The Preparation of Thiazole-4- and -5-carboxylates, and an Infrared Study of their Rotational Isomers

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Convenient general procedures have been developed for preparing series of thiazole-4- and -5-carboxylates containing alkyl and halogeno substituents. While both series of esters show i.r. carbonyl doublets caused by rotational isomerism, the more intense absorptions of the 4-carboxylates are the lower wavenumber components, whereas those of the 5-carboxylates are the higher wavenumber components. In both series the stronger bands arise from the thermochemically more stable forms; identification of these forms as the carbonyl *O,S-syn*-s-*trans* rotamers is more certain with the 4-carboxylates than with the 5-carboxylates.

THE intention of the present work was to study rotational isomerism in series of thiazole-4- and -5-carboxylates containing alkyl and halogeno substituents at the other positions of the heterocyclic nucleus, and to compare the results with those obtained in the recent examination of the corresponding 2-carboxylates.[1] Although a number of 4- and 5-carboxylates are reported in the literature,[2] many contain complex groups (at position 2 in the 4-carboxylates and as the alcohol moiety of the 5-carboxylates) and surprisingly few of the simplest esters have been described.

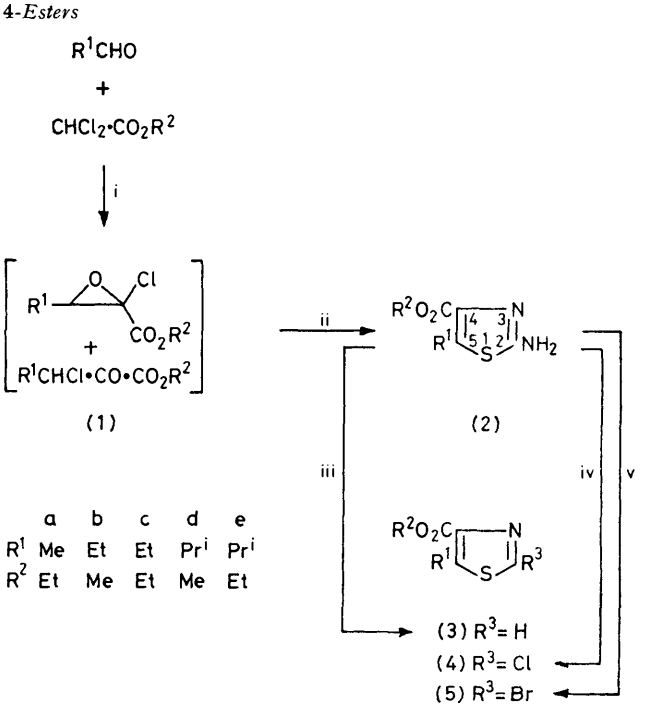
The preparative work is portrayed in Scheme 1. It was known [3] that the Darzens reaction of ethyl and methyl dichloroacetate with propanal gives mixtures of the α-chloroglycidic esters (predominantly) and the β-chloro-α-oxo-esters; both the products from methyl dichloroacetate reacted with thiourea to form the 2-aminothiazole-4-carboxylate (2b). A study of the first stage led to the present convenient procedure in which the mixtures of esters (1) were used to give the 2-amino-4-esters (2) in overall yields of *ca.* 40%. Bromination of dispersions of β-oxo-esters in water at 0 °C gave the α-bromo-derivatives (6) (free from contamination with the γ-bromo-isomers formed by prolonged contact with hydrogen bromide [4]) and thence the 2-amino-5-esters (7) in overall yields exceeding 85%. Replacement of the 2-amino-groups in both series of esters [(2) and (7)] by hydrogen, bromine, and chlorine was straightforward. The possibility of obtaining 2-fluoro-5-esters by nucleophilic displacement of a 2-bromo-substituent by fluoride ion was investigated with one ester (10a). However even the most successful procedure (Scheme 1) was both inconvenient and inefficient. Diazotisation of two 2-amino-5-esters (7b and d) under Olah's conditions [5] provided a much better route to the 2-fluoro-derivatives (9b and d). Other structural modifications (introduction of deuterium at position 2, and the preparation of methyl and t-butyl esters) required to clarify the subsequent spectrometric study were carried out by methods used previously with similar systems.[1,6]

