Substituted Imidazo[2,1-*b*]thiazoles from 2-Aminothiazoles and α-Bromo Ketones: Efficient Preparation and Proof of Structure

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The salts formed from α-aminothiazoles and α-bromo ketones ($RCOCH_2Br$) have been basified, and the products converted into amides. Examination of the amides established that they are 2-acylimino-2,3-dihydrothiazoles rather than 2-acylaminothiazoles. Thus the α-bromo ketones attack the *endo-N* of the 2-aminothiazoles, and the imidazo[2,1-*b*]thiazoles obtained by cyclising the salts have the substituent (R) of the bromo ketone at position 6. Efficient procedures have been developed for preparing a range of imidazo[2,1-*b*]thiazoles.

Related reactions of 2-aminothiazoles, with an α-bromo aldehyde and with ethyl bromoacetate, have been studied.

Four papers[1–4] contain the main previous work on imidazo-[2,1-*b*]thiazoles (**7**). In the original preparation[1] 2-amino-4-methylthiazole was heated at 100 °C with phenacyl bromide; the product obtained (in unspecified yield) on basification was formulated as 3-methyl-6-phenylimidazo[2,1-*b*]triazole [structure (**7Ba**) in Scheme 1]. Subsequent preparations,[2–4] from various 2-aminothiazoles and α-bromo ketones, were represented as proceeding in similar fashion, *i.e.*, with the substituent (R^3) of the α-bromo ketone occupying position 6 of the imidazothiazole nucleus. No evidence was adduced for the correctness of the proposed formulae which, as shown in Scheme 1, involve the assumption of initial attack at the *endo-N* of the aminothiazoles. Although certain electrophiles (notably alkyl halides) are known to react at this site of the ambient nucleophiles, others (such as acid chlorides and anhyrides) give products formed by substitution at the *exo-N*.[5] α-Bromo ketones are intermediate in their electrophilic reactivity; to assume for these a particular course of reaction is therefore unsatisfactory. In the present work it was planned to establish the structures of the known products, and to develop efficient procedures for preparing a wider range of imidazothiazoles required for subsequent studies of their substitution reactions. [Only the well-known 2-aminothiazoles (**1**; $R^1 = R^2 = H$ or Me) and (**1**; R^1 = Me or Et, $R^2 = H$) had been used as starting materials hitherto.[1–4]]

Distinction between the alternative structures for the imidazothiazoles, corresponding to reactions at different centres of the 2-aminothiazoles, is made more clearly by examining the intermediates in the synthesis rather than the final products. As discussed later, some of the intermediates [structures (**4**) or (**9**)] obtained by basifying the initial salts can be isolated. The amides formed by acylating these could be 2-acylimino-2,3-dihydrothiazoles [(**5**) and (**8**)] or 2-acylaminothiazoles [(**10**) and (**11**)], systems which, as discussed earlier,[6] have characteristically different i.r. C=O bands. From the results in Scheme 2 it emerges that the trifluoroacetyl and 2-thenoyl derivatives obtained here have structures (**5**) and (**8**) respectively, and hence that the imidazothiazoles are correctly represented by structure (**7**).

The salts (**3**) were obtained in high yield from a range of α-bromo ketones and 2-aminothiazoles. Chloroacetone is much less effective than bromoacetone, and this may explain why a less convenient route (starting from prop-2-ynyl bromide) was used in the earlier preparations[3] of the 6-methyl products (**7Af**) and (**7Bf**). The imines (**4**), formed by basifying the salts (**3**), differ widely in the ease with which they cyclise to the imidazothiazoles (**7**). Those (**4**; R = Me) derived from bromoacetone cyclise spontaneously and cannot be isolated; those with R^3 = (substituted) phenyl cyclise on heating in ethanol, but for those with R^3 = 2-thienyl cyclisation requires a higher temperature. This trend accords with the expected order of electrophilicity, *viz.*, acetyl > benzoyl > 2-thenoyl.

Preparation of the imidazothiazoles is effected more conveniently by reversing the order of the steps, *i.e.*, cyclisation of the salts (**3**) followed by basification. [One salt (**3Ee**), in which R^3 = 2-thienyl, remained unchanged under the general conditions, and the corresponding imidazothiazole (**7Ee**) was obtained only from the imine (**4Ee**).] Attempted purification of the *p*-nitrophenyl salt (**3Ad**), the least soluble of its type, by crystallisation from dimethylformamide gave the imidazothiazole (**7Ad**) directly in an overall yield of 68% from 2-aminothiazole. Mesomeric interaction between N-4 and the *p*-nitrophenyl group in the product may be expected to reduce its basicity and thus facilitate the loss of hydrogen bromide from the cyclised salt.

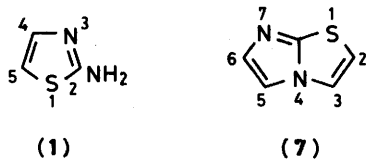
Related work on 2-aminothiazoles is shown in Scheme 3. The course of the reaction between 2-bromo-2-phenylethanal[7] (**15**) (prepared here by an improved procedure) and 2-aminothiazole is extremely sensitive to the nature of the solvent; tetrahydrofuran is the best for the present purpose. Even at 20 °C nucleophilic displacement of bromide is followed by cyclisation, and the salt (**16**) is formed directly (yield 37%). Unambiguous formulation of the derived base as 5-phenylimidazo[2,1-*b*]-thiazole (**17**) is not possible from spectrometric examination alone (Table); it is also necessary to know that the product is not the 6-phenyl compound (**7Aa**). 2-Aminobenzothiazole is reported,[8] without proof, to undergo *endo-N* reaction with ethyl chloroacetate. The work in Scheme 3 establishes that such is the case in the reactions of 2-aminothiazoles with ethyl bromoacetate.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 1750 Fourier Transform spectrometer using solutions in $CHCl_3$ and ^1H n.m.r. spectra on a Bruker WH300 (300 MHz) spectrometer using solutions of the salts (**3**) and (**6**) in $(CD_3)_2SO$ and solutions of the other compounds in $CDCl_3$. Mass spectra were obtained by in-beam electronic-impact unless stated otherwise. Solvents were dried and distilled before use in preparing the salts (**3**); THF refers to tetrahydrofuran, and petroleum to light petroleum, b.p. 85—95 °C.

