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THE PREPARATION OF 2-(HETEROCYCLYL)THIENO[3,2-b]PYRIDINE DERIVATIVES

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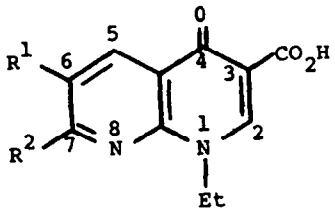
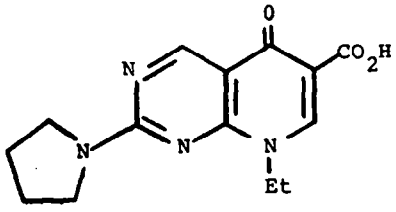
Abstract - The preparation of a series of 2-(heterocyclyl)-4-ethyl-4,7-dihydro -7-oxothieno[3,2-b]pyridine-6-carboxylic acids (5j-l) by aminolysis of the corresponding 2-bromo derivative (5i) is described. None of the compounds (5j-l) showed any interesting antibacterial activity.

Since the discovery of nalidixic acid[1] (1a) a number of structurally related synthetic antibacterials have emerged from this area now referred to as the 'quinolones'. More recently the spectra of antibacterial activity have been broadened with the advent of the second generation compounds thus resulting in a renaissance of clinical interest in this area[2]. Research has essentially developed along two broad fronts[3]. A large number of modifications have been made to the substituents attached to the bicyclic system in particular at N-1, C-6 and -7 (see structure 1) and has produced compounds such as enoxacin[4] (1b). The other major area of research has been the replacement of the 1,8-naphthyridine nucleus with other nuclei and this has resulted in compounds such as piromidic acid[5] (2), cinoxacin[6] (3) and norfloxacin[7] (4).



(1) a; R^1 = H, R^2 = Me
b; R^1 = F, R^2 = HN N-



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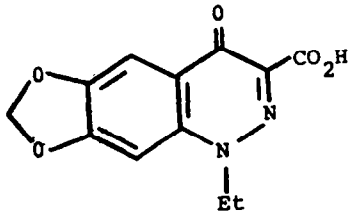

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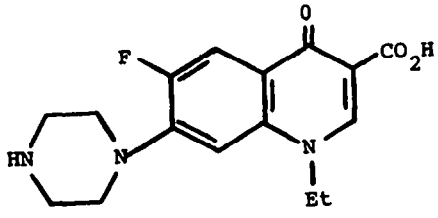

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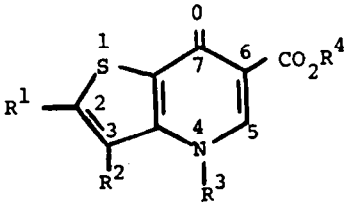
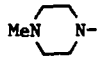
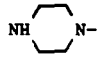
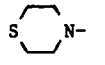
We sought to prepare a thienopyridine nucleus with the concept of replacing the benzene ring of the quinolone nucleus by thiophene, a known bioisostere in other fields of medicinal chemistry[8]. In particular we wished to prepare 2-substituted thieno[3,2-b]pyridines (5j-l) which from molecular models mimic the 7-substituted quinolones (e.g. 4).

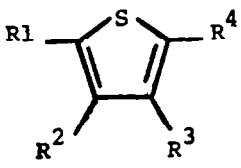


		R^1	R^2	R^3	R^4
(5)	a;	NO_2	H	Et	Et
	b;	NH_2	H	Et	Et
	c;	H	H	Et	Et
	d;	H	H	H	Et
	e;	H	H	Et	H
	f;	H	NO_2	Et	H
	g;	Br	H	H	Et
	h;	Br	H	Et	Et
	i;	Br	H	Et	H
	j;		H	Et	H
	k;		H	Et	H
	l;		H	Et	H

Our initial approach involved the preparation of a nitrothienopyridine (5a) with subsequent conversion to (5j-l) via the amine (5b). Nitration of acetamido derivative (6a) gave a 60:40 isomeric mixture of the nitro derivatives (6b) and (6c)[9] from which the desired 5-isomer (6b)[+] was isolated in 44% yield after chromatography. Acidic hydrolysis of (6b) with hydrochloric acid in ethanol gave only the amine (6d) and further hydrolysis under both basic and acidic conditions did not lead to an isolable product. The amine (6d) also failed to react with either ethyl propiolate or diethyl ethoxymethylenemalonate.

