N,N-Disubstituted 2-Aminothiazole-5-carbaldehydes: Preparation and Investigation of Structural Features

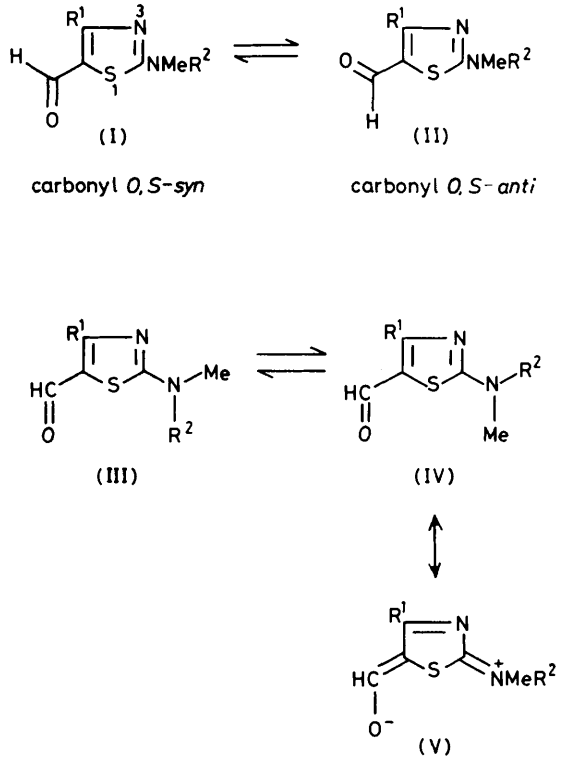
David W. Gillon, Ian J. Forrest, G. Denis Meakins,* Malcolm D. Tirel, and John D. Wallis
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY

Methods for preparing *N,N*-disubstituted 2-aminothiazoles have been investigated. 4-Substituted *N,N*-dimethyl-, *N*-benzyl-*N*-methyl-, and *N*-methyl-*N*-phenyl-amines were prepared and converted by Vilsmeier formylation into 2-amino-5-carbaldehydes which were examined by i.r. and ^{1}H n.m.r. spectrometry. The aldehyde group adopts the carbonyl *O,S-syn*-conformation. With the *N,N*-dimethyl and *N*-benzyl-*N*-methyl compounds the barrier to rotation of the amine group ($\Delta G^{\ddagger}$) is 50—55 kJ mol^{-1} and is insensitive to the nature of the 4-substituent. The amine group of the *N*-methyl-*N*-phenyl compounds has a marked preference for one orientation. This was shown by a crystallographic study of 4-t-butyl-2-(*N*-methyl-*N*-phenylamino)thiazole-5-carbaldehyde to have the phenyl group directed towards the sulphur atom of the thiazole ring.

The results of the physical methods overlap in establishing the importance of a mesomeric interaction between the functional groups of 2-aminothiazole-5-carbaldehydes.

The object of this work was to investigate features arising from the possibility of rotation of the functional groups in *N,N*-disubstituted 2-aminothiazole-5-carbaldehydes. It was thought that a mesomeric effect would operate in these molecules thus stabilising planar forms and thereby facilitating certain spectrometric studies by raising the rotational barriers (However, while pK_a measurements on 2-amino-5-nitrothiazoles indicate mesomeric interaction, the values of the 2-amino-5-carboxylates correspond closely with the figures calculated by assuming independent contributions of the groups.[1]) As with other heterocyclic systems [2] interest in the aldehyde group was concerned with its conformational preference, whether for the *syn*- or the *anti*-carbonyl *O,S*-form (Scheme 1). With regard to rotation of the amino-group, the main intention was to examine the effect of having dissimilar groups as *N*-substituents; the 2-dimethylamino-compounds were to be studied as models, and also to afford values which could be compared with the barrier of 2-dimethylamino-5-nitrothiazole.[3]