Although the i.r. results (Table 1) establish that both the 4- and the 5-carboxylates show rotational isomerism, there are marked contrasts between the gross spectrometric features of the two series. With the 4-carboxylates the lower wavenumber components of the carbonyl doublets (*l*-bands) are markedly predominant in the less polar solvent (carbon tetrachloride) but the components' intensities are similar in the more polar solvent (acetonitrile): with the 5-carboxylates the higher wavenumber components (*h*-bands) are the major bands of the carbon tetrachloride solutions and their relative intensities decrease less with increasing solvent polarity. Further, while the *h*- and *l*-bands of the 4-carboxylates exhibit, respectively, large and small shifts to lower wavenumber with increasing solvent polarity, both bands of the 5-carboxylates show medium displacements. These effects, and those of varying the structures of the esters, are remarkably constant within, and

SCHEME 1

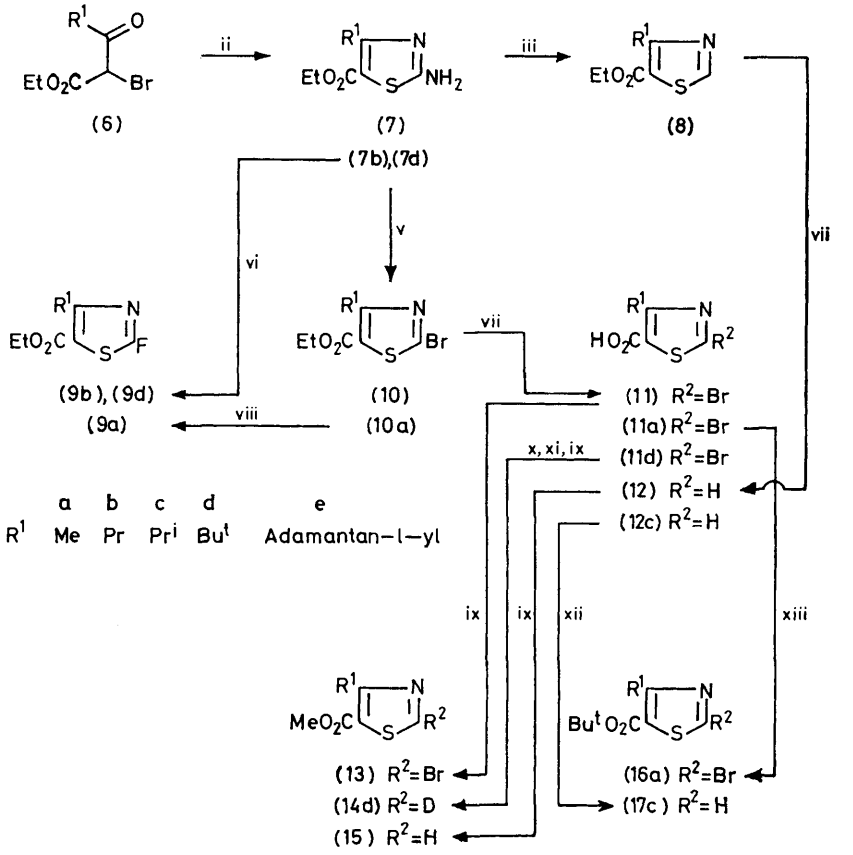
Preparative work

New thiazole esters and acids are listed in Table 2; references to known thiazoles involved here are given at the end of the Experimental section.



5-Esters

Reactions represented by general formulae were carried out with most or all of the sets; where only particular examples were studied these are specified.



Reagents: i, NaOMe–MeOH; ii, $H_2N)_2CS$; iii, $NaNO_2$–H_3PO_2; iv, HNO_2–NaCl–$CuSO_4$; v, HNO_2–NaBr–$CuSO_4$; vi, $NaNO_2$–$(HF)_n$–C_5H_5N; vii, KOH–H_2O; viii, KF–dicyclohexyl-18-crown-6-tetrahydrothiophen 1,1-dioxide; ix, CH_2N_2; x, Bu^nLi; xi, D_2O; xii, $(COCl)_2$, then $LiOBu^t$; xiii, $Me_2C{:}CH_2$–H_2SO_4

different between, the two series: they are expressed quantitatively in the lower part of Scheme 2 by showing how the positions and relative areas (A_h/A_l) of the parent esters' bands are influenced by introducing substituents or changing the solvent.

