioisosteres of quinolones **(1)**, were prepared[7-11] from 2-aminothiophene *via* adoption of the Gould-Jacobs method.[12] Compounds **(2a)**[7] and **(2b-d)**[8,9] are notable examples that were reported to exhibit a good level of activity against Gram-negative bacteria, and interest in this class is still at the beginning.



(1)

	R
a	C_2H_5
b	



(2)

	X
a	Me
b	CH=NOMe

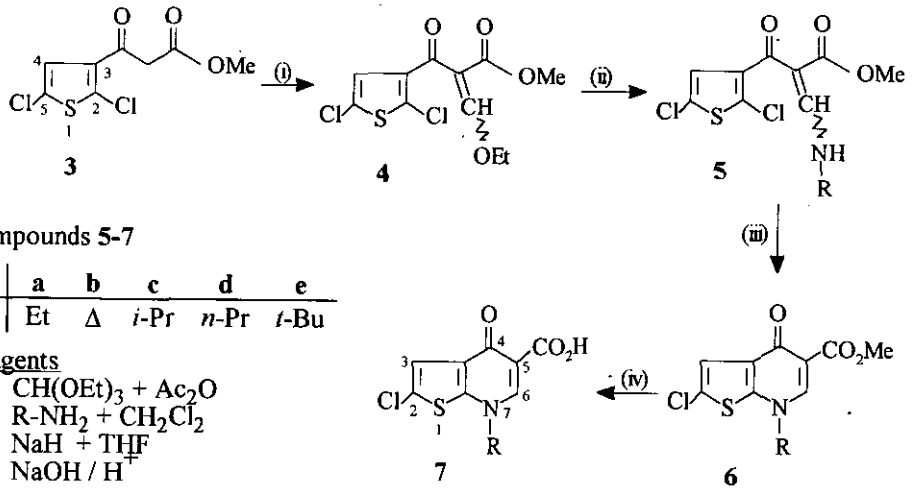
	X
c	$CH{=}NC_6H_4$-OH(*o*)
d	$CH{=}NC_6H_4$-OMe(*p*)

Substitution at the *N*-7 position has not so far been sufficiently investigated and optimized. The ethyl group represents the main variant at the *N*-7 position. Incorporation of other alkyl (methyl, *n*-propyl and *n*-butyl) substituents at this position was once described in a patent,[13] but their probable influence and role themselves as contributors to biological activity remain unexplored. Therefore, the present work aims at obtaining a selected set of 7-alkyl-2-chloro-4-oxothieno[2,3-*b*]pyridine-3-carboxylic acids **(7a-e)**[14] *via* a new route outlined in Scheme 1. Herein we describe their synthesis and antibacterial properties.

RESULT AND DISCUSSION

Synthesis – The preparation of compounds **(7a-e)** is achieved by utilizing 2,5-dichlorothiophene as a starting material, and constructing the pyridone nucleus thereon through series of conversions as illustrated in Scheme 1. In the event, 3-acetyl-2,5-dichlorothiophene (accessible from 2,5-dichlorothiophene by Friedel-Crafts acetylation)[15] is condensed with dimethyl carbonate in the presence of sodium hydride to afford the respective methyl 3-(2,5-dichlorothien-3-yl)-3-oxopropanoate **(3)**.[16] Treatment of the (latter) *β*-keto ester with triethyl orthoformate in acetic anhydride gave the corresponding methyl 3-ethoxyacrylate derivative **(4)** which serves as the common intermediate for the synthesis of the target compounds **(7a-e)**. Interaction of the (latter) enol ether **(4)** with the appropriate alkylamine resulted in smooth production of the respective 3-aminoacrylates **(5a-e)** which exist in solution as mixtures of *E*-(minor) and *Z*-(major) isomers. Base-induced cyclization of the enamino keto esters **(5a-e)** with NaH in tetrahydrofuran at ambient temperature yielded the expected methyl 4-oxothieno[2,3-*b*]pyridine-5-carboxylates **(6a-e)**. Saponification of the (latter) esters furnished the desired 1-alkyl-4-oxothieno[2,3-*b*] pyridine-5-carboxylic acids **(7a-e)**. Physical and analytical data for compounds **(5-7)** are provided in Table 1. The mass spectra of the (latter) compounds display the correct molecular ions, $M^{+\cdot}$, as suggested by their molecular formulas.