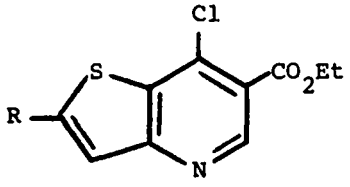
As an alternative approach to (5a) nitration of the 2,3-unsubstituted thieno[3,2-b]pyridine (5e) was examined. Aqueous sodium hydroxide hydrolysis of methyl 3-aminothiophene-2-carboxylate (6e) gave the sodium salt (6f) (85%) which on reaction with diethyl ethoxymethylenemalonate and acetic acid in toluene afforded (6g) (68%). Cyclisation to (5d) was effected in refluxing Dowtherm A and the product, obtained in 80% yield, was reacted with ethyl iodide and potassium carbonate in N,N-dimethylformamide (DMF) to give (5c). Saponification with aqueous sodium hydroxide afforded the acid (5e) in 72% yield. Subsequent nitration with fuming nitric acid in concentrated sulphuric acid unforunately resulted in formation of the undesired 3-nitro derivative (5f) exclusively. The ^{13}C n.m.r. was indicative of the 3-substitution. The signals for C-2 and -3 in the unsubstituted system (5e) occur as doublets at δ145.6 and 119.2 respectively and in the nitrated product (5f) at 145.1 (doublet) and 142.2 (singlet). Had nitration occurred at C-2 a signal at δ115-120 (doublet) for C-3 would have been present. Similarly nitration of (5c) and (5d) led to their 3-nitro derivatives only.

[+] Melting points incorrectly reported by Rossy[9] - see experimental



		R^1	R^2	R^3	R^4
(6)	a;	H	H	NHAc	CO_2Me
	b;	NO_2	H	NHAc	CO_2Me
	c;	H	NO_2	NHAc	CO_2Me
	d;	NO_2	H	NH_2	CO_2Me
	e;	H	H	NH_2	CO_2Me
	f;	H	H	NH_2	CO_2Na
	g;	H	H	$NHCH=C(CO_2Et)_2$	H
	h;	CO_2Me	H	H	NO_2
	i;	CO_2Me	H	NO_2	H
	j;	CO_2H	H	NO_2	H
	k;	CO_2Ag	H	NO_2	H
	l;	Br	H	NO_2	H
	m;	Br	H	NH_2	H
	n;	Br	H	$NHCH=C(CO_2Et)_2$	H

An alternative strategy via the bromide (5g) proved more successful. Nitration of methyl thiophene-2-carboxylate gave a 1:1 mixture of esters (6h) and (6i) from which the desired 4-nitro isomer (6i) was isolated in 20% yield by fractional crystallisation. Hydrolysis in aqueous sulphuric acid gave a quantitative yield of the carboxylic acid (6j) which was converted into its silver salt (6k) in 89% yield. The Hunsdiecker reaction with bromine in carbon tetrachloride on (6k) gave the 2-bromothiophene[10] (6l) in 54% yield. This was reduced with tin and concentrated hydrochloric acid to the unstable amine (6m) which on reaction with diethyl ethoxymethylenemalonate afforded (6n). The preparation of (5i) from (6n) has been previously described[11] via phosphorus oxychloride cyclisation to give a mixture of the 2-bromide (7a) and the 2-chloride (7b). This



(7) a; R = Br
b; R = Cl

mixture on reaction with ethyl bromide in a sealed tube at 130°C followed by alkaline hydrolysis resulted in formation of the 2-bromide (5i) only. In our hands the ester (5h) was more conveniently prepared in 71% yield by cyclisation of (6n) to (5g) in refluxing Dowtherm A followed by ethyl iodide and potassium carbonate treatment in DMF. Hydrolysis in aqueous sodium hydroxide gave the acid (5i) in 90% yield. Treatment of (5i) with N-methylpiperazine, piperazine and thiomorpholine in dimethylsulphoxide at 100°C afforded the amines (5j-l) in 74, 47 and 76% yields respectively.