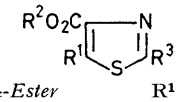
Since the 4-carboxylates resemble the 2-isomers in their main spectrometric features, the arguments used previously [1] can be applied here to identify the rotamer giving the *h*-band as the *anti*-s-*trans* form (18) in which there should be a marked degree of twisting between the heterocycle and the ester function. This correlation accounts for the higher sensitivity (intensity increase, wavenumber decrease) of the *h*-band to increasing solvent polarity. The observation of small shifts to lower wavenumber of both bands caused by changing the 5-substituent from ethyl to isopropyl is satisfactorily explained by an increased inductive effect, and it seems that the larger group does not significantly affect the degree of coplanarity of either form. With the 5-carboxylates the band assignments shown in Table 2 do not accommodate all the results and are to be regarded as tentative. (A full discussion of these and the alternative correlations has been presented elsewhere.[7])

The salient feature is that the *h*-band moves to *higher* wavenumber as the size of the 4-alkyl group increases, and this denotes a steric effect in which the ester group is twisted out of the plane of the thiazole ring. Earlier work [8] suggests that the form involved should have the 4-alkyl group abutting the ester's alkyloxy group, *i.e.* the *syn*-s-*trans* form (20). The result of introducing larger alkyl groups next to the ester function in both series can then be rationalised as follows. Forms (19) and (21) are the most nearly planar, and little further twisting occurs. Form (18) is also little affected, but in this case because there is already such a marked divergence between the planes. Only in form (20), where there is an intermediate degree of non-coplanarity, is the position sensitive to the size of the neighbouring alkyl group. It may be noted that the effects shown by methyl 2-bromo-4-trifluoromethylthiazole-5-carboxylate are in several respects the opposite of those found generally in 5-carboxylates. With the fluoro-compound the *h*-band is to be associated with the form in which the carbonyl and trifluoromethyl dipoles are more nearly parallel; since this is the *anti*-s-*trans* form (21) the assignments also are the reverse of the general ones.

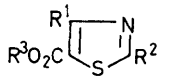
TABLE 1

Infrared bands of alkyl thiazole-4- and -5-carboxylates

The spectrometric work and curve resolution were carried out as described previously.[a] The components' positions (in cm^{-1} at 303 K) are followed, in parentheses, by their percentage areas. Enthalpy differences ($\Delta H°$/kJ mol^{-1}) between the forms giving rise to the doublets were obtained using solutions in CH_2Cl_2 over the range 258—348 K and are in the direction (form with higher cm^{-1}) ⟶ (form with lower cm^{-1}); the statistical errors in the $\Delta H°$ values are considered to be less than ± 600 J mol^{-1}.



4-*Ester*	R^1	R^1	R^3	CO Fundamental region: CCl_4		MeCN		CO Overtone region: CCl_4		$\Delta H°$
(3a)	Me	Et	H	1 738(12)	1 714(88)	1 723(49)	1 711(51)	3 459(13)	3 413(87)	−5.4
(5a)	Me	Et	Br	1 738(11)	1 715(89)	1 725(40)	1 713(60)	3 458(10)	3 414(90)	−5.1
(3b)	Et	Me	H	1 743(11)	1 721(89)	1 731(45)	1 720(55)	3 468(14)	3 422(86)	−4.6
(5b)	Et	Me	Br	1 745(11)	1 722(89)	1 733(41)	1 721(59)	3 470(13)	3 420(87)	−5.0
(3c)	Et	Et	H	1 738(15)	1 714(85)	1 724(43)	1 712(57)	3 456(16)	3 411(84)	−5.1
(5c)	Et	Et	Br	1 739(14)	1 715(86)	1 725(46)	1 714(54)	3 456(15)	3 412(85)	−5.5
(3d)	Pr^i	Me	H	1 739(9)	1 718(91)	1 727(39)	1 718(18)	3 458(12)	3 420(88)	
(4d)	Pr^i	Me	Cl	1 741(10)	1 719(90)	1 728(38)	1 719(62)	3 463(14)	3 421(86)	
(5d)	Pr^i	Me	Br	1 742(11)	1 719(89)	1 728(40)	1 719(60)	3 464(15)	3 422(85)	
(3e)	Pr^i	Et	H	1 733(9)	1 711(91)	1 719(39)	1 710(61)	3 447(10)	3 404(90)	
(5e)	Pr^i	Et	Cl	1 735(9)	1 713(91)	1 722(38)	1 712(62)	3 448(10)	3 408(91)	