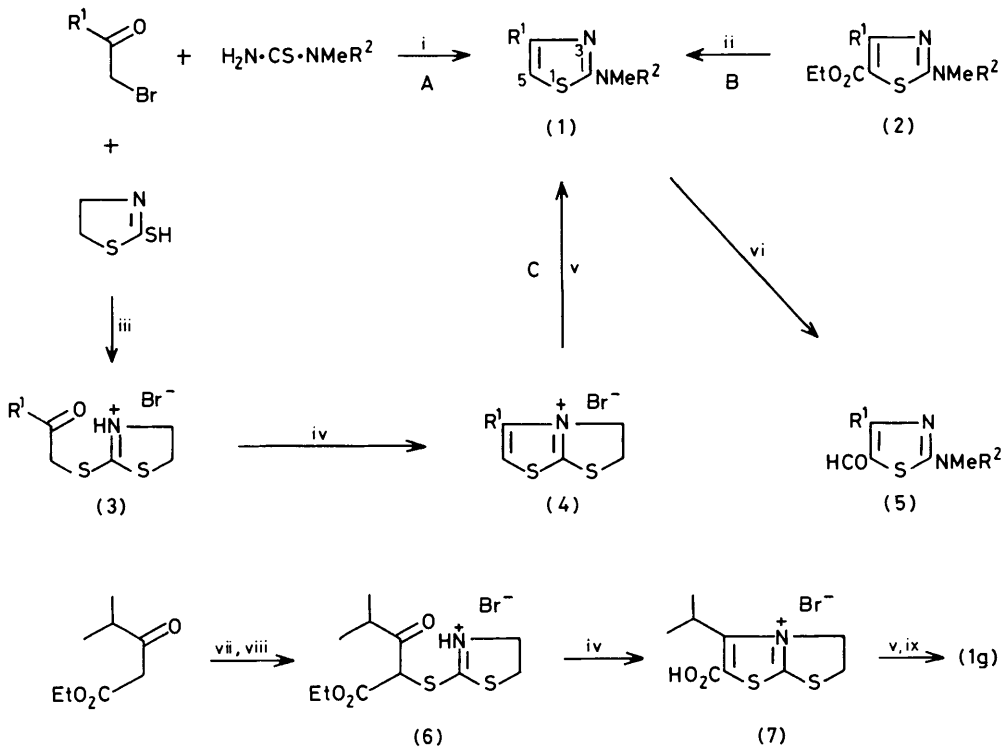
Scheme 2 summarises the preparations of *N,N*-disubstituted 2-aminothiazole-5-carbaldehydes (5). The few such compounds described previously [4] were obtained by Vilsmeier formylation of readily available 2-aminothiazoles, and include the aldehydes (5a—c). In the initial stages of the present work it was shown that this formylation is applicable generally with *N,N*-disubstituted 2-aminothiazoles and the requirement was then to prepare a range of suitable amine substrates. These are formed efficiently by the Hantzsch condensation (method A) which is the preferred route when the appropriate starting materials (an α-bromo-ketone and an *N,N*-disubstituted thiourea) are readily available. However, at the time of this work there was no good general route to *N,N*-disubstituted thioureas.† Some had been obtained by Wallach's method [5] (the addition of hydrogen sulphide to cyanamides) and others (*e.g.* the *N*-methyl-*N*-phenyl compound) by a lengthy procedure involving isomerisation of the substituted ammonium thiocyanates.[6] A newer method, leading to *N*-mono- and *N,N*-di-substituted thioureas,[7] is based on the addition of amines to silicon tetraisothiocyanate. We were able to reproduce the reported results with some amines (dimethylamine, aniline, and *N*-methylaniline) but with others (t-butylamine and benzylamine) the reactions, under a variety of conditions, produced thiocyanate salts rather than thioureas.



Scheme 1. Rotation of groups in 2-aminothiazole-5-carbaldehydes

Attention was therefore turned to a route C not requiring thioureas. Re-examination [8] of the reaction [9] between α-halogeno-ketones and Δ^2-thiazoline-2-thiol showed that, with dimethylformamide as solvent, either the thiazolinium salts (3) or the dihydrothiazolothiazolium salts (4) may be formed from the chloro-derivatives of β-diketones and β-oxo-esters. Further, treatment of the dihydrothiazolothiazolium salts with three secondary amines (dimethylamine, piperidine, and morpholine) led to 2-aminothiazoles. Our experiments established that the bicyclic salts (4) are not formed directly from simple α-bromo-ketones in dimethylformamide; how-

† Such a route (outlined by M. D. Brown, D. W. Gillon, G. D. Meakins, and G. H. Whitham, *J. Chem. Soc., Chem. Commun.*, 1982, 444) was developed subsequently and will be described later.



	R¹	R²	Route to (1) (Yield/%)
a;	H	Me	A(85)
b;	Me	Me	A(86)
c;	Me	Ph	A(84)
d;	Me	$PhCH_2$	A(85)
e;	$PhCH_2$	Me	B(78)
f;	$PhCH_2$	$PhCH_2$	B(76)
g;	Pr^i	Me	A(85), C(40) *
h;	Pr^i	$PhCH_2$	A(87)
i;	Bu^t	Me	A(85)
j;	Bu^t	Ph	A(83)
k;	Bu^t	$PhCH_2$	A(88)
l;	C_6H_4Br-*p*	Me	A(83), C(62)
m;	C_6H_4Br-*p*	$PhCH_2$	A(85)
n;	C_6H_4OH-*p*	Me	C(64)
o;	C_6H_4OMe-*p*	Me	A(85), C(67)
p;	C_6H_4OMe-*p*	$PhCH_2$	A(84)

* Sequence starting from ethyl 4-methyl-3-oxopentanoate.

Scheme 2. Preparation of *N,N*-disubstituted 2-aminothiazole-5-carbaldehydes. *Reagents:* i, EtOH or Me_2CO, heat; ii, 6M-HCl, heat; iii, Me_2CO, 20 °C or heat; iv, 6M-HBr, heat; v, Me_2NH–H_2O–EtOH, 20 °C; vi, $POCl_3$–HCO·NMe_2, 40 °C; vii, Br_2–CCl_4–H_2O; viii, Δ^2-thiazoline-2-thiol–dioxan, 20 °C; ix, $CHCl_3$, heat. [Apart from the amines (1a—c, o) (references are given by R. Barone, M. Chanon, and R. Gallo in 'Thiazole and Its Derivatives,' ed. J. V. Metzger, Wiley, New York, 1979, ch. 6), and the aldehydes (5a—c) [4] all the compounds (1)—(7) are new.]

ever, these salts are obtained in good yield by a two-stage procedure, *viz.*, formation of the thiazolinium salts (3) using a non-polar solvent and cyclisation by the original method.[9] With dimethylamine the salts (4) readily gave 2-dimethylaminothiazoles but, disappointingly, they did not react with *N*-methylaniline or *N*-methylbenzylamine.

The third route **B** involves 2-aminothiazole-5-carboxylates, themselves produced by the Hantzsch reaction. This is useful in certain cases where bromination of an unsymmetrical ketone gives a mixture of bromo-ketones or predominantly the undesired isomer. For example, bromination of ethyl 3-oxo-4-phenylbutanoate [10] (readily obtained by the nitrile variation of the Reformatsky reaction) serves as an equivalent for brominating the methyl group of 1-phenylpropan-2-one.