Compounds (5j), (5k) and (5l) exhibited very poor antibacterial activity.

EXPERIMENTAL

^{1}H N.m.r. data were recorded at either 60 MHz on a Perkin-Elmer R24A or 270MHz on a JEOL GX270 instrument and ^{13}C measurements were obtained using a JEOL GX270 spectrometer; all n.m.r. data were recorded at ambient temperatures with tetramethylsilane as internal standard. Mass spectra were obtained at 70eV using a VG 70-70F instrument operating at 8eV. Flash chromatography was carried out on Camlab silica gel 60 230-400 mesh. T.l.c. was performed routinely on all compounds using precoated Merck Kieselgel 60F_{254} plates.

Methyl 3-Acetylamino-4 (and 5-)-nitrothiophene-2-carboxylate (6b) and (6c) - An ice cooled solution of methyl 3-acetylaminothiophene-2-carboxylate (40.0g, 0.2mM) in concentrated sulphuric acid (75ml) was added to a mixture of fuming nitric acid (17ml, 0.4mM) and concentrated sulphuric acid (125ml) over 0.5h, keeping the temperature between -20 and -15°C. The reaction mixture was stirred at -20°C for a further 0.5h then poured onto ice (2kg), diluted with water (2l) and extracted with dichloromethane (3 x 300ml). The combined extracts were washed with water, brine and then dried ($MgSO_4$). Removal of the solvent gave a mixture of the 4- and 5-nitro derivatives (42.5g) which was crystallised from toluene to afford the 4-nitro isomer (6c) (13.4g, 27%) as a cream solid m.p. 177-8°C (lit.[9] 113-116°C) (Found: C, 39.6; H, 3.2; N, 11.3. $C_8H_8N_2O_5S$ required C, 39.3; H, 3.3; N, 11.5%); δH ($CDCl_3$) 2.2 (3H, s, $NHCOCH_3$), 3.9 (3H, s, $COCH_3$), 8.4 (1H, s, 5-H), and 9.4 (1H, br.s., NH); δ_C (CD_3SOCD_3) 22.8 (q, $NHCOCH_3$), 52.6 (q, CO_2CH_3), 121.0 (s, C-2), 132.8 (d, C-5), 133.4 (s, C-3), 142.9 (s, C-4), 160.5 ($NHCOCH_3$) and 168.8 (s, CO_2CH_3). The mother liquors were concentrated and purified by flash chromatography eluting with 2% methanol in dichloromethane to give the 5-nitro isomer (6b) (21.9g, 44%), m.p. 119-120°C (ethanol) (lit[9] m.p. 176-8°C) (Found: C, 39.5; H, 3.2; N, 11.5. $C_8H_8N_2O_5S$ requires C, 39.3; H, 3.3; N, 11.5%); δH ($CDCl_3$) 2.2 (3H, s, $NHCOCH_3$), 3.9 (3H, s, CO_2CH_3), 8.9 (1H, s, 4-H), and 10.0 (1H, br.s., NH); δ_C (CD_3SOCD_3) 23.6 (q, $NHCOCH_3$), 52.9 (q, CO_2CH_3), 122.6 (d, C-4), 115.2 (s, C-2), 140.5 (s, C-3), 152.3 (s, C-5), 161.8 (s, $NHCOCH_3$), and 168.3 (s, CO_2CH_3).

Methyl 3-Amino-5-nitrothiophene-2-carboxylate (6d) - Concentrated hydrochloric acid (2.5ml) was added to a solution of methyl 3-acetylamino-5-nitrothiophene-2-carboxylate (1.3g) in ethanol (15ml) at reflux. The reaction mixture was further refluxed for 0.5h, the solvent evaporated under reduced pressure and the residue washed with water to afford the title compound (6d) (0.86g, 80%) m.p. 160-5°C (Found: C, 35.4; H, 3.1; N, 13.7. $C_6H_6N_2O_4S$ requires C, 35.6; H, 3.0; N, 13.9%), ν_{max} (KBr) 3460, 3360, 1690, and 1620 cm^{-1}; δH ($CDCl_3$) 3.9 (3H, s, OCH_3), 7.0 (2H, br.s., NH_2), and 8.4 (1H, s, 4-H).