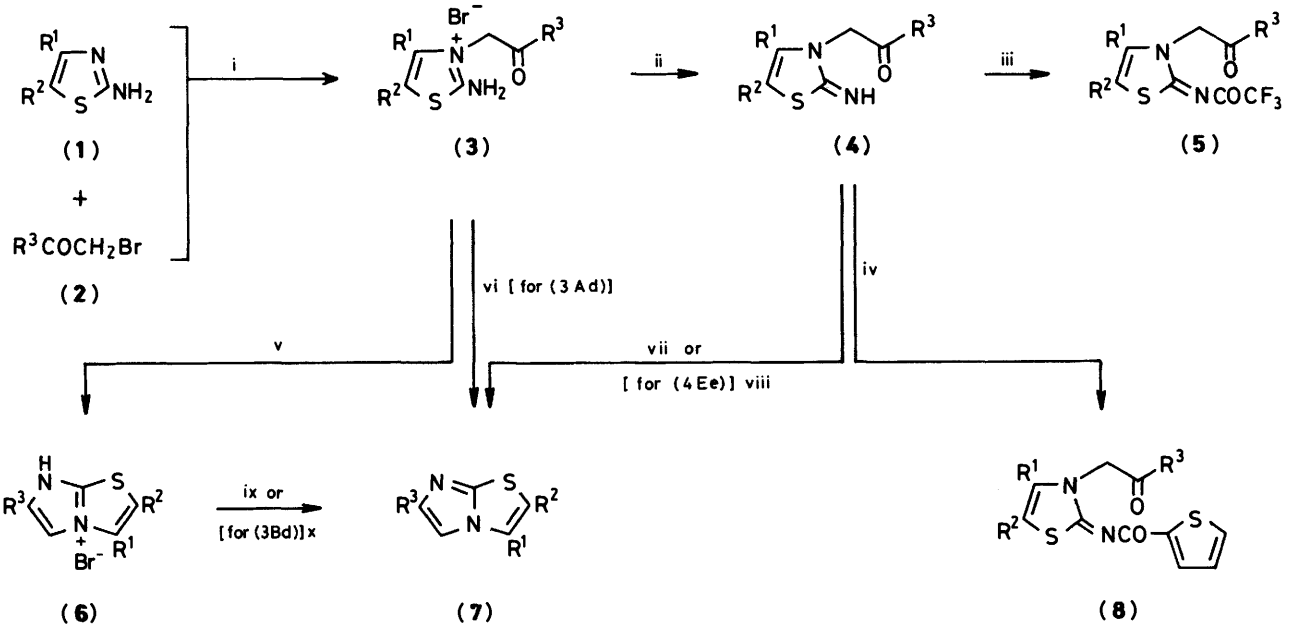
The amines (**1A**—**E**) are known compounds;[5] the amine (**1F**), whose preparation was inadvertently omitted from a paper[6] dealing with its derivatives, was obtained as follows. 2-Chloro-3-phenylpropanal[9] (10.1 g) was added during 15 min to a stirred

Scheme 1. Imidazo[2,1-*b*]thiazoles from 2-aminothiazoles and α-bromo ketones



(1) (7)

Reaction at *endo-N*



(1) + R^3COCH_2Br (2) (3) (4) (5) (6) (7) (8)

Reagents: i, Me_2CO or $CHCl_3$, 20 °C, or THF, 50 °C; ii, $NaHCO_3$–H_2O–$CHCl_3$, 20 °C; iii, $(CF_3CO)_2O$–PhMe, 20 °C; iv, 2-ThienylCOCl–C_5H_5N, 20 °C; v, EtOH or MeOH, heat; vi, $HCONMe_2$, 120 °C; vii, EtOH, 78 °C; viii, PhMe, 110 °C; ix, Na_2CO_3; x, KOH–EtOH

Compounds	A	B	C	D	E	F
R^1	H	Me	CH_2CO_2Et	$PhCH_2$	H	H
R^2	H	H	H	H	Et	$PhCH_2$
Compounds	a	b	c	d	e	f
R^3	Ph	C_6H_4F-*p*	C_6H_4Br-*p*	$C_6H_4NO_2$-*p*	2-Thienyl	Me

Compounds prepared (references are given to known compounds; the rest are new)

(3)	Aa[a]	Ab[b]	Ad[c]	Af	Ba	Bd	Bf	Ca	Dc	Ea	Ee	Ef	Fb
(4)	Aa				Ba			Ca	Dc	Ea	Ee		Fb
(5)	Aa				Ba			Ca	Dc	Ea	Ee		
(6)	Aa[a,d]	Ab		Af	Ba[d,e]	Bd	Bf	Ca		Ea		Ef	
(7)	Aa[a,d]	Ab	Ad	Af[d]	Ba[d,e]	Bd	Bf[d]	Ca		Ea	Ee	Ef	
(8)	Aa							Ca		Ea	Ee		

[a] Ref. 2. [b] Ref. 5. [c] Not fully characterised. [d] Ref. 3. [e] Ref. 1

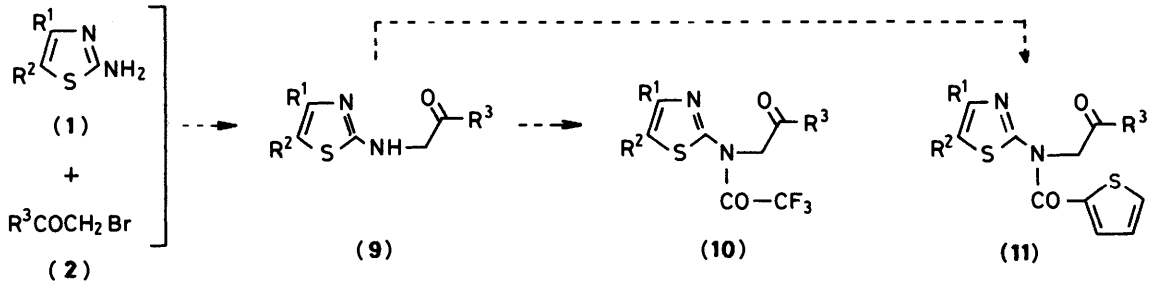
suspension of dry $MgSO_4$ (10 g) in a solution of thiourea (4.51 g) in Me_2CO (50 ml) which was boiled under reflux during the addition and then for a further 2 h. The mixture was diluted with ice–water (150 ml), basified with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, and then extracted with 5M HCl. Basification of the acid solution, and extraction with $CHCl_3$ afforded *2-amino-5-benzylthiazole* (**1F**) (8.68 g), m.p. 110—112 °C (from $CHCl_3$) (Found: C, 63.1; H, 5.3; N, 14.9. $C_{10}H_{10}N_2S$ requires C, 63.1; H, 5.3; N, 14.7%); *m/z* 190 (M^+, 100%).