The main spectrometric characteristics of the aldehydes (5) are summarised in Table 1. All have single carbonyl absorptions, and the solvent shifts (CCl_4 ⟶ MeCN) are of the usual magnitude.[2] While the effects of the 4-substituents are not large they are in the expected direction, as can be seen by the decreasing wavenumber in the series H > Me > Pr^i > Bu^t. The CHO ^{1}H n.m.r. signals are singlets at 305 K and remain as singlets over the temperature range examined [which extends to below the temperature at which aldehyde rotamers of types (I) and (II) (Scheme 1) would be expected to give separate signals [11]]. Thus, there is a general tendency for the aldehyde groups to exist predominantly or exclusively in one arrangement; the observation of nuclear Overhauser enhancements of the CHO signals on irradiation of 4-sub-

Table 1. I.r. and ^{1}H n.m.r. absorptions of the 2-aminothiazole-5-carbaldehydes (5) [a]

Compound	I.r. CO region		^{1}H N.m.r.			Compound	I.r. CO region		^{1}H n.m.r.		
	CCl_4	MeCN	*CHO*	*N*–CH_3	$\Delta G^{\ddagger}$		CCl^4	MeCN	*CHO*	N–CH_3	$\Delta G^{\ddagger}$
(5a)	1 651	1 639	9.64	3.18	55	(5i)	1 634	1 623	10.01	3.12	52
(5b)	1 647	1 636	9.75	3.16	55	(5j)	1 635	1 628	10.04	3.54	
(5c)	1 651	1 638	9.77	3.58		(5k)	1 635	1 624	10.07	3.02	55
(5d)	1 647	1 637	9.78	3.08	53	(5l)	1 638	1 632	9.66	3.21	51
(5e)	1 647	1 636	9.78	3.12	52	(5m)	1 638	1 632	9.70	3.13	54
(5f)	1 648	1 638	9.79	3.01	53	(5n)	1 639	1 630	9.54 [b]	3.14 [b]	
(5g)	1 643	1 632	9.80	3.16	55	(5o)	1 630	1 622	9.59	3.18	53
(5h)	1 644	1 634	9.82	3.06	52	(5p)	1 630	1 622	9.61	3.10	50

Nuclear Overhauser effects on CHO signal

Compound	(5b)	(5c)	(5g)	(5h)	(5i)	(5j)
Group irradiated	4-Me	4-Me	4-Me_2CH	4-Me_2CH	4-Bu^t	4-Bu^t
Signal of group irradiated	2.50s	2.51s	3.38m	3.41m	1.47s	1.45s
Enhancement (%) of CHO signal	6	7	11	15	21	20

[a] I.r. work was carried out as described previously (D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1959); band positions are in cm^{-1} at 303 K; ^{1}H n.m.r. signals (δ values at 305 K) and nuclear Overhauser enhancement effects were recorded using solutions in $CDCl_3$; the CHO, NMe, and NCH_2Ph signals (all singlets) were examined over the range 180—305 K using solutions in CD_2Cl_2. The $\Delta G^{\ddagger}$ values (kJ mol^{-1}) are the activation energies for rotation about the C(2)–N bond at 298 K. [b] In $(CD_3)_2SO$.

stituents (Table 1) suggests that the *O,S-syn*-rotamers (1) are the preferred forms. (4-Substituted thiazole-5-carbaldehydes with a free 2-position, in which the predominance of the *syn*-rotamers is indicated by the occurrence of extended W-coupling between the CHO and the C(2) protons, show similar n.O.e. effects.[12])

At temperatures below *ca.* −20 °C the *N,N*-dimethylamines exhibit two NMe signals (Δν = *ca.* 18 Hz at a source frequency of 90 MHz). Similarly the *N*-benzyl-*N*-methylamines give two pairs of signals (each one NMe and one NCH_2Ph resonance); the components of each pair have the expected intensity ratio (3 : 2) but the relative intensities of the pairs (*ca.* 7 : 3) show that one rotamer [(III) or (IV), Scheme 1] is considerably the more stable. This difference in stability is accentuated in the *N*-methyl-*N*-phenylamines, the NMe signals of which are singlets over the temperature range studied. (It is possible, but extremely unlikely, that the singlets originate from rotational barriers so low that, even at 180 K, the amine groups are rotating too rapidly for the detection of the individual forms by ^{1}H n.m.r. spectrometry.) In view of uncertainties about the probe temperatures (±2 °C) used here the results from the dimethyl- and benzylmethyl-amines were processed by the standard method [13] rather than line-shape analysis techniques.[14,15] (Further, the Δν values are relatively large and this would tend to reduce the difference between the results afforded by the two approaches.[16]) For all the *N,N*-dimethyl and *N*-benzyl-*N*-methyl compounds the barriers to rotation of the 2-amine group are in the range 50—55 kJ mol^{-1}; the lack of sensitivity towards the nature of the 4-substituent accords with the conclusion that the carbonyl-*O* is directed away from the 4-position. Depending upon the degree of mesomeric interaction between the 2- and 5-substituents the thiazole derivatives (5) may be regarded as aromatic aldehydes or as extended amides. The $\Delta G^{\ddagger}$ values bracket the figure (52 kJ mol^{-1}) found for 2-dimethylamino-5-nitrothiazole [3] and fall between those of heterocyclic carbaldehydes (*ca.* 26 kJ mol^{-1}) [15] and *N,N*-dimethylcarboxamides (*ca.* 65 kJ mol^{-1}); [14,17] the values for $HCO{\cdot}NMe_2$ and $HCO.CH{:}CH{\cdot}NMe_2$ (86 and 65 kJ mol^{-1} respectively) [18] are also relevant. Thus the ^{1}H n.m.r. results establish the operation of a marked mesomeric effect, a conclusion supported by comparing the i.r. values with those of 5-carbaldehydes lacking 2-substituents (CO bands at *ca.* 1 675 cm^{-1} in CCl_4 [12]).