Ethyl 2-Ethoxycarbonyl-3-(3-thienylamino)prop-2-enoate (6g) - A suspension of methyl 3-aminothiophene-2-carboxylate[12] (5.0g) in 1M-sodium hydroxide (35ml) was heated under reflux for 1h. The resulting solution was evaporated and the residue of sodium 3-aminothiophene-2-carboxylate dried over phosphorus pentaoxide under reduced pressure. The sodium salt was finely ground and suspended in toluene (60ml) and treated with diethyl ethoxymethylenemalonate (7.2g) and acetic acid (1.82g). The mixture was refluxed for 6h then the solvent evaporated under reduced pressure and the residue extracted with dichloromethane (100ml) and water (200ml). The organic layer was separated, washed with water (100ml), dried ($MgSO_4$) and evaporated to a pale brown solid. Purification by flash chromatography eluting with 2% methanol in dichloromethane and recrystallisation from diisopropyl ether gave the title compound (6g) (4.1g, 48%) as a cream solid m.p. 81-2°C (Found: C, 53.5; H, 6.6; N, 5.1. $C_{12}H_{15}NO_4S$ requires C, 53.5; H, 5.6; N, 5.2%); ν_{max} (KBr) 2980, 1680, 1630, and 1605 cm^{-1}; δH ($CDCl_3$) 1.3 (6H, 2t, 2 x CH_2CH_3), 4.2 and 4.3 (4H, 2q, 2 x CH_2CH_3) 6.9 - 7.3 (3H, m, 3 x thienyl-H), 8.4 (1H, d, NHCH), and 11.0 (1H, d, J 13Hz, NH).

Ethyl 4-Ethyl-4,7-dihydro-7-oxothieno[3,2-b]pyridine-6-carboxylate (5c) - Diester (6g) (5.0g) was added to refluxing Dowtherm A (50ml) over 5 min. under nitrogen. The reaction mixture was refluxed for a further 15 min. then cooled and diluted with petroleum ether (b.p. 40-60°C) (100ml). The precipitated solid was filtered off, washed with petroleum ether (b.p. 40-60°C) and crystallised from DMF to give the title compound (5c) (3.3g, 80%) as a pale brown solid m.p. 284°C (decomp.); ν_{max} (KBr) 3060, 1690, 1605, 1550, and 1280cm^{-1}; δH (CF_3CO_2D) 1.6 (3H, t, $CH_2\underline{CH_3}$), 4.7 (2H, q, $\underline{CH_2}CH_3$), 7.8 (1H, d, J 6Hz, 3-H), 8.5 (1H, d, J 6Hz, 2-H), and 9.2 (1H, s, 5-H); A mixture of ethyl 7-hydroxythieno[3,2-b]pyridine-6-carboxylate (5.03g), potassium carbonate (12.3g) and DMF (150ml) was stirred at 100°C under nitrogen. After 5 min. a mixture of ethyl iodide (28.2g) and DMF (20ml) was added dropwise over 15 min. Stirring was continued at 100°C for 2h when the mixture was cooled, filtered through celite and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane and water, the organic layer separated then washed with water, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue crystallised from ethanol-diethyl ether to give the title compound (5c) (4.22g, 75%); m.p. 160°C. (Found: C, 57.3; H, 5.2; N, 5.5. $C_{12}H_{13}NO_3S$ requires C, 57.3; H, 5.2; N, 5.6%). ν_{max} (KBr) 3100, 2980, 1695, 1610, 1585 and 1510 cm^{-1}; δH ($CDCl_3$) 1.4 (3H, t, $CH_2\underline{CH_3}$), 1.5 (3H, t, $CH_2\underline{CH_3}$), 4.3 (2H, q, $\underline{CH_2}CH_3$), 4.4 (2H, q, $\underline{CH_2}CH_3$), 7.2 and 7.8 (2H, 2d, J 6Hz, 2- and 3-H), and 8.4 (1H, s, 5-H).