5-*Ester*	R^1	R^2	R^3							
(15a)	Me	H	Me	1 724(89)	1 711(11)	1 720(79)	1 705(21)	3 432(91)	3 401(10)	1.9
(13a)	Me	Br	Me	1 727(90)	1 709(10)	1 724(80)	1 703(20)	3 438(92)	3 400(8)	
(8a)	Me	H	Et	1 720(85)	1 707(15)	1 716(74)	1 701(26)	3 422(86)	3 394(14)	2.4
(10a)	Me	Br	Et	1 722(90)	1 705(10)	1 719(84)	1 699(16)	3 428(88)	3 393(12)	1.8
(9a)	Me	F	Et	1 723(75)	1 704(25)	1 720(70)	1 699(30)	3 420(74)	3 394(26)	1.9
(16a)	Me	Br	Bu^t	1 717(80)	1 698(20)	1 714(71)	1 693(29)	3 418(80)	3 380(20)	2.1
(15b)	Pr	H	Me	1 725(82)	1 710(18)	1 720(72)	1 705(28)	3 432(79)	3 403(21)	2.4
(13b)	Pr	Br	Me	1 727(85)	1 708(15)	1 724(77)	1 703(23)	3 436(87)	3 398(13)	
(8b)	Pr	H	Et	1 720(75)	1 706(25)	1 716(65)	1 700(35)	3 422(76)	3 396(24)	
(10b)	Pr	Br	Et	1 723(85)	1 704(15)	1 720(72)	1 699(28)	3 426(74)	3 395(26)	
(9b)	Pr	F	Et	1 724(79)	1 703(21)	1 721(68)	1 698(32)	3 425(81)	3 384(29)	
(15c)	Pr^i	H	Me	1 726(86)	1 708(14)	1 721(75)	1 703(25)	3 430(84)	3 397(26)	2.0
(8c)	Pr^i	H	Et	1 722(83)	1 704(17)	1 717(73)	1 697(27)	3 422(80)	3 390(20)	
(10c)	Pr^i	Br	Et	1 724(87)	1 702(13)	1 721(76)	1 697(24)	3 424(86)	3 385(14)	2.4
(17c)	Pr^i	H	Bu^t	1 716(79)	1 699(21)	1 709(70)	1 689(30)	3 410(79)	3 375(21)	1.8
(15d)	Bu^t	H	Me	1 730(96)	1 704(4)	1 725(94)	1 698(6)	3 443(92)	3 388(8)	
(14d)	Bu^t	D	Me	1 729(96)	1 703(4)	1 725(94)	1 698(6)	3 442(91)	3 387(9)	
(13d)	Bu^t	Br	Me	1 733(94)	1 698(6)	1 730(91)	1 694(9)	3 447(92)	3 376(8)	
(8d)	Bu^t	H	Et	1 725(93)	1 697(7)	1 720(86)	1 691(14)	3 433(93)	3 372(7)	
(10d)	Bu^t	Br	Et	1 728(91)	1 694(9)	1 725(86)	1 690(14)	3 440(85)	3 370(15)	
(9d) *	Bu^t	F	Et	1 729(94)	1 691(6)	1 726(84)	1 686(16)	3 413(87)	3 333(13)	
(10e)	Adamantan-1-yl	H	Et	1 725(91)	1 692(9)	1 720(88)	1 687(12)	3 426(80)	3 366(20)	
(8e)	Adamantan-1-yl	Br	Et	1 726(94)	1 690(6)	1 723(87)	1 686(13)	3 431(80)	3 360(20)	
	CF_3	Br	Me	1 758(58)	1 720(42)	1 741(83)	1 717(17)	3 486(60)	3 424(40)	

[a] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1959. [b] Ref. 1.

* Additional bands (absorbances *ca.* 20% of total) at 1 708 cm^{-1} in CCl_4 and 1 707 cm^{-1} in MeCN.

The enthalpy differences between the rotamers are higher in the 4-carboxylates than in the 5-carboxylates but, if the band assignments are correct with the latter, the *syn*-s-*trans* forms are thermochemically more stable in both series.

EXPERIMENTAL

The general reactions in Scheme 1 are illustrated by examples and these are followed by the specific reactions in the lower part of the Scheme. The characterisation of all new compounds is shown in Table 2; a complete account of their properties is given in Theses.[9]

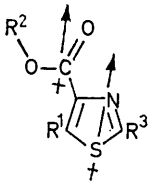
The Methyl 5-Isopropylthiazole-4-carboxylates (2d), (3d), *and* (4d).—The liquids required for the following reaction were rigorously dried immediately before use. A solution prepared from Na (3 g) and MeOH (50 ml) was added during 45 min to a solution of methyl dichloroacetate (20 g) and isobutyraldehyde (14 ml) in Et_2O (50 ml) which was stirred vigorously at 0 °C. After 1 h at 0 °C Et_2O (50 ml) and brine were added, and the layers were separated. The Et_2O solution was dried and evaporated to give material (16.2 g) which was dissolved in MeOH (60 ml) containing thiourea (8.5 g). The solution was boiled under reflux for 4 h, concentrated *in vacuo*, and neutralised with 18M-NH_4OH. Extraction with CH_2Cl_2 gave the 2-aminothiazole (2d) (17.3 g, after crystallisation from EtOH–H_2O).