General procedures are illustrated by the preparations of the series (**3Aa**)—(**8Aa**); analogues are listed after each preparation, and variations from the general procedures are noted under the individual products. An abbreviated form is used in reporting the products' characteristics. Thus a standard entry such as *2-amino-4-methyl-3-phenylacylthiazolium bromide* (**3Ba**) (yield 81%), m.p. 211—212 °C (from EtOH) (Found: C, 45.8; H, 4.1; N, 9.1. $C_{12}H_{13}BrN_2OS$ requires C, 46.0; H, 4.2; N, 8.9%) is shortened to (**3Ba**) (81), m.p. 211—212 (EtOH) (45.8, 4.2, 8.9. $C_{12}H_{13}BrN_2OS$, 46.0, 4.2, 8.9). Full characterisations of the products are recorded elsewhere.[10]

The Thiazolium Salts (**3**).—A solution of $PhCOCH_2Br$ (7.96 g) in Me_2CO (30 ml) was added during 30 min to a stirred

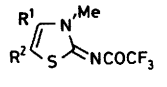
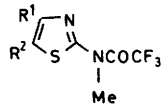
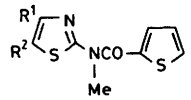
Scheme 2. Verification of reaction at *endo-N* of 2-aminothiazoles (Scheme 1)

Alternative structures, reaction at *exo-N*



Comparison of i.r. C=O bonds ($\nu_{max.}$/cm^{-1}) (for solutions in $CHCl_3$)

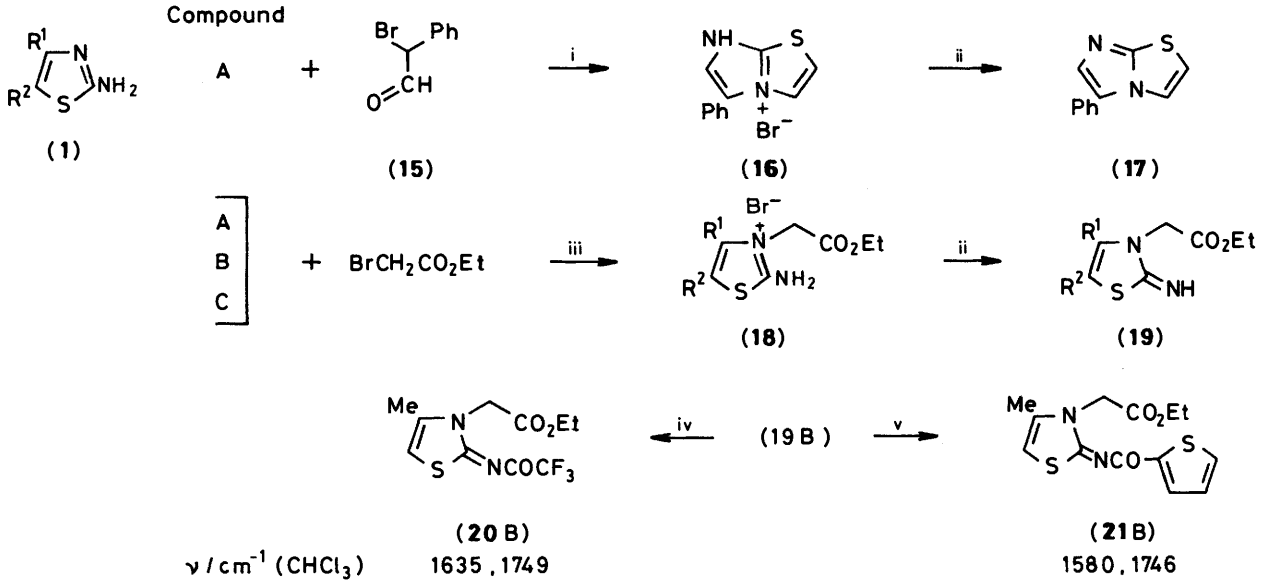
Letters denoting R^1 and R^2 groups are as Scheme 1. Compounds (**12**), (**13**), and (**14**) are models for structures (**5**), (**10**), (**11**), respectively.

	Compound	ν	Compound	ν(CF$_3$CO)	ν(R^{3}CO)	
 (12)	**B**[a]	1 633	(5) **Aa**	1 630	1 700	(1 730, CO_2Et)
	D	1 635	**Ba**	1 630	1 700	
	E[a]	1 632	**Ca**	1 630	1 700	
	F[a]	1 632	**Dc**	1 635	1 704	
			Ea	1 632	1 702	
 (13)	**B**[a]	1 690	**Ee**	1 632	1 680	
	E[a]	1 690	**Fb**	1 632	1 706	
				ν(Thienyl-CO)	ν(R^{3}CO)	
 (14)	**A**	1 625	(8) **Aa**	1 580	1 702	(1 730, CO_2Et)
	B	1 625	**Ba**	1 580	1 705	
	E	1 624	**Ca**	1 580	1 700	
			Ea	1 580	1 703	
			Ee	1 584	1 678	

[a] Ref. 6.

Scheme 3. Related reactions of 2-aminothiazoles

Letters denoting R^1 and R^2 groups are as in Scheme 1.