4-Ethyl-4,7-dihydro-7-oxothieno[3,2-b]pyridine-6-carboxylic acid (5e) - A suspension of the ethyl ester (5d) (0.94g) in aqueous 1M-sodium hydroxide (7.5ml) was refluxed for 0.75h. The resulting solution was cooled, diluted with water (30ml) and acidified with 1M-hydrochloric acid (10ml). The white precipitate was collected, washed with water and crystallised from a mixture of DMF (15ml) and water (10ml) to give the title compound (5e) (0.60g; 72%) m.p. 228°C (Found: C, 53.6; H, 3.9; N, 6.2. $C_{10}H_9NO_3S$ requires C, 53.8; H, 4.1; N, 6.3%), ν_{max} (KBr) 3120, 2060, 2980, 1720, 1610, 1495, and 1450 cm^{-1}; δH (CF_3CO_2D) 1.82 (3H, t, $CH_2\underline{CH_3}$), 4.90 (2H, q, $\underline{CH_2}CH_3$), 7.86 and 8.65 (2H, 2d, J 5.5 Hz, 2- and 3-H), and 9.30 (1H, s, 5-H); δ_c (CF_3CO_2D) 15.5 (q, $CH_2\underline{CH_3}$), 56.2 (t, $\underline{CH_2}CH_3$), 107.1 (s, C-6), 119.2 (d, C-3), 128.5 (s, C-7a), 145.6 (d, C-2), 148.1 (d, C-5), 151.3 (s, C-3a), 170.0 and 171.7 (2s, C-7 and CO_2H).

4-Ethyl-4,7-dihydro-3-nitro-7-oxothieno[3,2-b]pyridine-6-carboxylic acid (5f) - A solution of the acid (5e) (1.7g) in concentrated sulphuric acid (5ml) was added dropwise to a mixture of fuming nitric acid (1.0ml) and concentrated sulphuric acid (10ml) at -20°C over 10 min. The mixture was stirred at -20°C over 10 min. The mixture was stirred at -20°C for 0.5h, allowed to warm to 0°C and then poured onto ice. The solid was collected, washed with water, dried and crystallised from DMF/ethanol to give the title compound (5f) (0.65g, 32%) m.p. 205-6°C (Found: C, 44.9; H, 2.8; N, 10.4. $C_{10}H_8N_2O_5S$ requires C, 44.8; H, 3.0; N, 10.4%), ν_{max} (KBr) 3100, 1735, 1610, 1550, and 1430 cm^{-1}; δH (CF_3CO_2D) 1.76 (3H, t, $CH_2\underline{CH_3}$), 4.94 (2H, q, $\underline{CH_2}CH_3$), 9.31 (1H, s, 5-H), and 9.43 (1H, s, 2-H); δ_c (CF_3CO_2D) 16.4 (q, $CH_2\underline{CH_3}$), 58.5 (t, $\underline{CH_2}CH_3$), 109.2 (s, C-6), 130.0 (s, C-7a), 140.3 (s, C-3a), 142.2 (s, C-3), 145.3 (d, C-2), 152.1 (d, C-5), 170.6 and 170.9 (2s, C-7 and CO_2H).

Methyl 4-nitrothiophene-2-carboxylate (6i) - A solution of methyl thiophene-2-carboxylate (42.5g) in concentrated sulphuric acid (120ml) was a cooled in ice and added dropwise over 0.5h to a mixture of fuming nitric acid (35ml) and concentrated sulphuric acid (230ml), maintaining the temperature between -15 and -20°C. The reaction mixture was allowed to rise to 0°C over 0.5h and then poured onto ice (3kg) and extracted with dichloromethane (2 x 500ml). The combined extracts were washed with water, saturated aqueous sodium hydrogen carbonate and water then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a 1:1 mixture of the 4- and 5-nitro derivatives (55.6g). Two crystallisations from diethyl ether (200ml) gave methyl 4-nitrothiophene-2-carboxylate (11.5g, 21%) m.p. 98-100°C (lit.[13] 100-1°C) ν_{max} (film) 3100, 3090, 1710, 1540, and 1520 cm^{-1}; δH ($CDCl_3$) 3.95 (3H, s, CO_2CH_3), 8.22 (1H, d, J 1.6Hz, 3-H), and 8.47

(1H, d, J 1.6Hz, 5-H).