A solution of $NaNO_2$ (1.5 g) in H_2O (6 ml) was added slowly beneath the surface of a stirred solution of the foregoing amine (2 g) in aq. 30% H_3PO_2 (53 ml) at −5 °C, and the solution was stirred for a further 1 h at 0 °C. The cooling bath was removed for 2 h, then replaced while a cool solution of NaOH (8.5 g) in H_2O (100 ml) was added slowly. The solution was neutralised with $NaHCO_3$ and

SCHEME 2

4-Carboxylates

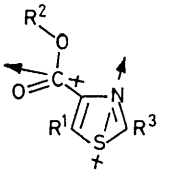
h-Band



(18)

carbonyl *O,S*-anti-s-*trans*

l-Band



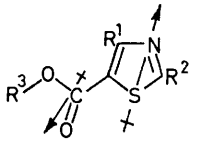
(19)

syn-s-*trans*

	R^1	R^2	R^3	Solvent	*h*-Band	*l*-Band	A_h/A_l
Ester (3a)	Me	Et	H	CCl_7	1 738 cm^{-1}	1 714 cm^{-1}	*ca.* 0.15
Δ values (cm^{-1})	Et				0	0	
	Pr^i				−3	−3	
		Me			+7	+7	
			Cl, Br		+2	+2	
				MeCN	−14	−1	*ca.* 0.8

5-Carboxylates

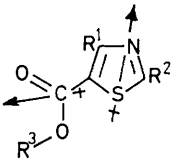
h-Band



(20)

syn-s-*trans*

l-Band



(21)

anti-s-*trans*

	R^1	R^3	R^2	Solvent	*h*-Band	*l*-Band	A_h/A_l
Ester (8a)	Me	Et	H	CCl_4	1 720 cm^{-1}	1 707 cm^{-1}	*ca.* 8
Δ values (cm^{-1})	Pr				0	0	
	Pr^i				+2	−2	
	Bu^t				+6	−9	
		Me			+5	+5	
			F, Br		+3	−2	
				MeCN	−4	−5	*ca.* 3

extracted with Et_2O. Distillation of the material so obtained gave the methyl ester (3d) (1.3 g).

A solution of $NaNO_2$ (1.7 g) in H_2O (6 ml) was added during 20 min beneath the surface of a stirred solution at 0 °C containing the amine (2 d) (2 g), $CuSO_4$ (3.3 g), NaCl (2.6 g), and H_2SO_4 (100 g) in H_2O (75 ml). After a further 30 min at 0 °C and 30 min at 20 °C the mixture was diluted with brine (200 ml) and extracted with Et_2O to give material which was distilled in steam. Extraction of the distillate with Et_2O gave the methyl 2-chloro-ester (4d) (1.45 g), which was purified by distillation *in vacuo*.

Replacement of NaCl (2.6 g) by NaBr (2.6 g) in the foregoing experiment gave the methyl 2-bromo-ester (5d) (1.5 g).

The Ethyl and Methyl 4-t-Butylthiazole-5-carboxylates (8d), (10d), (13d) *and* (14d).—Br_2 (26 g) was added during 30 min to a stirred dispersion of ethyl 4,4-dimethyl-3-oxopentanoate (27.5 g) in H_2O (75 ml) at 0 °C. After a further 30 min extraction with Et_2O gave an oil (37.3 g), shown by ^1H n.m.r. to be ethyl 2-bromo-4,4-dimethyl-3-oxopentanoate (6d). This oil (25.6 g) was added to a solution of thiourea (7.9 g) in EtOH (80 ml), boiling under reflux, at such a rate that the solution continued boiling. After 1 h, ice–H_2O (150 ml) was added and the mixture was neutralised with 18M-NH_4OH. Collection of the insoluble material gave the 2-amine (7d) (22 g) which crystallised from MeOH.

Treatment of the amine (5.7 g) with $NaNO_2$–H_3PO_2 as described previously gave the ethyl ester (8d) (2.45 g), b.p. 80—82 °C at 0.6 mmHg.

A slurry of the amine (11.4 g) and a solution of NaBr (12.4 g) in H_2O (80 ml) was added to a stirred solution at −8 °C of $CuSO_4$ (15 g) and H_2SO_4 (175 ml) in H_2O (425 ml). A solution of $NaNO_2$ (8 g) in H_2O (25 ml) was added beneath the surface of the mixture during 30 min, and the mixture was allowed to warm to 8 °C during 1 h. Extraction with Et_2O gave the ethyl 2-bromo-ester (10d) (9.1 g) which crystallised from EtOH–H_2O.