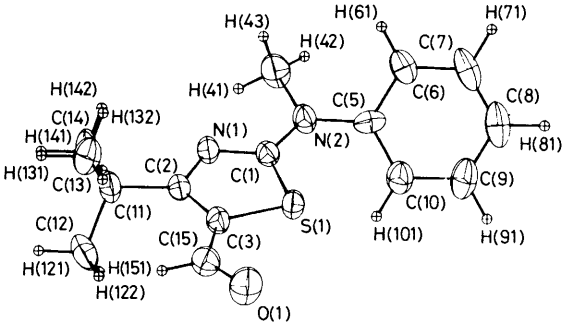
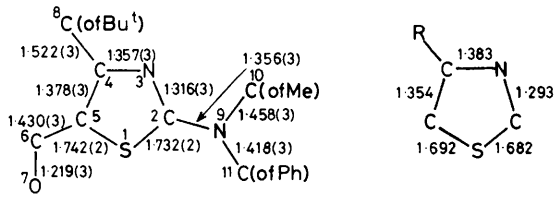


Figure 1. Thermal ellipsoid plot for 4-t-butyl-2-(*N*-methyl-*N*-phenylamino)thiazole-5-carbaldehyde (5j) using SNOOPI (E. K. Davies, ' SNOOPI User Guide,' Chemical Crystallography Laboratory, Oxford University, 1981) with ellipsoids drawn at the 50% probability level

In order to support some of these conclusions and to establish the orientation of the phenyl group in the stable conformation of the *N*-methyl-*N*-phenylamines the aldehyde (5j) was examined by *X*-ray crystallography. This led to the structure shown in Figure 1; some bond lengths and the deviations of various atoms from the plane of the thiazole ring are listed in Figure 2. The phenyl group is directed towards the sulphur rather than the ring nitrogen atom, and is inclined at 47.6° to the thiazole plane. [This orientation is also adopted by the 2-*N*-phenyl group of 4-methyl-5-(*N*-methyl-*N*-phenylamino)-2-(*N*-phenylamino)thiazole, in which the corresponding angle is 48.7°.[19]] In agreement with the spectrometric work the formyl group is seen to be very nearly in plane and to have the *O,S-syn*-conformation. The exocyclic nitrogen atom deviates little (0.044 Å) from the plane containing the carbon atoms attached to it, and this plane is inclined only slightly (at an angle of 7.1°) to the thiazole plane; the nitrogen's lone pair is thus suitably oriented for conjugation with the thiazole system. Comparison between compound (5j) and a reference thiazole (8) [20] with regard to the length of the bonds in the thiazole rings (Figure 2) reveals significant differences, *viz.*, that the 3,4-bond is shorter and the other bonds are longer in the 2-amino-5-carbaldehyde (5j). Further, the C(5)–CO bond



Deviations of atoms from the best plane through the thiazole ring of the 5-carbaldehyde (5j)

Atom	Deviation (Å)	Atom	Deviation (Å)
S(1)	0.005	O(7)	−0.101
C(2)	−0.004	C(8)	0.000
N(3)	0.001	N(9)	−0.040
C(4)	0.003	C(10)	−0.267
C(5)	−0.005	C(11)	−0.012
C(6)	−0.064		

Figure 2. Bond lengths (Å) for 4-t-butyl-2-(*N*-methyl-*N*-phenylamino)thiazole-5-carbaldehyde (5j) and 4-(benzo[*d*]imidazol-2-yl)-thiazole (8) [20]

of compound (5j) is shorter (by 0.043 Å) than the corresponding bond of a simple benzaldehyde.[21] From the crystallographic work it may be concluded that the heterocyclic ring of compound (5j) differs considerably from the standard 6π-electron thiazole system; in compound (5j) the lone pair of the sulphur atom is involved to a much smaller degree and, as suggested by the spectrometric results, canonical form (V) (Scheme 1) representing an extended amide makes an important contribution to the structure.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 521 spectrometer at a spectral slit-width of 1.7 cm^{-1}. The spectrometers (and the irradiating frequencies) used for ^1H n.m.r. work were: Perkin-Elmer R32 (90 MHz) for routine spectra, Bruker WH 90 (90 MHz) for variable temperature work, and Bruker WH 300 (300 MHz) for nuclear Overhauser enhancements. Since the procedures for preparing the individual 2-amines (1) and 5-aldehydes (5) are similar only typical examples are given. The preparations of the 5-esters (2e, f) will be described later. Table 2 shows the characterisation of the series of new compounds (1)—(5).

Reactions of Amines with Silicon Tetraisothiocyanate.—A stream of N_2 was bubbled through 30% aqueous Me_2NH at 30 °C, then through a condenser and a long drying tower (KOH pellets), and into a stirred solution of $Si(NCS)_4$ (10 g) in dry C_6H_6 (100 ml) at 20 °C. After 1 h the gas stream was stopped, the solution was boiled under reflux for 1.5 h, and evaporated at 100 °C/20 mmHg. Pr^iOH (90 ml)–H_2O (10 ml) was added, the mixture was boiled under reflux for 1.5 h, filtered while hot, and evaporated. The residue crystallised from Pr^iOH to give *N,N*-dimethylthiourea (10.1 g), m.p. 158—159 °C (lit.,[5] m.p. 159 °C), *m/z* 104 (M^+, 100%).