4-Nitrothiophene-2-carboxylic acid (6j) - Methyl 4-nitrothiophene-2-carboxylic acid (11.5g) was added to a mixture of concentrated sulphuric acid (57ml) and water (170ml) and heated under reflux for 1.5h. After cooling the mixture was extracted with diethyl ether (3 x 200ml) and the combined extracts were washed with water and brine then dried ($MgSO_4$) and evaporated under reduced pressure to yield 4-nitrothiophene-2-carboxylic acid (10.6g, 100%) m.p. 152-4°C (benzene) (lit.[13] 154°C), ν_{max} (KBr) 3110, 3090, 1690, 1540, and 1525 cm^{-1}; δH ($CDCl_3$ + CD_3SOCD_3) 8.2 (1H, d, 3-H), 8.7 (1H, d, J 1.5Hz, 5-H), and 11.3 (1H, s, CO_2H).

2-Bromo-4-nitrothiophene (6l) - 4-Nitrothiophene-2-carboxylic acid (11.7g) was dissolved in 0.2M-sodium hydroxide (337ml), 1M-silver nitrate (71ml) was added slowly with stirring and the precipitate that formed was collected by filtration, washed with water and dried under reduced pressure over phosphorus pentaoxide to give the silver salt (6k) (16.8g, 89%). A solution of bromine (9.75g) in carbon tetrachloride (40ml) was added dropwise to a suspension of the silver salt (16.8g) in carbon tetrachloride (140ml) under reflux over a period of 2h. The reaction mixture was refluxed for a further 0.5h then filtered while hot and the residue was washed with hot carbon tetrachloride (3 x 30ml). The filtrate and washings were combined and washed with aqueous sodium hydrogen sulphite, aqueous sodium carbonate and water then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled to give the title compound as a colourless liquid (6.8g, 54%), b.p. 64-8°C / 0.6 mm Hg (lit.[10] b.p. 105-110°C / 55mm Hg), ν_{max} (film) 3120, 1540, 1500, 1440, 1370, and 1330 cm^{-1}; δH ($CDCl_3$) 7.7 (1H, d, 3-H) and 8.3 (1H, d, J 18Hz, 5-H).

Ethyl 3-(2-Bromo-3-thienylamino)-2-ethoxycarbonylprop-2-enoate (6n) - 2-Bromo-4-nitrothiophene (3.42g) was added dropwise to concentrated hydrochloric acid (35ml) with vigorous stirring in an ice/salt bath. Tin powder (3.4g) was added portionwise so that the temperature remained below 3°C. The reaction mixture was stirred for a further 15 min. before water (100ml) was slowly added and the resulting solution washed with diethyl ether (discarded). The aqueous solution was layered with diethyl ether (100ml) and cooled in an ice bath before addition of 6.25M-sodium hydroxide (80ml). The organic layer was separated, washed with water and brine, then dried ($MgSO_4$) and evaporated under reduced pressure to give 4-amino-2-bromothiophene (6m) (2.2g, 75%) as a pale yellow oil which was used immediately in the next state. A mixture of the amine (6m) (2.2g) and diethyl ethoxymethylenemalonate (2.64g) in toluene (15ml) was heated at 105°C for 20 min. in a stream of nitrogen and then at 90°C under reduced pressure for 15 min. The residue was purified by flash chromtography eluting with 50% diethylether-petroleum ether (b.p. 40-60°C) to give the product (3.3g) which was crystallised from hexane to afford the title compound (6n) (2.67g, 62%) as light brown needles m.p. 76-7°C (lit.[11] m.p. 81-2°C), ν_{max} (KBr) 2980, 1690, 1645, and 1600 cm^{-1}; δH ($CDCl_3$) 1.3 (6H, t+t, $CO_2CH_2\underline{CH_3}$), 4.3 (4H, q+q, $-CO_2\underline{CH_2}CH_3$), 6.8 and 7.0 (2H, d+d, J 1.8Hz, 3- and 5-H) and 11.0 (1H, d, J 14Hz, NH).

