

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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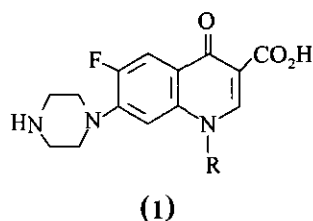
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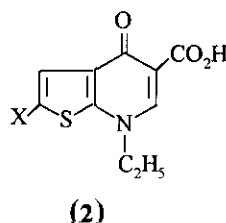
Abstract — A selected set of 7-alkyl-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acids (**7**) and their methyl esters (**6**) were prepared by cyclization of the respective 3-*N*-alkylamino-2-(2,5-dichloro-3-thienoyl)acrylates (**5**) which, in turn, are accessible *via* methyl 3-(2,5-dichlorothien-3-yl)-3-oxopropanoate (**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 prepared⁷⁻¹¹ 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.



	R
a	C ₂ H ₅
b	



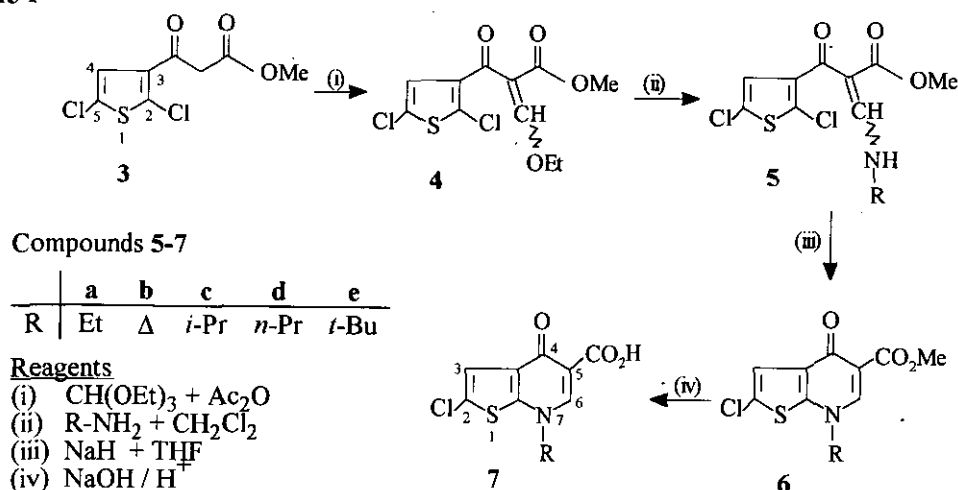
	X		X
a	Me	c	CH=NC ₆ H ₄ -OH(<i>o</i>)
b	CH=NOMe	d	CH=NC ₆ H ₄ -OMe(<i>p</i>)

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^{+} , as suggested by their molecular formulas.

Scheme 1



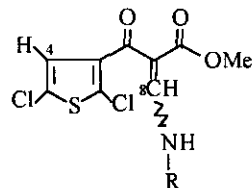
This expedient synthetic approach is modeled on that reported⁴ for the preparation of 1-cyclopropylquinolones from ethyl 2-halobenzoylacetate precursors. Compared to the Gould-Jacobs

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

¹H-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)

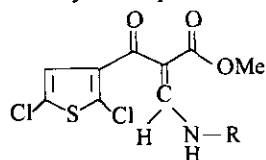
Compd. No	Yield (%)	Mp (°C)	Mol. Formula (Mol. Mass)	% Analyses (calcd / found)			
				C	H	N	S
5a	71	118-119	C ₁₁ H ₁₁ NO ₃ Cl ₂ S (308.18)	42.87	3.60	4.54	10.40
				42.70	3.61	3.61	10.19
5b	56	99-100	C ₁₂ H ₁₁ NO ₃ Cl ₂ S (320.19)	45.01	3.46	4.37	10.01
				45.19	3.60	4.34	9.89
5c	65	85-86	C ₁₂ H ₁₃ NO ₃ Cl ₂ S (322.21)	44.73	4.07	4.35	9.95
				45.02	4.34	4.11	10.12
5d	58	83-84	C ₁₂ H ₁₃ NO ₃ Cl ₂ S (322.21)	44.73	4.07	4.35	9.95
				45.00	4.14	4.12	9.83
5e	55	85-86	C ₁₃ H ₁₅ NO ₃ Cl ₂ S (336.24)	46.44	4.50	4.17	9.54
				46.32	4.73	4.22	9.75
6a	74	201-202	C ₁₁ H ₁₀ NO ₃ ClS (271.72)	48.62	3.71	5.15	11.80
				48.51	4.00	5.00	11.64
6b	72	275-276	C ₁₂ H ₁₀ NO ₃ ClS (283.73)	50.80	3.55	4.94	11.30
				51.00	3.86	4.99	11.19
6c	80	149-150	C ₁₂ H ₁₂ NO ₃ ClS (285.75)	50.44	4.23	4.90	11.22
				50.18	4.15	4.84	11.06
6d	58	102-103	C ₁₂ H ₁₂ NO ₃ ClS (285.75)	50.44	4.23	4.90	11.22
				50.16	4.23	5.18	11.48
6e	78	206-207	C ₁₃ H ₁₄ NO ₃ ClS (299.78)	52.09	4.71	4.67	10.70
				52.16	4.91	4.55	10.52
7a	86	227-228	C ₁₀ H ₈ NO ₃ ClS (257.70)	46.61	3.13	5.44	12.44
				46.80	3.12	5.56	12.38
7b	88	223-224	C ₁₁ H ₈ NO ₃ ClS (269.71)	48.99	2.99	5.19	11.89
				48.87	2.80	5.15	11.82
7c	93	245-246	C ₁₁ H ₁₀ NO ₃ ClS (271.72)	48.62	3.71	5.15	11.80
				48.84	3.88	5.00	11.66
7d	95	195-196	C ₁₁ H ₁₀ NO ₃ ClS (271.72)	48.62	3.71	5.15	11.80
				48.78	3.67	5.27	11.91
7e	87	240-241	C ₁₂ H ₁₂ NO ₃ ClS (285.75)	50.44	4.23	4.90	11.22
				50.60	4.12	4.82	11.22