A mixture of the ethyl ester (8d) (2 g) and KOH (1 g) in H_2O (3 ml) was boiled under reflux for 1.5 h, diluted with H_2O (15 ml), washed with Et_2O, and acidified with 2.7M-HCl. Extraction with Et_2O gave 4-t-butylthiazole-5-carboxylic acid (12d) (1.43 g) which crystallised from Me_2CO–H_2O. The ethyl 2-bromo-ester (10d) (2.92 g), KOH (0.56 g), and H_2O (5 ml) similarly gave the 2-bromo-acid (11d) (2.1 g). Treatment of solutions of the acids (12d) and

TABLE 2

Characterisation of new thiazole derivatives

Systematic names are formed by adding thiazole-4(or 5)-carboxylate (for esters) and thiazole-5-carboxylic acid (for acids) to the material in the first column

4-Esters	M.p. (°C)	B.p. (°C) bath temp./ mmHg	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(2a) Ethyl 2 amino-5-methyl	171—172		44.9	5.3	15.2	$C_7H_{10}N_2O_2S$	45.2	5.4	15.1
(3a) Ethyl 5-methyl	90—91		48.8	5.3	8.3	$C_7H_9NO_2S$	49.1	5.3	8.2
(5a) Ethyl 2-bromo-5-methyl	51—52		33.9	3.1	5.3	$C_7H_8BrNO_2S$	33.6	3.2	5.6
(3b) Methyl 5-ethyl	34—35		49.2	5.3	8.0	$C_7H_9NO_2S$	49.1	5.3	8.0
(5b) Methyl 2-bromo-5-ethyl		98—100/0.25	33.8	3.2	5.6	$C_7H_8BrNO_2S$	33.6	3.2	5.6
(2c) Ethyl 2-amino-5-ethyl	151—152		48.1	6.1	13.8	$C_8H_{12}N_2O_2S$	48.0	6.0	14.0
(3c) Ethyl 5-ethyl		100—102/0.9	51.7	5.9	7.4	$C_8H_{11}NO_2S$	51.9	6.0	7.6
(5c) Ethyl 2-bromo-5-ethyl	26—28		36.7	3.6	5.4	$C_8H_{10}BrNO_2S$	36.4	3.8	5.3
(2d) Methyl 2-amino-5-isopropyl	150—151		48.0	6.1	14.0	$C_8H_{12}N_2O_2S$	48.0	6.0	14.0
(3d) Methyl 5-isopropyl		99—101/0.8	51.9	6.05	7.4	$C_8H_{11}NO_2S$	51.9	6.0	7.6
(4d) Methyl 2-chloro-5-isopropyl	42—43		43.85	4.55	6.35	$C_8H_{10}ClNO_2S$	43.75	4.6	6.4
(5d) Methyl 2-bromo-5-isopropyl		104—106/0.2	36.65	3.6	5.35	$C_8H_{10}BrNO_2S$	36.4	3.8	5.3
(2e) Ethyl 2-amino-5-isopropyl	122—123		50.35	6.8	13.1	$C_9H_{14}N_2O_2S$	50.4	6.6	13.1
(3e) Ethyl 5-isopropyl		102—104/1.1	54.5	6.6	7.0	$C_9H_{13}NO_2S$	54.2	6.6	7.0
(4e) Ethyl 2-chloro-5-isopropyl		86—88/0.1	46.3	5.1	6.0	$C_9H_{12}ClN_2O_2S$	46.2	5.2	6.0
5-Esters									
(9a) Ethyl 2-fluoro-4-methyl		102—104/0.8	44.2	4.2	7.4	$C_7H_8FNO_2S$	44.4	4.3	7.4
(13a) Methyl 2-bromo-4-methyl		80—82/0.15	30.8	2.5	5.9	$C_6H_6BrNO_2S$	30.5	2.5	6.0
(16a) t-Butyl 2-bromo-4-methyl		94—96/0.1	39.2	4.5	4.8	$C_9H_{12}BrNO_2S$	38.9	4.4	5.0
(7b) Ethyl 2-amino-4-propyl	137—138		50.5	6.6	13.2	$C_9H_{14}N_2O_2S$	50.4	6.6	13.1