Aniline (3.64 ml) was added during 10 min to a stirred solution of $Si(NCS)_4$ (2.6 g) in C_6H_6 (60 ml). Further treatment as in the foregoing experiment gave *N*-phenylthiourea (4.2 g), m.p. 153—154 °C (lit.,[6] m.p. 154 °C), *m/z* 152 (M^+, 32%). Similarly *N*-methylaniline gave *N*-methyl-*N*-phenylthiourea (78%), *m/z* 166 (M^+, 57%).

The reaction between Bu^tNH_2 (dried and freshly distilled) and $Si(NCS)_4$ was carried out as described.[7] Variations investigated included adding the amine very slowly or as a solution in C_6H_6, and changing the time and temperature (20—80 °C) of the first stage, the composition of the Pr^iOH–H_2O mixture used for the hydrolysis, and the time and temperature of the second stage. All experiments gave t-butylammonium thiocyanate (50—80%), m.p. 124—125 °C (lit.,[22] m.p. 123—125 °C), $\nu_{max.}$ 2 040 cm^{-1}, *m/z* 58 (100%). Similarly benzylamine, under a variety of conditions, gave benzylammonium thiocyanate, m.p. 95—96 °C (lit.,[23] m.p. 95—96 °C), $\nu_{max.}$ 2 043 cm^{-1}.

4-(4-*Bromophenyl*)-2-*dimethylaminothiazole* (1l).—(*a*) Route A. A suspension of 4-bromophenacyl bromide (2.88 g) in EtOH (40 ml) was added during 15 min to a solution of *N,N*-dimethylthiourea (1.3 g) in EtOH (20 ml) which was boiling under reflux, and the boiling was continued for a further 2 h. The addition of ice–water (100 ml), basification with 18M-NH_3, and isolation with Et_2O gave the *amine* (1l) (2.43 g after crystallisation from MeOH).

(*b*) Route C. Solutions of 4-bromophenacyl bromide (19 g) in Me_2CO (200 ml) and Δ²-thiazoline-2-thiol (8.3 g) in Me_2CO (100 ml) were mixed at 20 °C and stirred for 30 min. The precipitate was collected, washed with Me_2CO, and dried at 100 °C to give the *thiazolinium bromide* (3l) (24.9 g). A solution of this salt in 6M-HBr (130 ml) was boiled under reflux for 6 h and evaporated at 100 °C/18 mmHg. The residue was washed with Me_2CO and crystallised from MeOH to give the *thiazolium bromide* (4l) (19 g). 25% Aqueous Me_2NH (10 ml) was added to a solution of the foregoing salt (11.8 g) in MeOH (110 ml) at 20 °C and the solution was stirred for 14 h. Evaporation of the solvent, the addition of H_2O, and isolation with $CHCl_3$ gave the amine (1l) (11.9 g after crystallisation from MeOH).

4-*Benzyl*-2-(N-*benzyl*-N-*methylamino*)*thiazole* (1f).—Route B. A solution of ethyl 4-benzyl-2-(*N*-benzyl-*N*-methylamino)-thiazole-5-carboxylate (2f) (11 g) in 6M-HCl (150 ml) was boiled under reflux for 6 h, cooled, and basified with 18M-NH_3. The oil obtained by extraction with $CHCl_3$ was distilled to give the 2-*amine* (1f) (6.6 g).

2-*Dimethylamino*-4-(1-*methylethyl*)*thiazole* (1g).—(*a*) Route A. Bromination of 3-methylbutan-2-one in MeOH by the literature method [24] gave material, b.p. 83—87 °C/50 mmHg, shown by ^1H n.m.r. examination to contain 1-bromo-3-methylbutan-2-one (93%) and the 3-bromo-isomer (7%). Condensation of this material (10 g) with *N,N*-dimethylthiourea (7.2 g) in EtOH [as described for the 2-amine (1l)] and distillation of the product gave the 2-*amine* (1g) (8.1 g).

(*b*) Route C. A solution of Br_2 (6.7 ml) in CCl_4 (50 ml) was added during 1 h to ethyl 4-methyl-3-oxopentanoate [25] (20.4 g) in a stirred dispersion of CCl_4 (70 ml)–H_2O (70 ml) at 0 °C. After 45 min the CCl_4 layer was separated, dried, and evaporated at 25 °C/18 mmHg to give an oil (30.3 g) shown by ^1H n.m.r. examination to be mainly (*ca.* 95%) ethyl 2-bromo-4-methyl-3-oxopentanoate. This material (29.9 g) was added to a solution of Δ²-thiazoline-2-thiol (15 g) in dioxan (100 ml) at 20 °C. After 12 h the insoluble powder was collected, washed with Et_2O, and dried to give 2-(1-ethoxycarbonyl-3-methyl-2-oxobutylthio)-Δ²-thiazolinium bromide (6) (40.5 g), m.p. 179—184 °C; δ [$(CD_3)_2SO$] 5.10 (2 H, m, 5-H), 4.23 (2 H, q, OCH_2Me), 4.09 (2 H, m, 6-H), 3.40 (1 H, m, $CHMe_2$), 1.27 (3 H, t, OCH_2Me), and 1.09 (6 H, d, $CHMe_2$); *m/z* 276 (cation, 1%) and 186 (100). A solution of the foregoing salt (18.7 g) in 6M-HBr (110 ml) was boiled under reflux for 5 h, and evaporated at 80 °C/15 mmHg. The residue crystallised from MeOH to give 2-*carboxy*-3-(1-*methylethyl*)-5,6-*dihydrothiazolo*[2,3-*b*]*thiazolium bromide* (7) (10.9 g), m.p. 203—205 °C (Found: C, 34.9; H, 3.9; N, 4.5; S, 20.4. C_9H_{12}-