Reagents: i, THF, 20 °C; ii, $NaHCO_3$–H_2O–$CHCl_3$, 20 °C; iii, Me_2CO, 20 °C; iv, $(CF_3CO)_2O$–PhMe, 20 °C; v, 2-ThienylCOCl–C_5H_5N, 20 °C

Table. ^{1}H N.m.r. spectra of imidazo[2,1-*b*]thiazoles

Positions (δ values, solutions in $CDCl_3$) of signals, singlets unless shown otherwise

Compound	(7Aa)	(7Ab)	(7Af)	(7Ba)	(7Bd)	7(Bf)	(7Ca)	(7Ea)	(7Ee)	(7Ef)	(15)
2-H	6.83[a]	6.84[a]	6.75[a]	6.41[b]	6.52[b]	6.33[b]	6.71[b]				6.92[a]
3-H	7.46[a]	7.46[a]	7.33[a]					7.15[c]	7.11	7.04[c]	7.68[a]
5-H	7.75	7.70	7.20	7.63	7.78	7.09[b]	7.69	7.63	7.53	7.06[b]	(7.53, 6-H)

[a] *d*, *J ca.* 4.5 Hz. [b] Split by small coupling (*J ca.* 0.9 Hz) to neighbouring Me. [c] t, *J* 1.3 Hz).

Substituent shifts of 2-H (basic value 6.72), 3-H (7.33), and 5-H (7.23) signals

Substituent	2-Et	3-Me	3-CH_2CO_2Et	6-Me	6-Ph	6-C_6H_4F-*p*	6-$C_6H_4NO_2$-*p*	2-Thienyl
2-H		−0.42	−0.12	+0.03	+0.11	+0.12	+0.22	+0.08
3-H	−0.30			0.00	+0.13	+0.13	*ca.* +0.2[d]	
5-H	−0.13	−0.11	−0.06	−0.03	+0.52	+0.47	+0.67	+0.43

[d] Assessed from spectrum of compound (**7Ad**) in $(CD_3)_2SO$.

solution of 2-aminothiazole (4.01 g) in Me_2CO (30 ml) at 20 °C, and stirring was continued for 1 d. The precipitate was collected, washed with cold Me_2CO, and crystallised from MeOH to give 2-amino-3-phenacylthiazolium bromide (**3Aa**) (9.71 g), m.p. 186—188 (lit.,[2] 197—198); δ 5.81 (2 H, s, CH_2); $\nu_{max.}$ 1 687 cm^{-1}; *m/z* (f.a.b.), 219 [$(M - Br)^+$, 100%].

Analogues (prepared in Me_2CO unless otherwise stated): 2-Amino-3-*p*-fluorobenzoylmethylthiazolium bromide (**3Ab**) (prepared in THF at 50 °C) (79), m.p. 236—237 (lit.,[11] 235—237) (MeOH). 2-Amino-3-*p*-nitrobenzoylmethylthiazolium bromide (**3Ad**) (83), m.p. 260—270 (decomp.). 3-*Acetonyl*-2-*aminothiazolium bromide* (**3Af**) (prepared from filtered solutions of the reactants in Me_2CO, followed by copious washing of the product with cold Me_2CO and prolonged drying over P_2O_5 at 20 °C/3 mmHg) (81), m.p. 139—140 (30.5, 3.8, 11.7. $C_6H_9BrN_2OS$, 30.43, 3.8, 11.8). Product (**3Ba**), see entry in earlier section about abbreviated form. 2-*Amino*-4-*methyl*-3-p-*nitrobenzoylmethylthiazolium bromide* (**3Bd**) [prepared as for the salt (**3Af**)] (82), m.p. 265—270 (decomp.) (40.3, 3.3, 11.8. $C_{12}H_{12}BrN_3O_3S$, 40.2, 3.4, 11.7). 3-*Acetonyl*-2-*amino*-4-*methylthiazolium bromide* (**3Bf**) [prepared as for the salt (**3Af**)] (86), m.p. 235—238 (33.6, 4.3, 11.2. $C_7H_{11}N_2OS$, 33.5; 4.4, 11.15). 2-*Amino*-4-*ethoxycarbonylmethyl*-3-*phenacylthiazolium bromide* (**3Ca**) (79), m.p. 148—149 (EtOH) (46.8, 4.4, 7.1. $C_{15}H_{17}BrN_2OS$, 46.75; 4.4, 7.3). 2-*Amino*-4-*benzyl*-3-p-*bromophenacylthiazolium bromide* (**3Dc**) (prepared in THF at 50 °C) (80), m.p. 253—255 (MeOH) (46.4, 3.5, 6.0. $C_{18}H_{16}Br_2N_2OS$, 46.2, 3.4, 6.0). 2-*Amino*-5-*ethyl*-3-*phenacylthiazolium bromide* (**3Ea**) (prepared in $CHCl_3$ at 20 °C) (78), m.p. 170—172 (EtOH) (47.95, 4.8, 8.7. $C_{13}H_{15}BrN_2OS$, 47.7, 4.6, 8.55). 2-*Amino*-5-*ethyl*-3-(2-*thenoylmethyl*)*thiazolium bromide* (**3Ee**) (prepared in $CHCl_3$ at 20 °C) (73), m.p. 173—174 (EtOH), (39.6, 3.8, 8.2. $C_{11}H_{13}BrN_2OS_2$, 39.6, 3.9, 8.4). 3-*Acetonyl*-2-*amino*-5-*ethylthiazolium bromide* (**3Ef**) [prepared as for the salt (**3Af**)] (79), m.p. 126—127 (36.1, 4.9, 10.3. $C_8H_{13}BrN_2OS$, 36.2, 4.9, 10.6). 2-*Amino*-5-*benzyl*-3-p-*fluorophenacylthiazolium bromide* (**3Fb**) (prepared in THF at 50 °C) (83), m.p. 179—180 (Pr^iOH) (53.0, 4.0, 6.8. $C_{18}H_{16}FBrN_2OS$, 53.1, 4.0, 6.9).