Table 2. ^1H -Nmr Spectral data of compounds (5a-e) (δ -values)^f

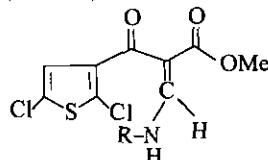
Compd. No	R	CO ₂ CH ₃ Z/E	H-4 Z/E	H-8 Z/E	H-1' Z/E	H-2' Z/E	H-3' Z/E	N-H Z/E	Ratio (Z/E)
5a	CH ₂ -CH ₃ 1' 2'	3.62/3.63 (3H,s)	6.78/6.89 (1H,s)	8.09/7.92 (1H,d) J = 14.2 Hz	3.46 (2H,m)	1.32/1.30 (3H,t) J = 7.3 Hz		10.85/9.35 (1H,br d) J = 14.2 Hz	3.1/1
5b	 1' 2'	3.60/3.62 (3H,s)	6.75/6.87 (1H,s)	8.15/7.96 (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 : CDCl₃

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)-

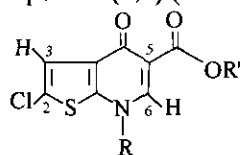


(E)-

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

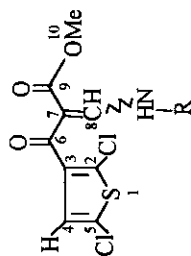
(ii) Compounds (6a-e) (Table 3): Each of the thiophene H-3 and pyridone H-6 protons' singlets have been shifted downfield more than their acyclic precursors (5a-e). This deshielding, *versus* H-4 and H-8, might be due to the added ring current paramagnetic effect of the hetero-bicyclic system.

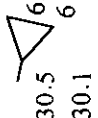
Table 3. ^1H -Nmr Spectral data of compounds (6,7) (δ -values)^f



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 ₂ CH ₂ CH 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-(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 ₂ CH ₂ CH 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)	

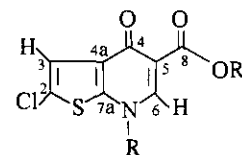
^f Nmr Solvent : CDCl₃

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

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	$\text{CH}_2 - \text{CH}_3$ 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	$\text{CH} - (\text{CH}_3)_2$ 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	$\text{CH}_2 - \text{CH}_2 - \text{CH}_3$ 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	$\text{C} - (\text{CH}_3)_3$ 54.3 29.7 54.2 29.8

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 : CDCl₃ for **6a-e** and **7a,b,e** DMSO-d₆ 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 $\mu\text{g}/\text{ml}$, each). The *N*-propyl derivatives (**7c,d**) were, however, less active (MIC = 8.0 $\mu\text{g}/\text{ml}$ and 16.0 $\mu\text{g}/\text{ml}$, 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-dichlorothiophen-3-yl)-3-ethoxy-3-oxopropanoate (**3**)¹⁶

This intermediate synthon was prepared by condensation of 3-acetyl-2,5-dichlorothiophene¹⁵ 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 gelatinous 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 1N aqueous NaOH, and acidification of the alkaline filtrate with 4N 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

We wish to thank the Arab Pharmaceutical Manufacturing Company (APM) and the Higher Council for Science and Technology (HCST), Amman-Jordan, for financial support.

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14. Compound (7a) (presented in Scheme 1) was previously prepared^{10,11} by the Gould-Jacobs method, reported^{7,10} to be more potent than nalidixic acid, and is used in Japan as a new synthetic antibacterial preparation [T-14097].¹⁰
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Received, 12th August, 1996