Scheme 1



This expedient synthetic approach is modeled on that reported[4] for the preparation of 1-cyclopropylquinolones from ethyl 2-halobenzoylacetate precursors. Compared to the Gould-Jacobs

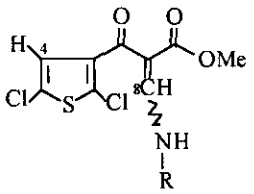
method, the present synthetic route is more versatile and can generate many *N*-7 substituted analogues of compounds **(7)** quite easily.

^{1}H-Nmr spectral data- (i) Compounds **(5a-e)** (Table 2) : Each of the protons' signals appear as two sets of unequal peak areas, reflecting the existence of *Z/E* diastereomers of which the *Z*-isomer predominates.

Table 1. Physical and Analytical Data for Compounds **(5-7)**

Compd. No	Yield (%)	Mp (°C)	Mol. Formula (Mol. Mass)	% Analyses (calcd / found)			
				C	H	N	S
5a	71	118-119	$C_{11}H_{11}NO_3Cl_2S$	42.87	3.60	4.54	10.40
			(308.18)	42.70	3.61	3.61	10.19
5b	56	99-100	$C_{12}H_{11}NO_3Cl_2S$	45.01	3.46	4.37	10.01
			(320.19)	45.19	3.60	4.34	9.89
5c	65	85-86	$C_{12}H_{13}NO_3Cl_2S$	44.73	4.07	4.35	9.95
			(322.21)	45.02	4.34	4.11	10.12
5d	58	83-84	$C_{12}H_{13}NO_3Cl_2S$	44.73	4.07	4.35	9.95
			(322.21)	45.00	4.14	4.12	9.83
5e	55	85-86	$C_{13}H_{15}NO_3Cl_2S$	46.44	4.50	4.17	9.54
			(336.24)	46.32	4.73	4.22	9.75
6a	74	201-202	$C_{11}H_{10}NO_3ClS$	48.62	3.71	5.15	11.80
			(271.72)	48.51	4.00	5.00	11.64
6b	72	275-276	$C_{12}H_{10}NO_3ClS$	50.80	3.55	4.94	11.30
			(283.73)	51.00	3.86	4.99	11.19
6c	80	149-150	$C_{12}H_{12}NO_3ClS$	50.44	4.23	4.90	11.22
			(285.75)	50.18	4.15	4.84	11.06
6d	58	102-103	$C_{12}H_{12}NO_3ClS$	50.44	4.23	4.90	11.22
			(285.75)	50.16	4.23	5.18	11.48
6e	78	206-207	$C_{13}H_{14}NO_3ClS$	52.09	4.71	4.67	10.70
			(299.78)	52.16	4.91	4.55	10.52
7a	86	227-228	$C_{10}H_8NO_3ClS$	46.61	3.13	5.44	12.44
			(257.70)	46.80	3.12	5.56	12.38
7b	88	223-224	$C_{11}H_8NO_3ClS$	48.99	2.99	5.19	11.89
			(269.71)	48.87	2.80	5.15	11.82
7c	93	245-246	$C_{11}H_{10}NO_3ClS$	48.62	3.71	5.15	11.80
			(271.72)	48.84	3.88	5.00	11.66
7d	95	195-196	$C_{11}H_{10}NO_3ClS$	48.62	3.71	5.15	11.80
			(271.72)	48.78	3.67	5.27	11.91
7e	87	240-241	$C_{12}H_{12}NO_3ClS$	50.44	4.23	4.90	11.22
			(285.75)	50.60	4.12	4.82	11.22

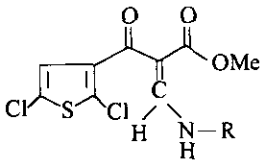
Table 2. ^{1}H-Nmr Spectral data of componds **(5a-e)** (δ-values)[f]