Table 2. Characterisation of new thiazole derivatives

Compound	M.p. (°C)	B.p. (°C) Bath temp./ mmHg	Analysis: Found (%) C	H	N	Molecular formula	Requires (%) C	H	N
(1d) 2-(*N*-Benzyl-*N*-methylamino)-4-methylthiazole		101—103/0.2	66.2	6.5	12.9	$C_{12}H_{14}N_2S$	66.0	6.5	12.8
(5d) 2-(*N*-Benzyl-*N*-methylamino)-4-methylthiazole-5-carbaldehyde	91—92		63.5	5.8	11.5	$C_{13}H_{14}N_2OS$	63.4	5.7	11.4
(1e) 4-Benzyl-2-dimethylaminothiazole		88—91/0.01	65.7	6.3	12.5	$C_{12}H_{14}N_2S$	66.0	6.5	12.8
(5e) 4-Benzyl-2-dimethylaminothiazole-5-carbaldehyde	92—93		63.2	5.8	11.2	$C_{13}H_{14}N_2OS$	63.4	5.7	11.4
(1f) 4-Benzyl-2-(*N*-benzyl-*N*-methylamino)-thiazole		118—121/0.01	73.2	6.3	9.3	$C_{18}H_{18}N_2S$	73.4	6.2	9.5
(5f) 4-Benzyl-2-(*N*-benzyl-*N*-methylamino)-thiazole-5-carbaldehyde	112—114		70.6	5.6	8.7	$C_{19}H_{18}N_2OS$	70.8	5.6	8.7
(1g) 2-Dimethylamino-4-(1-methylethyl)-thiazole		53—55/0.01	56.1	8.45	16.6	$C_8H_{14}N_2S$	56.4	8.3	16.5
(5g) 2-Dimethylamino-4-(1-methylethyl)-thiazole-5-carbaldehyde			54.7	7.0	13.65	$C_9H_{14}N_2OS$	54.5	7.1	14.1
(1h) 2-(*N*-Benzyl-*N*-methylamino)-4-(1-methylethyl)thiazole		150—152/1.5	68.1	7.4	11.2	$C_{14}H_{18}N_2S$	68.25	7.4	11.4
(5h) 2-(*N*-Benzyl-*N*-methylamino)-4-(1-methylethyl)thiazole-5-carbaldehyde	80—81		65.75	6.45	10.1	$C_{15}H_{18}N_2OS$	65.7	6.6	10.2
(1i) 4-t-Butyl-2-dimethylaminothiazole		101—103/11	58.4	8.4	15.15	$C_9H_{16}N_2S$	58.65	8.75	15.2
(5i) 4-t-Butyl-2-dimethylaminothiazole-5-carbaldehyde	96—98		56.7	7.6	13.0	$C_{10}H_{16}N_2OS$	56.6	7.6	13.2
(1j) 4-t-Butyl-2-(*N*-methyl-*N*-phenylamino)-thiazole	35—36		68.1	7.4	11.55	$C_{14}H_{18}N_2S$	68.2	7.4	11.4
(5j) 4-t-Butyl-2-(*N*-methyl-*N*-phenylamino)-thiazole-5-carbaldehyde	119—120		65.8	6.6	10.1	$C_{15}H_{18}N_2OS$	65.7	6.6	10.2
(1k) 2-(*N*-Benzyl-*N*-methylamino)-4-t-butylthiazole	52—53		69.2	7.5	10.6	$C_{15}H_{20}N_2S$	69.2	7.7	10.8
(5k) 2-(*N*-Benzyl-*N*-methylamino)-4-t-butylthiazole-5-carbaldehyde	84—85		66.9	6.9	9.6	$C_{16}H_{20}N_2OS$	66.6	7.0	9.7
(1l) 4-(4-Bromophenyl)-2-dimethylamino-thiazole	89—90		46.8	4.0	9.8	$C_{11}H_{11}BrN_2S$	46.6	3.9	9.9
(5l) 4-(4-Bromophenyl)-2-dimethylamino-thiazole-5-carbaldehyde	165—166		46.2	3.7	8.8	$C_{12}H_{11}BrN_2OS$	46.3	3.6	9.0
(1m) 2-(*N*-Benzyl-*N*-methylamino)-4-(4-bromophenyl)thiazole	104—105		56.5	4.4	7.8	$C_{17}H_{15}BrN_2S$	56.8	4.2	7.8
(5m) 2-(*N*-Benzyl-*N*-methylamino)-4-(4-bromophenyl)thiazole-5-carbaldehyde	101—102		55.8	3.8	7.3	$C_{18}H_{15}BrN_2OS$	55.8	3.9	7.2
(1n) 4-(4-Hydroxyphenyl)-2-dimethylamino-thiazole	161—163		59.9	5.6	12.8	$C_{11}H_{12}N_2OS$	60.0	5.5	12.7
(5n) 4-(4-Hydroxyphenyl)-2-dimethylamino-thiazole-5-carbaldehyde	215—217		57.8	5.0	11.1	$C_{12}H_{12}N_2O_2S$	58.05	4.9	11.3
(5o) 4-(4-Methoxyphenyl)-2-dimethylamino-thiazole-5-carbaldehyde	118—119		59.5	5.5	10.4	$C_{13}H_{14}N_2O_2S$	59.5	5.4	10.7
(1p) 2-(*N*-Benzyl-*N*-methylamino)-4-(4-methoxyphenyl)thiazole	79—80		69.4	5.6	9.2	$C_{18}H_{18}N_2OS$	69.6	5.85	9.0
(5p) 2-(*N*-Benzyl-*N*-methylamino)-4-(4-methoxyphenyl)thiazole-5-carbaldehyde	82—83		67.1	5.4	8.3	$C_{19}H_{18}N_2O_2S$	67.4	5.4	8.3
(3l) 2-(4-Bromophenacylthio)-Δ^2-thiazolinium bromide	164—165		33.3	2.9	3.7	$C_{11}H_{11}Br_2NOS_2$	33.3	2.8	3.5
(4l) 3-(4-Bromophenyl)-5,6-dihydro-thiazolo[2,3-*b*]thiazolium bromide	256—258		35.1	2.5	3.8	$C_{11}H_9Br_2NS_2$	34.9	2.4	3.7
(4n) 3-(4-Hydroxyphenyl)-5,6-dihydro-thiazolo[2,3-*b*]thiazolium bromide [a]	233—234		42.2	3.0	4.2	$C_{11}H_{10}BrNOS_2$	41.8	3.2	4.4
(3o) 2-(4-Methoxyphenacylthio)-Δ^2-thiazolinium bromide	165—168		41.5	4.1	4.0	$C_{12}H_{13}BrNO_2S_2$	41.4	4.1	4.0
(4o) 3-(4-Methoxyphenyl)-5,6-dihydro-thiazolo[2,3-*b*]thiazolium bromide [b]	233—234		43.8	3.7	4.1	$C_{12}H_{12}BrNO_2S_2$	43.7	3.7	4.3