The Imines (**4**).—A suspension of 2-amino-3-phenacylthiazolium bromide (**3Aa**) (4.05 g) in 1M $NaHCO_3$ (100 ml)–$CHCl_3$ (100 ml) was stirred vigorously at 20 °C for 20 min. The aqueous layer was extracted with more $CHCl_3$; the $CHCl_3$ solutions were combined, washed with brine, dried, filtered, and concentrated at 20 °C/15 mm to a volume of *ca.* 8 ml. Petroleum (60 ml) was added and the solution was concentrated (on a Rotovac, without external heating or cooling) at 15 mmHg for *ca.* 30 min, during which time crystalline material was deposited. This was collected and dried to give 2-*imino*-3-*phenacyl*-2,3-*dihydrothiazole* (**4Aa**) (2.91 g), m.p. 105—106 (60.4, 4.8, 12.6. $C_{11}H_{10}N_2OS$, 60.5, 4.6, 12.8); δ 5.21 (2 H, s, CH_2), 6.01 (1 H, d, *J* 4.5 Hz, 5-H), and 6.73 (1 H, d, *J* 4.5 Hz, 4-H); $\nu_{max.}$ 3 345 (NH), 1 704 (CO), and 1 590 (CN) cm^{-1}; *m/z* (c.i.) 219 [$(M + 1)^+$, 100%].

Analogues: 2-*Imino*-4-*methyl*-3-*phenacyl*-2,3-*dihydrothiazole* (**4Ba**) (76), m.p. 96—98 (62.2, 5.0, 11.9. $C_{12}H_{12}N_2OS$, 62.0, 5.2, 12.1). 4-*Ethoxycarbonylmethyl*-2-*imino*-3-*phenacyl*-2,3-*dihydrothiazole* (**4Ca**) (59), m.p. 62—64 (59.4, 5.4, 9.0. $C_{15}H_{16}N_2S$, 59.2, 5.3, 9.2), $\nu_{max.}$ 1 734, 1 708, and 1 594 cm^{-1}. 4-*Benzyl*-3-p-*bromophenacyl*-2-*imino*-2,3-*dihydrothiazole* (**4Dc**) (72), m.p. 148—149 (low temperature crystallisation from MeOH) (55.7, 4.0, 7.2. $C_{18}H_{15}BrN_2OS$, 55.8, 3.9, 7.2). 5-*Ethyl*-2-*imino*-3-*phenacyl*-2,3-*dihydrothiazole* (**4Ea**) (80), m.p. 142—143 (63.6, 5.8, 11.65. $C_{13}H_{14}N_2OS$, 63.4, 5.75, 11.4). 5-*Ethyl*-2-*imino*-3-(2-*thenoylmethyl*)-2,3-*dihydrothiazole* (**4Ee**) (81), m.p. 84—85 (52.2, 4.8, 11.0. $C_{11}H_{12}N_2OS_2$, 52.35, 4.8, 11.1). 5-*Benzyl*-3-*p*-*fluorophenacyl*-2-*imino*-2,3-*dihydrothiazole* (**4Fb**) (78), m.p. 119—120 (low temperature crystallisation from MeOH) (66.0, 4.7, 8.7. $C_{18}H_{15}FN_2OS$, 66.3, 4.6, 8.6).

The Trifluoroacetylimines (**5**).—Trifluoroacetic anhydride (2.05 g) was added to a stirred solution of the imine (**4Aa**) (1.02 g) in dry PhMe (25 ml) at 20 °C. After 2 d the solution was poured into brine (50 ml)–$CHCl_3$ (50 ml), and the mixture was basified to pH 9 with 1M $NaHCO_3$. Extraction of the aqueous layer with more $CHCl_3$, and work-up of the combined $CHCl_3$ solutions gave 3-*phenacyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**5Aa**) (1.15 g), m.p. 146—147 ($CHCl_3$–petroleum) (49.9, 2.75, 8.8. $C_{13}H_9F_3N_2O_2S$, 49.7, 2.9, 8.9); *m/z* 314 (M^+, 12%), 245 (47), 105 (100), and 77 (46); $\nu_{max.}$ in Scheme 2.

Analogues: 4-*Methyl*-3-*phenacyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**5Ba**) (76), 169—170 (petroleum) (51.0, 3.3, 8.6. $C_{14}H_{11}F_3N_2O_2S$, 51.2, 3.4, 8.6); *m/z* 328 (M^+, 31%), 259 (7), and 105 (100). 4-*Ethoxycarbonylmethyl*-3-*phenacyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**5Ca**) (58), 118—120 (petroleum) (51.1, 3.7, 7.1. $C_{17}H_{15}F_3N_2O_4S$, 51.0, 3.8, 7.0); *m/z* 400 (M^+, 60%), 331 (75), and 105 (100). 4-*Benzyl*-3-p-*bromophenacyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**5Dc**) (79), 194—196 (EtOH) (49.7, 3.0, 5.7. $C_{20}H_{14}BrF_3N_2O_2S$, 49.7, 2.9, 5.8); *m/z* 483 (M^+, 50%) 414 (50), and 183 (100%). 5-*Ethyl*-3-*phenacyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**5Ea**) (65), 131—132 ($CHCl_3$–petroleum) (52.75, 3.75, 8.3. $C_{15}H_{13}F_3N_2O_2S$, 52.6, 3.85, 8.2); *m/z* 342 (M^+, 31%), 273 (100), and 105 (87). 5-*Ethyl*-3-(2-*thenoylmethyl*)-2-*trifluoroacetylimino*-2,3-

dihydrothiazole (**5Ea**) (65), 131—132 ($CHCl_3$–petroleum) (52.75, 3.75, 8.3. $C_{15}H_{13}F_3N_2O_2S$, 52.6, 3.85, 8.2); *m/z* 342 (M^+, 31%), 273 (100), and 105 (87). 5-*Ethyl*-3-(2-*thenoylmethyl*)-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**5Ee**) (69), m.p. 106—107 ($CHCl_3$–petroleum) (44.9, 3.2, 7.8. $C_{13}H_{11}F_3N_2O_2S_2$, 44.8, 3.2, 8.05); *m/z* (c.i.) 349 [$(M + 1)^+$, 100%] and 279 (42).