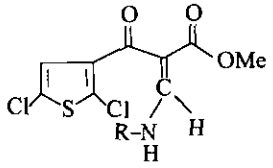
Compd. No	R	CO_2CH_3 Z/E	H-4 Z/E	H-8 Z/E	H-1'	H-2' Z/E	H-3' Z/E	N-H Z/E	Ratio (Z/E)
5a	CH_2-CH_3 1' 2'	3.62/3.63 (3H,s)	6.78/6.89 (1H,s)	8.09/7.92 (1H,d) J = 14.2 Hz	3.46 (2H,m)	1.32/1.30 (3H,t) J = 7.3 Hz		10.85/9.35 (1H,br d) J = 14.2 Hz	3.1/1
5b	 1' 2'	3.60/3.62 (3H,s)	6.75/6.87 (1H,s)	8.15/7.96 (1H,d) J = 13.8 Hz	2.92 (1H,m)	0.83 (4H,m)		10.80/9.34 (1H,br d) J = 13.8 Hz	3.0/1
5c	CH-$(CH_3)_2$ 1' 2'	3.59/3.60 (3H,s)	6.75/6.86 (1H,s)	8.10/7.94 (1H,d) J = 14.2 Hz	3.63 (1H,m)	1.33/1.30 (6H,d) J = 6.6 Hz		10.82/9.35 (1H,br d) J = 14.2 Hz	3.6/1
5d	CH_2-CH_2-CH_3 1' 2' 3'	3.62/3.63 (3H,s)	6.78/6.88 (1H,s)	8.07/7.89 (1H,d) J = 14.2 Hz	3.37 (2H,m)	1.67/1.68 (2H,m)	0.99/0.97 (3H,t) J = 7.4 Hz	10.84/9.36 (1H,br d) J = 14.2 Hz	3.5/1
5e	- C-$(CH_3)_3$ 2'	3.62/3.64 (3H,s)	6.77/6.88 (1H,s)	8.18/8.05 (1H,d) J = 14.5 Hz		1.40/1.38 (9H,s)		11.20/9.66 (1H,br d) J = 14.5 Hz	3.9/1

[f] Nmr Solvent : $CDCl_3$

The exchangeable N-H proton resonates around δ 9.7-11.2, while the thiophene H-4 proton appears around δ 6.7-6.9. The vinyl H-8 proton is highly deshielded (δ 8-8.2) due to the mesomeric effect of the



(Z)-

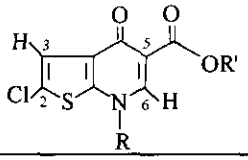


(E)-

two carbonyls and to the inductive effect of the adjacent nitrogen. Signal assignments to the different R-protons are straightforward.

(ii) Compounds **(6a-e)** (Table 3) : Each of the thiophene H-3 and pyridone H-6 protons' singlets have been shifted downfield more than their acyclic precursors **(5a-e)**. This deshielding, *versus* H-4 and H-8, might be due to the added ring current paramagnetic effect of the hetero-bicyclic system.

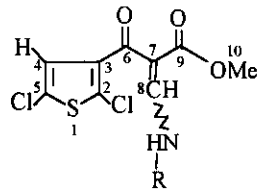
Table 3 . ^{1}H-Nmr Spectral data of compounds **(6,7)** (δ-values)[f]

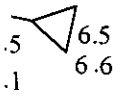


Compd. No	R	R'	H-3	H-6	H-1'	H-2'	H-3'
6b		3.89 (3H,s)	7.39 (1H,s)	8.34 (1H,s)	3.52 (1H,m)	1.25 (4H,m)	
6c	$CH(CH_3)_2$ 1' 2'	3.93 (3H,s)	7.47 (1H,s)	8.40 (1H,s)	4.23 (1H,m)	1.63 (6H,d) J = 6.7 Hz	
6d	$CH_2CH_2CH_3$ 1' 2' 3'	3.87 (3H,s)	7.40 (1H,s)	8.25 (1H,s)	3.93 (2H,t) J = 7.2 Hz	1.94 (2H,m)	0.99 (3H,t) J = 7.3 Hz
6e	$C\text{-}(CH_3)_3$ 2'	3.91 (3H,s)	7.47 (1H,s)	8.67 (1H,s)		1.83 (9H,s)	
7b		14.94 (1H,s)	7.42 (1H,s)	8.60 (1H,s)	3.63 (1H,m)	1,32 (4H,m)	
7c	$CH(CH_3)_2$ 1' 2'	15.14 (1H,s)	7.49 (1H,s)	8.62 (1H,s)	4.39 (1H,m)	1.69 (6H,d) J = 6.6 Hz	
7d	$CH_2CH_2CH_3$ 1' 2' 3'	15.09 (1H,s)	7.47 (1H,s)	8.63 (1H,s)	4.14 (2H,t) J = 6.9 Hz	2.03 (2H,m)	1.05 (3H,t) J = 7.3 Hz
7e	$-C(CH_3)_3$ 2'	15.04 (1H,s)	7.49 (1H,s)	8.86 (1H,s)		1.86 (9H,s)	