[a] Obtained by boiling the salt (3o) with 6M-HBr for 6 h. [b] Obtained by heating the salt (3o) with 6M-HBr at 50 °C for 4 h.

$BrNO_2S_2$ requires C, 34.8; H, 3.9; N, 4.5; S, 20.7%); δ (DCl–D_2O) 5.07 (2 H, d of d, 5-H), 4.46 (2 H, d of d, 6-H), 4.28 (1 H, m, C*H*Me_2), and 1.59 (6 H, d, CH*Me*$_2$); *m/z* 309 and 311 (M^+, *ca.* 60%) and 186 (100). 25% Aqueous Me_2NH (26 ml) was added to a stirred suspension of the bromide (10) (14 g) in EtOH (70 ml) at 20 °C. After 5 h the solution was evaporated at 50 °C/15 mmHg, H_2O (50 ml) was added, and the mixture was extracted with $CHCl_3$ (3 × 40 ml). The $CHCl_3$

Table 3. Bond lengths of 4-t-butyl-2-(*N*-methyl-*N*-phenylamino)-thiazole-5-carbaldehyde (5j) with estimated standard deviations in parentheses

Bond	Length (Å)	Bond	Length (Å)
S(1)–C(1)	1.732(2)	C(3)–C(15)	1.430(3)
S(1)–C(3)	1.742(2)	C(5)–C(6)	1.396(4)
O(1)–C(15)	1.219(3)	C(5)–C(10)	1.381(4)
N(1)–C(1)	1.316(3)	C(6)–C(7)	1.384(4)
N(1)–C(2)	1.357(3)	C(7)–C(8)	1.365(5)
N(2)–C(1)	1.356(3)	C(8)–C(9)	1.374(5)
N(2)–C(4)	1.458(3)	C(9)–C(10)	1.394(4)
N(2)–C(5)	1.418(3)	C(11)–C(12)	1.537(4)
C(2)–C(3)	1.378(3)	C(11)–C(13)	1.530(4)
C(2)–C(11)	1.522(3)	C(11)–C(14)	1.528(4)

solution was dried, filtered, and boiled under reflux for 4 h. Evaporation of the solution and distillation of the residue gave the 2-amine (1g) (5.2 g).

4-Benzyl-2-(N-benzyl-N-methylamino)thiazole-5-carbaldehyde (5f).—A solution of $POCl_3$ (0.6 g) in $HCO{\cdot}NMe_2$ (dried over KOH; 2 ml) was added during 5 min to a solution of the 2-amine (1f) (1 g) in $HCO{\cdot}NMe_2$ (8ml) which was stirred at 20 °C. The solution was stirred at 40 °C for 4 h, basified with aqueous Na_2CO_3, and the material isolated with $CHCl_3$ was chromatographed on SiO_2 (60 g). Elution with pentane–Et_2O (2 : 3) gave the *5-aldehyde* (5f) (0.81 g).

Crystallographic Data for the 5-Carbaldehyde (5j).—$C_{15}H_{18}NOS$, M, 274.4, monoclinic, $P2_1/n$, $a = 9.326(2)$, $b = 8.722(5)$, $c = 17.805(4)$ Å, $\beta = 93.55(3)°$, $\mu = 1\,445$ Å^3, $Z = 4$, $D_c = 1.27$ g cm^{-3}, μ(Mo-K_α) = 2.18 cm^{-1}, final R-value 0.045 for 2 247 reflections with $I \geqslant 3\sigma(I)$.