The 2-Thenoylimines (**8**).—Thiophene-2-carbonyl chloride (0.68 g) was added to a stirred solution of the imine (**4Aa**) (1.01 g) in dry pyridine (10 ml) at 20 °C. After 2 d the solution was poured into ice–water (40 ml), and extracted with AcOEt. CCl_4 (50 ml) was added to the material so obtained, and the mixture was evaporated at 80 °C/15 mmHg. The evaporation with CCl_4 was repeated, and the residue was crystallised from EtOH to give 3-*phenacyl*-2-(2-*thenoylimino*)-2,3-*dihydrothiazole* (**8Aa**) (1.11 g), m.p. 161—162 (58.4, 3.5, 8.4. $C_{16}H_{12}N_2O_2S_2$, 58.5, 3.7, 8.5); δ 5.70 (2 H, s, CH_2), 6.76 and 7.06 (each 1 H, d, *J* 4.5 Hz, thiazole 5-H and 4-H respectively, 7.03, 7.38, and 7.78 (each 1 H, d of d, *J* 4.7 and 4.3, 4.7 and 0.9, 4.3 and 0.9 Hz, thiophene 4-H, 3-H, and 5-H), 7.58 (2 H, t), 7.70 (1 H, t), and 8.10 (2 H, d) (all *J* values 7.9 Hz, phenyl 3-H and 5-H, 4-H, and 2-H, and 6-H); $\nu_{max.}$ in Scheme 2.

Analogues: 4-*Ethoxycarbonylmethyl*-3-*phenacyl*-2-(2-*thenoylimino*)-2,3-*dihydrothiazole* (**8Ca**) (69), m.p. 123—125 (EtOH) (57.9, 4.2, 6.8. $C_{20}H_{18}N_2O_4S_2$, 57.95, 4.4, 6.8). 5-*Ethyl*-3-*phenacyl*-2-(2-*thenoylimino*)-2,3-*dihydrothiazole* (**8Ea**) (71), m.p. 145—146 ($CHCl_3$–petroleum) (60.65, 4.4, 7.7. $C_{18}H_{16}N_2O_2S_2$, 60.65, 4.5, 7.85). 5-*Ethyl*-2-(2-*thenoylimino*)-3-(2-*thenoylmethyl*)-2,3-*dihydrothiazole* (**8Ee**) (67), m.p. 136—137 ($CHCl_3$–*petroleum*) (53.1, 4.0, 7.7. $C_{16}H_{14}N_2O_2S_3$, 53.0, 3.9, 7.7).

The Imidazothiazolium Salts (**6**).—A solution of 2-amino-3-phenacylthiazolium bromide (**3Aa**) (5.25 g) in MeOH (150 ml) was boiled under reflux for 3 h, concentrated at 80 °C to *ca.* 50 ml, filtered, and cooled slowly. Collection of the crystalline material gave 6-phenyl-7*H*-imidazo[2.1-*b*]thiazolium bromide (**6Aa**) (4.05 g), m.p. 125—127 (lit.,[2] 123—124); δ[$(CD_3)_2SO$] 7.55, 8.16 (each 1 H, d, *J* 4.7 Hz), and 8.47 (1 H, s) (2-H, 3-H, and 5-H, respectively), and 7.39 (1 H, t), 7.50 (2 H, t), and 7.82 (2 H, d) (*J* values 7.4 Hz, phenyl 4-H, 3-H and 5-H, and 2-H and 6-H); *m/z* (f.a.b.) 201 [$(M - Br)^+$, 100%].

Analogues: 6-p-*Fluorophenyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Ab**) (87), m.p. 222—223 (MeOH) (60.1, 3.8, 12.9. $C_{11}H_7BrFN_2S$, 60.3, 3.7, 12.8); *m/z* 219 (100%). 6-*Methyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Af**) (84), m.p. 170—171 (EtOH) (33.0, 3.1, 12.85. $C_6H_7BrN_2S$, 32.9, 3.2, 12.8); *m/z* 139 (100%). 3-Methyl-6-phenyl-7*H*-imidazo[2.1-*b*]thiazolium bromide (**6Ba**) (90), m.p. 223—225 (lit.,[1] 198—224, and lit.,[3] 310) (MeOH); *m/z* 215 (100%). 3-*Methyl*-6-p-*nitrophenyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Bd**) (88), m.p. >250 (MeOH) (42.5, 3.2, 12.1. $C_{12}H_{10}BrN_3O_2S$, 42.4, 3.0, 12.35); *m/z* 260 (100%). 3,6-*Dimethyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Bf**) (87), m.p. >250 (MeOH) (36.2, 3.8, 11.9. $C_7H_9BrN_2S$, 36.1, 3.9, 12.0); *m/z* 153 (100%). 3-*Ethoxycarbonylmethyl*-6-*phenyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Ca**) (85), m.p. 165—166 ($CHCl_3$) (48.9, 4.2, 7.6. $C_{15}H_{15}BrN_2O_2S$, 49.05, 4.1, 7.6); *m/z* 287 (100%). 2-*Ethyl*-6-*phenyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Ea**) (80), m.p. 122—123 (EtOH) (50.4, 4.3, 9.1. $C_{13}H_{13}BrN_2S$, 50.5, 4.25, 9.05); *m/z* 229 (100%). 2-*Ethyl*-6-*methyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**6Ef**) (84), m.p. 126—127 (EtOH) (38.8, 4.4, 11.1. $C_9H_{11}BrN_2S$, 38.9, 4.5, 11.35); *m/z* 167 (100%).

The Imidazo[2,1-b]*thiazoles.*—(a) *From the salts* (**6**). A solution of 6-phenyl-7*H*-imidazo[2,1-*b*]thiazolium bromide (**6Aa**) (3.24 g) in 2M Na_2CO_3 (60 ml) –$CHCl_3$ (60ml) was stirred vigorously at 20 °C for 20 min. Extraction of the aqueous layer with more $CHCl_3$, and work-up of the combined $CHCl_3$ solutions gave 6-phenylimidazo[2,1-*b*]thiazole (**7Aa**) (1.95 g), m.p. 146—147 (lit.,[2] 145—146), and lit.,[3] 144—145 (from $CHCl_3$–petroleum); *m/z* (c.i.) 200 (M^+, 100%); ^{1}H n.m.r. signals (of all imidazothiazoles) in Table 1.