[f] Nmr Solvent : $CDCl_3$

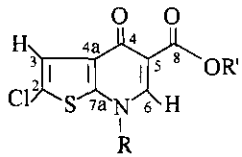
Table 4 . ^{13}C-Nmr Spectral data of compounds **(5a-e)** (δ-values)[f]



Compd. No	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	R
5a	140.2	124.6	126.3 127.2	125.8 126.0	186.9	100.7 100.5	160.4 160.1	167.3	51.3 51.1	CH_2 - CH_3 45.1 15.7 44.8 15.9
5b	139.9	124.8	126.3 127.2	125.8 126.0	186.8	101.3 101.0	160.9 160.7	167.0	51.3 51.1	 30.5 6.5 30.1 6.6
5c	140.1	124.6	126.3 127.1	125.7 125.9	186.7	100.4 100.2	158.5 158.4	167.4	51.3 51.1	CH - $(CH_3)_2$ 51.9 23.3 51.7 23.4
5d	140.2	124.6	126.4 127.2	125.8 126.0	186.9	100.7 101.0	160.8 160.6	167.3	51.3 51.1	CH_2 - CH_2 - CH_3 52.1 23.7 11.0 51.8 23.9
5e	140.2	124.6	126.4 127.2	125.8 125.9	186.6	100.4 100.1	156.5 156.4	167.6	51.3 51.1	C - $(CH_3)_3$ 54.3 29.7 54.2 29.8

[f] Nmr Solvent : $CDCl_3$

Table 5 . ^{13}C-Nmr Spectral data of compounds **(6,7)** (δ-values)[f]



Compd. No	C-2	C-3	C-4	C-5	C-6	C-4a	C-7a	C-8	R'	R
6b	132.1	123.0	169.7	114.8	145.6	125.7	148.6	165.9	52.2	36.8 ▽ 7.6
6c	133.2	123.6	169.7	115.4	140.9	124.8	146.9	166.4	52.3	CH - $(CH_3)_2$ 58.4 21.8
6d	133.0	123.4	176.2	114.9	145.5	125.0	147.0	166.1	52.2	CH_2 - CH_2 - CH_3 58.5 22.1 10.9
6e	135.1	122.1	169.4	113.5	143.3	125.6	143.7	166.6	52.2	C - $(CH_3)_3$ 64.8 28.8
7b	129.7	121.8	173.6	112.8	144.9	128.2	151.1	166.4		37.8 ▽ 7.8
7c	129.3	121.8	172.7	112.1	141.7	126.3	149.5	165.7		CH - $(CH_3)_2$ 60.3 20.8
7d	129.6	121.7	173.0	112.1	146.0	126.6	149.7	166.0		CH_2 - CH_2 - CH_3 58.7 21.7 10.7
7e	132.4	120.7	173.1	111.9	142.4	128.0	146.1	166.9		C - $(CH_3)_3$ 66.5 28.9

[f] Nmr Solvent : $CDCl_3$ for **6a-e** and **7a,b,e** DMSO-d_6 for **7c,d**

(iii) Compounds **(7a-e)** (Table 3) : The exchangeable-CO_2H proton resonates in the range δ 14-15. The δ-values and multiplicity of the different protons are comparable to those of the corresponding parent esters **(6a-e)**.

^{13}C-Nmr spectral data (Tables 4 and 5) - DEPT experiments were performed to differentiate between the different carbons of compounds **(5-7)**. The spectra of compounds **(5,6)** show a signal around δ 52 corresponding to the CH_3-carbon of the ester group which is absent in the spectra of the corresponding acids **(7a-e)**. Compounds **(5-7)** exhibit two signals in the range δ 178-180 and δ 166 that are assigned to the carbonyl carbons of the keto and ester groups, respectively. Signals in the region δ 110-150 account for the remaining thiophene and vinyl carbons. These signals were, however, shifted downfield in compounds **(6,7)** due to the formation of the fused hetero-ring system, making these carbons more deshielded (added ring current effect) compared to those of their acyclic precursors **(5a-e)**.