(8b) Ethyl 4-propyl		120—122/2.5	54.5	6.65	7.0	$C_9H_{13}NO_2S$	54.2	6.6	7.0
(9b) Ethyl 2-fluoro-4-propyl		72—74/0.1	49.5	5.5	6.4	$C_9H_{12}FNO_2S$	49.75	5.6	6.45
(10b) Ethyl 2-bromo-4-propyl		101—103/0.2	39.1	4.25	5.0	$C_9H_{12}BrNO_2S$	38.9	4.35	5.0
(13b) Methyl 2-bromo-4-propyl		54—56/0.2	36.6	3.9	5.3	$C_8H_{10}BrNO_2S$	36.4	3.8	5.3
(15b) Methyl 4-propyl	38—40	92—94/0.9	51.7	5.9	7.7	$C_8H_{11}NO_2S$	51.9	6.0	7.6
(7c) Ethyl 2-amino-4-isopropyl	176—178		50.2	6.6	13.1	$C_9H_{14}N_2O_2S$	50.4	6.6	13.1
(8c) Ethyl 4-isopropyl		93—95/0.8	54.3	6.5	7.15	$C_9H_{13}NO_2S$	54.2	6.6	7.0
(10c) Ethyl 2-bromo-4-isopropyl	47—49		39.2	4.2	5.1	$C_9H_{12}BrNO_2S$	38.9	4.35	5.0
(15c) Methyl 4-isopropyl		94—96/1.1	51.5	5.9	7.5	$C_8H_{11}NO_2S$	51.9	6.0	7.6
(17c) t-Butyl 4-isopropyl		110—112/0.8	58.0	7.6	6.2	$C_{11}H_{17}NO_2S$	58.1	7.5	6.2
(7d) Ethyl 2-amino-4-t-butyl	108—109		52.7	7.2	12.2	$C_{10}H_{16}N_2O_2S$	52.6	7.1	12.3
(8d) Ethyl 4-t-butyl	45—46		56.5	7.1	6.6	$C_{10}H_{15}NO_2S$	56.3	7.1	6.6
(9d) Ethyl 4-t-butyl-2-fluoro		81—83/0.2	52.2	6.3	6.0	$C_{10}H_{14}FNO_2S$	51.9	6.1	6.1
(10d) Ethyl 2-bromo-4-t-butyl	51—52		41.1	4.8	4.9	$C_{10}H_{14}BrNO_2S$	41.1	4.8	4.8
(13d) Methyl 2-bromo-4-t-butyl	39—41		39.0	4.6	5.15	$C_9H_{12}BrNO_2S$	38.9	4.3	5.0
(15d) Methyl 4-t-butyl		68—70/0.1	54.3	6.5	7.05	$C_9H_{13}NO_2S$	54.2	6.6	7.0
(14d) Methyl 4-t-butyl-2-deuterio		68—70/0.1	54.3	—	6.8	$C_9H_{12}DNO_2S$	54.0	—	7.0
(7e) Ethyl 4-(adamantan-1-yl)-2-amino	225—227		62.7	7.3	9.2	$C_{16}H_{22}N_2O_2S$	62.7	7.2	9.1
(8e) Ethyl 4-(adamantan-1-yl)	147—159		65.5	7.2	4.8	$C_{16}H_{21}NO_2S$	69.95	7.3	4.8
(10e) Ethyl 4-(adamantan-1-yl)-2-bromo	102—103		52.1	5.3	3.9	$C_{16}H_{20}BrNO_2S$	51.9	5.4	3.8
5-Carboxylic acids									
(11a) 2-Bromo-4-methyl	175—178		26.9	1.7	6.4	$C_5H_4BrNO_2S$	27.0	1.8	6.3
(11b) 2-Bromo-4-propyl	148—151		33.8	3.1	5.8	$C_7H_8BrNO_2S$	33.6	3.2	5.6
(12b) 4-Propyl	141—143		49.2	5.4	8.2	$C_7H_9NO_2S$	49.1	5.3	8.2
(12c) 4-Isopropyl	162—163		49.1	5.1	8.1	$C_7H_9NO_2S$	49.1	5.3	8.2
(11d) 2-Bromo-4-t-butyl	156—159		36.8	4.1	5.2	$C_8H_{10}BrNO_2S$	36.4	3.8	5.3
(12d) 4-t-Butyl	189—192		52.0	5.9	7.7	$C_8H_{11}NO_2S$	51.9	6.0	7.6

(11d) in Et_2O with CH_2N_2 in Et_2O gave the methyl ester (15d) (85%) and the methyl 2-bromo-ester (13d) (90%), respectively.