Analogues prepared similarly: 6-p-*Fluorophenylimidazo*-[2,1-b]*thiazole* (**7Ab**) (84), m.p. 99—100 ($CHCl_3$–petroleum) (60.4, 3.2, 12.8. $C_{11}H_7FN_2S$, 60.5, 3.2, 12.8); *m/z* 218 (100%). 6-Methylimidazo[2,1-*b*]thiazole (**7Af**) (79), b.p. 106—107/3 mmHg (lit.,[3] 83—85/0.1 mmHg); *m/z* 138 (100%). 3-Methyl-6-phenyl-imidazo[2,1-*b*]thiazole (**7Ba**) (80), m.p. 113—114 (lit.,[1] 113.5, and lit.,[3] 112—113.3) (petroleum); *m/z* 214 (100%). 3,6-Dimethylimidazo[2,1-*b*]thiazole (**7Bf**) (84), b.p. 115—117/3 mmHg (lit.,[3] 86—88/0.35 mmHg), m.p. 63—64 (lit.,[3] 96—97); *m/z* 152 (100%). 3-*Ethoxycarbonylmethyl*-6-*phenylimidazo*[2,1-b]*thiazole* (**7Ca**) (73), m.p. 71—72 (petroleum) (62.7, 4.8, 10.0. $C_{15}H_{14}N_2O_2S$, 62.9, 4.9, 9.8); *m/z* (c.i.) 287 (100%). 2-*Ethyl*-6-*phenylimidazo*[2,1-b]*thiazole* (**7Ea**) (88), m.p. 125—127 ($CHCl_3$–petroleum) (68.25, 5.2, 12.1. $C_{13}H_{12}N_1S$, 68.4, 5.3, 12.25); *m/z* 228 (100%). 2-*Ethyl*-6-*methylimidazo*[2,1-b]*thiazole* (**7Ef**) (87), b.p. 86—88/0.4 mmHg (57.8, 5.85, 16.9. $C_8H_{10}N_2S$, 57.8, 6.05, 16.85); *m/z* (c.i.) 167 (100%).

A solution of KOH (0.51 g) in EtOH (10 ml) was added to a stirred solution of 3-methyl-6-*p*-nitrophenyl-7*H*-imidazo-[2,1-*b*]thiazolium bromide (2.95 g) in EtOH (150 m l) at 20 °C. After 30 min the solvent was removed at 40 °C/15 mmHg, and the residue was boiled with AcOEt (100 ml). Filtration of the hot solution, concentration of the filtrate to *ca.* 20 ml, and slow cooling of the solution gave 3-*methyl*-6-p-*nitrophenylimidazo*-[2,1-b]*thiazole* (**7Bd**) (1.61 g), m.p. 240—242 (55.4, 3.5, 16.3. $C_{12}H_9N_3O_3S$, 55.6, 3.5, 16.2); *m/z* (c.i.) 260 [$(M + 1)^+$, 100%].

(b) *From the salt* (**3Ad**). A solution of 2-amino-3-*p*-nitrobenzoylmethylthiazolium bromide (**3Ad**) (10.07 g) in dimethylformamide (200 ml) was kept at 120 °C for 15 min, filtered, and cooled slowly. The yellow crystalline product was collected, washed with dimethylformamide and then acetone, and dried to give 6-p-*nitrophenylimidazo*[2,1-b]*thiazole* (**7Ad**) (6.25 g), m.p. >250 (54.0, 2.75, 17.2. $C_{11}H_7N_3O_2S$, 53.9, 2.9, 17.1); δ[$(CD_3)_2SO$] 7.35 (1 H, d, *J* 4.5 Hz, 2-H), 8.00 (1 H, d, *J* 4.5 Hz, 3-H), and 8.52 (1 H, s, 5-H); *m/z* 245 (M^+, 100%) and 199 (41).

(c) *From the imines* (**4**). A solution of 2-imino-3-phenacyl-2,3-dihydrothiazole (**4Aa**) (1.62 g) in EtOH (100 ml) was boiled under reflux for 1 h. Evaporation afforded 6-phenylimidazo-[2,1-*b*]thiazole (**7Aa**) (1.25 g), m.p. and mixed m.p. 145—146. Similarly the imines (**4Ba**), (**4Ca**), and (**4Ea**) gave the imidazothiazoles (**7Ba**), (**7Ca**), and (**7Ea**) in yields of 80—85%.

A solution of 5-ethyl-2-imino-3-(2-thenoylmethyl)-2,3-dihydrothiazole (**4Ee**) in EtOH was refluxed for 2 h. The residue obtained by evaporation was shown by ^{1}H n.m.r. to consist largely of the starting material. A solution of the imine (**4Ee**) (2.06 g) in PhMe (80 ml) was boiled under reflux for 4 h, and then evaporated at 100 °C/15 mmHg). The residue was dissolved in $CHCl_3$, and treated with activated charcoal. Evaporation, and crystallisation from $CHCl_3$–petroleum gave 2-*ethyl*-6-(2-*thienyl*)*imidazo*[2,1-b]*thiazole* (**7Ee**) (1.08 g), m.p. 116—118 (56.3, 4.35, 11.9. $C_{11}H_{10}N_2S_2$, 56.4, 4.3, 11.95); *m/z* (M^+, 100%) and 129 (48).

The Trifluoroacetylimine (**12D**).—A mixture of 2-amino-4-benzylthiazole (**1D**) (3.92 g) and MeI (4.2 g) was stirred at 50 °C for 2 h, and then evaporated at 15 mmHg. The material so obtained crystallised from MeOH to give 2-*amino*-4-*benzyl*-3-*methylthiazolium iodide* (5.52 g), m.p. 190—191 (40.1, 4.2, 8.35. $C_{11}H_{13}IN_2S$, 39.8, 3.9, 8.4). This salt (3.35 g) was stirred vigorously with 2M NaOH (100 ml) at 20 °C for 1 h. Isolation with $CHCl_3$, gave a product (1.58 g) [δ 3.15 (3 H, s, NMe), 3.62 (2 H, s, CH_2), 5.35 (1 H, s, 5-H), 6.17 (1 H, C=NH), and 7.28 (5 H, s, Ph)] formulated as 4-benzyl-2-imino-3-methyl-2,3-dihydrothiazole; this on treatment with trifluoroacetate anhydride as described for the products (**5**), afforded 4-*benzyl*-

3-*methyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**12D**) (1.92 g), m.p. 137—139 (Pr^iOH) (52.1, 3.6, 9.3. $C_{13}H_{11}F_3N_2OS$, 52.0, 3.7, 9.3); *m/z* 300 (M^+, 15%) and 231.