Bioassay- The *in vitro* antibacterial activity of compounds **(7a-e)** against *E. coli* ATCC 10536 were evaluated by the minimal inhibitory concentration (MIC) technique according to the macrodilution method.[17]

The *N*-7-cyclopropyl derivative **(7b)** showed the highest potency (MIC = 0.5 μg / ml), quite higher than the *N*-ethyl **(7a)** and the *N-tert*-butyl **(7e)** analogues (MIC = 2.0 μg/ml , each). The *N*-propyl derivatives **(7c,d)** were, however, less active (MIC = 8.0 μg/ml and 16.0 μg/ml , respectively). These results demonstrate that *N*-alkyl substituents exert influence on the potency of 4-thieno[2,3-*b*]pyridones **(7a-e)** in a trend comparable to that reported for their bioisostere 1-alkyl-4-quinolones. By analogy to recent reports[18,19] on the exceptional potency of ciprofloxacin **(1b)**, the excellent in vitro antibacterial property of **7b** relative to **7a,c-e,** can be attributed to its *N*-7-cyclopropyl substitution.

EXPERIMENTAL

2,5-Dichlorothiophene, cyclopropylamine, and the required alkylamines were purchased from Acros. Melting points were determined on an Electrothermal Mel. Temp. apparatus and are uncorrected. Nmr spectra were recorded on a Bruker-WM 400 and 300 MHz instruments with TMS as internal reference. Electron impact (EI) mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were carried out by M. H. W. Laboratories, Arizona, USA.

Methyl 2-(2,5-dichlorothien-3-yl)-3-ethoxy-3-oxopropanoate (3)[16]

This intermediate synthon was prepared by condensation of 3-acetyl-2,5-dichlorothiophene[15] with dimethyl carbonate in the presence of 80% NaH, following a recently reported procedure.[16]

Methyl 2-(2,5-dichloro-3-thenoyl)-3-ethoxy acrylate (4)

A stirred mixture of **3** (5.3 g, 21 mmol), triethyl orthoformate (4.6 g, 32 mmol) and acetic anhydride (8.6 g, 85 mmol) was heated at 130-135 °C for 3 h with removal of the ethyl acetate formed during the reaction. The resulting solution was evaporated under reduced pressure (2 mmHg; 100 °C; 1 h) to give the title compound in almost quantitative yield as brown viscous oil which was used as such in subsequent steps.

Methyl 3-*N*-cyclopropylamino-2-(2,5-dichloro-3-thenoyl)acrylate (5b)

To a stirred solution of compound **(4)** (10.0 g, 38 mmol) in dichloromethane (80 ml) was dropwise added aminocyclopropane (3.3 g, 58 mmol) in dichloromethane (20 ml) under cooling (ice-water, 2-5 °C) during 30 min. The reaction mixture was then stirred at room temperature for 24 h. The solution was evaporated to dryness, and the residual solid product was recrystallized from benzene / *n*-hexane.

The 3-alkylamino analogues **(5a,c-e)** were prepared by use of the same procedure described above in the preparation of compound **(5b)**, replacing aminocyclopropane with the appropriate aminoalkane.

Methyl 2-chloro-7-cyclopropyl-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxylate (6b)

To a stirred solution of compound **(5b)** (5.0 g, 15 mmol) in dry tetrahydrofuran (80 ml), cooled to 8-10 °C, was added portionwise sodium hydride (suspension in oil, 80%) (0.51 g, 17 mmol). Stirring was continued at ambient temperature for 3-4 h. Acetic acid (2 ml) was added, and the reaction solution was concentrated in vacuo to a small volume (~ 5 ml). Water (40 ml) was then added, the precipitated solid product was filtered, washed with water, triturated with ethanol (2 ml), dried, and recrystallized from chloroform / ether.

The above cyclization procedure was repeated, replacing **5b** with **5a,c-e** to give the respective compounds **(6a,c-e)**.

2-Chloro-7-cyclopropyl-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid (7b)

A suspension of the methyl ester **(6b)** (1.0 g, 3.5 mmol) in ethanolic sodium hydroxide (0.2 M, 40 ml) was stirred at ambient temperature for 40-60 min. the resulting gelatenous solution was then acidified with 2N HCl to pH 2. The precipitated solid product was filtered, washed with water (10 ml), ethanol (10 ml) and dried. A sample of **7b** was further purified by dissolution in 1*N* aqueous NaOH, and acidification of the alkaline filtrate with 4*N* HCl.

Compounds **(7a,c-e)** were prepared by saponification of the corresponding esters **(6a,c-e)** using the same experimental procedure as described above for the preparation of compound **(7b)**.

ACKNOWLEDGMENTS

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