2-Bromo-4-ethyl-4,7-dihydro-7-oxothieno[3,2-b]pyridine-6-carboxylic acid (5i) - The malonate derivative (6n) (2.67g) was added portionwise to refluxing Dowtherm A under nitrogen over 5 min. The reaction mixture was refluxed for a further 15 min. and then cooled and the precipitate collected, washed with petroleum ether (b.p. 40-60°C) to give ethyl 2-bromo-7-hydroxythieno-[3,2-b]pyridine-6-carboxylate (5g) (2.06g, 89%) m.p. 295°C (DMF), ν_{max} (KBr) 3050, 1700, 1605, and 1545 cm^{-1}; δH (CF_3CO_2D) 1.1 (3H, t, $CO_2CH_2\underline{CH_3}$), 4.3 (2H, q, $CO_2\underline{CH_2}CH_3$), 7.4 (1H, s, 3-H), and 8.8 (1H, s, 5-H). A mixture of potassium carbonate (5.8g) and thienopyridine (5g) (2.5g) in DMF (25ml) was heated at 100°C then treated with a solution of ethyl iodide (12.5g) in DMF (10ml) over a period of 10 min. The reaction mixture was stirred at 100°C for a further 2h. The excess reagent

and solvent were removed under reduced pressure and the residue partitioned between water (150ml) and dichloromethane (100ml). The organic layer was separated, washed with water and dried ($MgSO_4$). After removal of the solvent under reduced pressure the product was purified by flash chromatography with 2% ethanol in chloroform as eluant and crystallised from ethyl acetate to give ethyl 2-bromo-4-ethyl-4,7-dihydro-7-oxothieno[3,2-b]pyridine-6-carboxylate (5h) (1.64g, 60%) m.p. 184-5°C, ν_{max} (KBr) 3070, 2980, 1725, and 1620 cm^{-1}; δH (CD_3SOCD_3) 1.2 (6H, t+t, $CH_2\underline{CH_3}$ x 2), 4.2 (4H, q+q, $\underline{CH_2}CH_3$ x 2), 7.9 (1H, s, 3-H), and 8.5 (1H, s, 5-H). 0.2M-Sodium hydroxide (30ml) was added to the ethyl ester (5h) (1.0g) and heated at 100°C for 1h. The reaction mixture was cooled and acidified with 1M-hydrochloric acid (6.5ml). The product was filtered off, washed with water, dried and crystallised from DMF-ethanol to give the title compound (5i) (0.826g, 90%) as colourless needles m.p. 284°C (lit.[11] m.p. 292-293.5°C) (Found: C, 39.8; H, 2.8, N, 4.7. $C_{10}H_8BrNO_3S$ requires C, 39.8; H, 2.7; N, 4.6%), λ_{max} (0.05M-NaOH) 209 (εm 4,110), 257 (4,340), and 301 nm (4,100); ν_{max} (KBr) 3100, 1720, 1610, and 1460 cm^{-1}; δH (CF_3CO_2D) 1.79 (3H, t, $CH_2\underline{CH_3}$), 4.82 (2H, q, $\underline{CH_2}CH_3$), 7.88 (1H, s, 3-H), and 9.24 (1H, s, 5-H); δ_C (CF_3CO_2D) 16.1 ($CH_2\underline{CH_3}$), 57.0 ($\underline{CH_2}CH_3$), 108.4 (C-6), 123.2 (C-3), 130.3 (C-7a), 138.5 (C-2), 148.8 (C-5), 151.8 (C-3a), 168.9 and 172.1 (C-7 and CO_2H).