The 2-Fluoro-esters (9a), (9b), *and* (9d).—A mixture of KF (dried over P_2O_5 *in vacuo* at 250 °C; 2.6 g) and tetrahydrothiophen 1,1-dioxide (distilled *in vacuo* and stored over molecular sieves; 20 ml) was heated at 0.5 mmHg until the dioxide began to distil (*ca.* 103 °C). Ethyl 2-bromo-4-methylthiazole-5-carboxylate (10a) (2.5 g) and dicyclohexyl-18-crown-6 (0.7 g) were added, and the stirred mixture was boiled under reflux (*ca.* 140 °C) *in vacuo* (15 mmHg) for 3 h. The temperature was increased to 170 °C and the material which distilled was dissolved in Et_2O, washed with H_2O, and dried, and the solvent was evaporated. Distillation of the residue gave the ethyl 4-methyl-2-fluoro-ester (9a) (0.95 g), *m/z* 189 (M^+, 40%) and 144 (100).

$NaNO_2$ (dried at 140 °C for 3 d; 1.76 g) was added to a solution of ethyl 2-amino-4-propylthiazole-5-carboxylate (7b) (3.5 g) in poly-HF–C_5H_5H (supplied by Aldrich Chemicals; 50 ml) and the mixture was stirred at 20 °C for 1 h under N_2 in a closed apparatus. Ice–H_2O (50 ml) was added, and the mixture was extracted with Et_2O. The Et_2O solution was washed with saturated aq. $NaHCO_3$, dried, and evaporated, and the residue was distilled at 70—75 °C (bath temp.) and 0.01 mmHg. The distillate (1.8 g) was further purified by preparative g.l.c. on a Pye R105 Chromatograph (5 m column of 15% OV17 on Embacel, N_2 flow of 60 ml min^{-1}) to give the ethyl 4-propyl-2-fluoro-ester (9b), *m/z* 217 (M^+, 61%) and 189 (100). Ethyl 2-amino-4-t-butylthiazole-5-carboxylate (7d) (2.28 g) similarly gave the ethyl 4-t-butyl-2-fluoro-ester (9d) (1.3 g), *m/z* 231 (M^+, 14%) and 170 (100).

Methyl 4-t-Butyl-2-deuteriothiazole-5-carboxylate (14d).—A

solution of 2-bromo-4-t-butylthiazole-5-carboxylic acid (11d) (1 g) in dry tetrahydrofuran (5 ml) was added slowly to 1.5M-Bu^{n}Li in hexane (6 ml) diluted with tetrahydrofuran (15 ml) which was stirred at −70 °C under N_2. Tetrahydrofuran (10 ml) was added, and the mixture was stirred at −70 °C for 1 h. D_2O (2 ml) in tetrahydrofuran (4 ml) was added slowly, the cooling bath was removed, and after 30 min 0.6M-HCl (125 ml) was added. Extraction with EtOAc gave 4-t-butyl-2-deuteriothiazole-5-carboxylic acid [as (12d) but with R^2 = D] (0.65 g), *m/z* 186 (M^+, 40%) and 171 (100), no signal at τ 1.2. Treatment of this acid (0.5 g) with CH_2N_2 gave the methyl 2-deuterio-ester (14d) (0.42 g).

The t-*Butyl Esters* (16a) *and* (17c).—The 4-methyl-5-bromo-acid (11a) (2.22 g) on treatment with $Me_2C{=}CH_2$ and H_2SO_4 by the standard technique [10] gave the t-butyl 4-methyl-5-bromo-ester (16a) (0.47 g).

Treatment of the 4-isopropyl-5-acid (12c) (0.85 g) with oxalyl chloride and reaction of the resulting chloride with LiOBu^t (as described [1] for a thiazole-2-carboxylic acid) gave the t-butyl 4-isopropyl-ester (17c) (0.55 g).

Known Compounds.—References to known compounds involved as intermediates or products in the present work are: methyl 2-amino-5-ethylthiazole-4-carboxylate [3] (2b), ethyl 2-amino-4-methylthiazole-5-carboxylate [11] (7a), ethyl 4-methylthiazole-5-carboxylate [12] (8a), ethyl 2-bromo-4-methylthiazole-5-carboxylate (10a), m.p. 65—67 °C (lit.,[13] 70—71 °C; lit.,[14] 210—211 °C), methyl 4-methylthiazole-5-carboxylate [12] (15a), methyl 2-bromo-4-trifluoromethylthiazole-5-carboxylate,[1] and 4-methylthiazole-5-carboxylic acid [12] (12a).

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