5-*Phenylimidazo*[2,1-b]*thiazole* (**17**).—A solution of Br_2 (20.2 g) in dry CH_2Cl_2 (20 ml) was added during 1 h in to a stirred solution of phenylacetaldehyde (distilled immediately before use, b.p. 58—60 °C/3 mmHg; 15.1 g) in dioxane (100 ml)–CH_2Cl_2 (100 ml) at 0 °C. A solution of $NaHCO_3$ (15 g) in water (100 ml) was added, and stirring was continued for 30 min. The layers were separated, and the aqueous layer was extracted with more CH_2Cl_2 (100 ml). The CH_2Cl_2 solutions were combined, washed with brine (×3), and dried ($MgSO_4$). Removal of solvent at 20 °C/15 mmHg gave material (17.6 g) shown by ^1H n.m.r. examination to be 2-bromo-2-phenylethanal[7] (**15**) [δ 6.02 (1 H, d, CHBr) and 9.32 (1 H, d, CHO)] of 94% purity. A solution of this aldehyde (13.62 g) in dry THF (10 ml) was added during 30 min to a stirred solution of 2-aminothiazole (6.41 g) in THF (25 ml) at 20 °C, and stirring was continued for 1 h. The insoluble material was collected, and washed with a little cold THF. Crystallisation from EtOH gave 5-*phenyl*-7H-*imidazo*[2,1-b]*thiazolium bromide* (**16**) (6.62 g), m.p. 240—241 (47.1, 3.1, 9.9. $C_{11}H_9BrN_2S$, 47.0, 3.2, 10.0); δ[$(CD_3)_2SO$] 7.70 (1 H, d, *J* 4.5, 2-H), 8.03 (1 H, s, 6-H), and 8.41 (1 H, d, *J* 4.5, 3-H); *m/z* (f.a.b.) 201 [$(M - Br)^+$, 100%]. Basification of the foregoing salt (2.15 g) by the general procedure ($NaHCO_3$) gave 5-*phenylimidazo*[2,1-b]*thiazole* (**15**) (1.25 g), b.p. 141—143/15 mmHg, m.p. 87—88 (66.1, 3.9, 13.9. $C_{11}H_8N_2S$, 66.0, 4.0, 14.0); *m/z* 200 (M^+, 100%).

Products from 2-*Aminothiazoles and Ethyl Bromoacetate*.—The compounds shown in Scheme 3 were obtained using the general procedures described earlier (work in Scheme 1). The products were: 2-*Amino*-3-*ethoxycarbonylmethylthiazolium bromide* (**18A**) (72), m.p. 142—144 (EtOH) (31.6, 4.2, 10.4. $C_7H_{11}BrN_2O_2S$, 31.5, 4.2, 10.5). 2-*Amino*-3-*ethoxycarbonylmethyl*-4-*methylthiazolium bromide* (**18B**) (89), m.p. 168—169 (EtOH) (34.0, 4.6, 10.1. $C_8H_{13}BrN_2O_2S$, 34.2, 4.7, 10.0). 2-*Amino*-3-*ethoxycarbonylmethyl*-5-*ethylthiazolium bromide* (**18E**) (78), m.p. 141—143 (EtOH) (36.55, 5.0, 9.4. $C_9H_{15}BrN_2O_2S$, 36.6, 5.1, 9.5). 3-*Ethoxycarbonylmethyl*-2-*imino*-2,3-*dihydrothiazole* (**19A**) (58), b.p. 97—102 (bath temp.)/3 mmHg, m.p. 64—65 (45.2, 5.3, 15.0. $C_7H_{10}N_2O_2S$, 45.1, 5.4, 15.0); δ 1.31 (3 H, t, *J* 7.2) and 4.25 (2 H, q, *J* 7.2) (CO_2Et), 4.46 (2 H, s, NCH_2), 5.82 (1 H, d, *J* 4.4 Hz, 5-H), and 6.42 (1 H, d, *J* 4.4 Hz, 4-H); $\nu_{max.}$ 1 748 cm^{-1}; *m/z* 186 (M^+, 52%) and 1 145 (100). 3-*Ethoxycarbonylmethyl*-2-*imino*-4-*methyl*-2,3-*dihydrothiazole* (**19B**) (72), b.p. 105—110 (bath temp.)/3 mmHg, m.p. 67—69 (48.1, 6.0, 14.1. $C_8H_{12}N_2O_2S$, 48.0, 6.0, 14.0). 3-*Ethoxycarbonylmethyl*-5-*ethyl*-2-*imino*-2,3-*dihydrothiazole* (**19C**) (65), b.p. 108—111 (bath temp.)/3 mmHg, m.p. 88—90 (50.6, 6.55, 13.0. $C_9H_{14}N_2O_2S$, 50.45, 6.6, 13.1). 3-*Ethoxycarbonylmethyl*-4-*methyl*-2-*trifluoroacetylimino*-2,3-*dihydrothiazole* (**20B**) (76), m.p. 86—87 (petroleum) (40.6, 3.5, 9.3. $C_{10}H_{11}F_3N_2O_3$, 40.5, 3.7, 9.45); $\nu_{max.}$ 1 749 (CO_2Et) and 1 635 cm^{-1} ($COCF_3$); *m/z* 296 (M^+, 31%) and 227 (100). 3-*Ethoxycarbonylmethyl*-4-*methyl*-2-(2-*thenoylimino*)-2,3-*dihydrothiazole* (**21B**) (72), 89—90 (EtOH) (50.5, 4.1, 11.6. $C_{10}H_{10}N_2OS_2$, 50.4, 4.2, 11.75); $\nu_{max.}$ 1 746 (CO_2Et) and 1 580 cm^{-1} (thenoyl); *m/z* (c.i.) 239 [$(M + 1)^+$, 33%] and 148 (100).

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