4-Ethyl-4,7-dihydro-2-(4-methyl-1-piperazinyl)-7-oxothieno[3,2-b]pyridine-6-carboxylic acid (5j) - A mixture of the 2-bromo derivative (5i) (0.14g), N-methylpiperazine (0.20g) and dimethylsulphoxide (2ml) was heated at 100°C for 2.5h and then evaporated under reduced pressure. The residue was washed with water, dried and recrystallised from aqueous DMF to give the title compound (5j) (0.11g, 74%) m.p.>300°C, λ_{max} (0.05M-NaOH) 273 (εm 4,370) and 327nm (4,210); ν_{max} (KBr) 1700, 1620, and 1520 cm^{-1}; δH (CD_3SOCD_3) 1.38 (3H, t, $CH_2\underline{CH_3}$), 2.25 (3H, s, NCH_3), 3.42 and 2.48 (8H, 2m, piperazinyl-H_2), 4.32 (2H, q, $\underline{CH_2}CH_3$), 6.54 (1H, s, 3-H), 8.57 (1H, s, 5-H) and 15.93 (1H, br.s., CO_2H); δ_C (CD_3SOCD_3) 14.6 ($CH_2\underline{CH_3}$), 45.4 (NCH_3), 49.7 ($\underline{CH_2}CH_3$), 53.4 and 49.1 (piperazinyl C), 91.4 (C-3), 108.8 (C-6), 114.1 (C-7a), 143.8 (C-5), 148.0 (C-3a), 164.3 (C-2), 166.3 and 170.3 (C-7 and CO_2H); m/z 321 (M^+, 50%), 277 (100), 192 (15), and 70 (50) (Found: M^+, 321.1149. $C_{15}H_{19}N_3O_3S$ requires 321.1147).

4-Ethyl-4,7-dihydro-7-oxo-2-(1-piperazinyl)thieno[3,2-b]pyridine-6-carboxylic acid (5k) - A mixture of the 2-bromo derivative (5i) (0.141g) piperazine (0.165g) and dimethylsulphoxide (2ml) was heated at 100°C for 2h and then evaporated under reduced pressure. The residue was washed with water, dried and recrystallised from aqueous ethanol to give the title compound (5k) (0.067g, 47%) m.p. 300°C, λ_{max} (0.05M-NaOH) 214 (εm 4,240), 273 (4,460), and 328 nm. (4,280); δH (CD_2SOCD_3) 1.39 (3H, t, $CH_2\underline{CH_3}$), 3.46 and 3.02 (8H, 2 x s, piperazinyl H_2), 4.33 (2H, q, $\underline{CH_2}CH_3$), 6.58 (1H, s, 3-H), and 8.58 (1H, s, 5-H); δ_C (CD_3SOCD_3) 14.4 ($CH_2\underline{CH_3}$), 49.0 and 43.7 (piperazinyl C), 49.4 ($\underline{CH_2}CH_3$), 91.4 (C-3), 108.5 (C-6), 113.8 (C-7a), 143.6 (C-5), 147.7 (C-3a), 164.3 (C-2), 166.1 and 170.1 (C-7 and CO_2H); m/z 307 (M^+, 55%), 263 (100), 221 (60), 206 (18), and 56 (25) (Found: M^+, 307.0985, $C_{14}H_{17}N_3O_3S$ requires 307.0990).

4-Ethyl-4,7-dihydro-7-oxo-2-(4-thiomorpholinyl)thieno[3,2-b]pyridine-6-carboxylic acid (5l) - A mixture of the 2-bromo derivative (5i) (0.11g), thiomorpholine (0.15g) and dimethylsulphoxide (1.5ml) was heated at 110°C for 2h and then evaporated under reduced pressure. The residue was washed with water, dried and recrystallised from aqueous DMF to give the title compound (5l) (0.09g, 76%) m.p. 290°C, λ_{max} (0.05M-NaOH) 214 (εm 4,240), 273 (4,460), and 328 nm. (4,280); ν_{max} (KBr) 1710, 1615, 1510, and 1430 cm^{-1}; δH (CD_3SOCD_3) 1.38 (3H, t, $CH_2\underline{CH_3}$), 2.75 and 3.78 (8H, 2 x m, thiomorpholinyl H_2), 4.32 (2H, q, $\underline{CH_2}CH_3$), 6.57 (1H, s, 3-H), 8.57 (1H, s, 5-H), and 15.9 (1H, br.s., CO_2H); δ_C (CD_2SODC_3) 14.4 ($CH_2\underline{CH_3}$), 49.4 ($\underline{CH_2}CH_3$), 25.0 and 51.8 (thiomorpholinyl C), 91.5 (C-3), 108.6 (C-6), 113.7 (C-7a), 143.6 (C-5), 148.0 (C-3a), 163.4 (C-2), 166.0 and 170.1 (C-7 and CO_2H); m/z 324 (M^+, 45%), 280 (100), 223 (54), and 73 (40) (Found: 324.0631. $C_{14}H_{16}N_2O_3S_2$ requires 324.0603).

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