Bond lengths and fractional atomic co-ordinates of the 2-aminothiazole-5-carbaldehyde (5j) are given in Tables 3 and 4 respectively. The crystallographic work was carried out as follows. A large crystal of the 5-carbaldehyde was obtained from light petroleum (b.p. 60—80 °C). Oscillation and Weissenberg photographs showed the crystal to be monoclinic with a 2_1 axis in the unique direction and a glide plane perpendicular. The crystal was transferred to an Enraf Nonius CAD4-F four-circle diffractometer. Cell parameters were determined from the setting angles of 25 reflections found by the SEARCH routine, and then refined using 6 reflections and their three equivalences in the monoclinic crystal system. Diffraction intensities were measured by $\omega/2\theta$ scans out to $\theta = 28°$ using Mo-K_α X-radiation, orientation and intensity standards being checked periodically. The space group $P2_1/n$ was determined from the systematic absences. After the application of Lorentz and polarisation corrections, the rejection of systematic absences, and the merging of equivalent reflections, structure amplitudes were derived for 2 247 unique reflections with $I \geqslant 3\sigma(I)$. The 'direct methods' programme MULTAN 80 (P. Main, Department of Physics, York University, 1980) revealed all the non-hydrogen atoms except the four Me carbon atoms. The structure was then refined by full-matrix least squares using isotropic temperature factors with SHELX 76 (G. M. Sheldrick, Cambridge University, 1976) and CRYSTALS (J. R. Carruthers, Chemical Crystallography Laboratory, Oxford University, 1975). A subsequent difference Fourier synthesis revealed C(4) and one of the t-butyl Me carbons, C(14). The two missing Me groups of the t-butyl substituent, C(12) and C(13), were placed subject to the constraints that their distances from C(11) were 1.540 Å and that all the inter-carbon distances between C(12), C(13), and C(14) were 2.516 Å. After further refinement the positions of the hydrogen atoms were calculated and the constraints on the constituents of the t-butyl substituent were removed. Non-hydrogen atoms were assigned anisotropic temperature factors and refinement was continued. The positions of the Me hydrogen atoms were checked by eliminating them from the model, calculating new structure factors, and carrying out a difference Fourier synthesis. The C(4) hydrogen atoms were found to have been located correctly but the fact that no similar electron density peaks were found in the region of C(12)—C(14) suggested that the t-butyl hydrogen atoms may be disordered. The Me hydrogen atoms were restored to the model and the positions of those attached to C(4) were included in the refinement subject to the Waser constraints that C–H = 1.000(5) Å and that all the angles at C(14) involving at least one hydrogen atom were 108.5(10)°. Weights for the final rounds of refinement were calculated from the Chebyshev series (J. R. Carruthers and D. J. Watkin, *Acta Crystallogr., Sect. A*, 1979, 698), $w = [244.95t_0(X) + 334.22t_1(X) + 99.876t_2(X)]^{-1}$ where $(X) = F_o/F_{max.}$. The structure converged at a final R-value of 0.045.

Tables of bond anisotropic temperature factors, and structure factors are deposited as a Supplementary Publication (SUP No. 23474, 23 pp.).*

Table 4. Fractional atomic co-ordinates of the 2-aminothiazole-5-carbaldehyde (5j)

Atom	x/a	y/b	z/c
C(1)	1.015 8(2)	0.423 9(3)	0.366 1(1)
C(2)	0.833 3(2)	0.584 9(3)	0.369 5(1)
C(3)	0.796 9(2)	0.486 3(3)	0.425 7(1)
C(4)	1.217 2(3)	0.469 2(4)	0.291 1(2)
C(5)	1.209 7(3)	0.235 2(3)	0.369 8(1)
C(6)	1.357 6(3)	0.237 2(3)	0.387 3(2)
C(7)	1.426 2(3)	0.103 9(4)	0.411 7(2)
C(8)	1.350 9(4)	−0.028 6(4)	0.419 8(2)
C(9)	1.205 0(4)	−0.030 8(3)	0.403 5(2)
C(10)	1.133 4(3)	0.101 0(3)	0.377 5(2)
C(11)	0.753 6(3)	0.727 8(3)	0.341 2(1)
C(12)	0.594 1(3)	0.694 2(4)	0.320 9(2)
C(13)	0.768 0(4)	0.850 7(3)	0.402 5(2)
C(14)	0.819 4(4)	0.787 9(4)	0.270 4(2)
C(15)	0.681 8(3)	0.488 1(3)	0.475 1(2)
N(1)	0.956 4(2)	0.548 7(2)	0.336 6(1)
N(2)	1.141 8(2)	0.371 0(2)	0.342 0(1)
S(1)	0.923 34(7)	0.339 77(7)	0.436 69(4)
O(1)	0.667 2(2)	0.392 6(3)	0.524 0(1)
H(41)	1.147(1)	0.511(2)	0.251 5(9)
H(42)	1.292(2)	0.409(2)	0.267(1)
H(43)	1.263(2)	0.556(2)	0.320 1(8)
H(61)	1.4126	0.3347	0.3826
H(71)	1.5337	0.1052	0.4232
H(81)	1.4020	−0.1246	0.4377
H(91)	1.1489	−0.1276	0.4110
H(101)	1.0275	0.0982	0.3645
H(121)	0.5451	0.7908	0.3026
H(122)	0.5476	0.6564	0.3665
H(123)	0.5852	0.6149	0.2805
H(131)	0.7166	0.9455	0.3844
H(132)	0.8725	0.8750	0.4134
H(133)	0.7262	0.8122	0.4489
H(141)	0.7672	0.8820	0.2518
H(142)	0.9234	0.8141	0.2820
H(143)	0.8129	0.7076	0.2300
H(151)	0.6092	0.5727	0.4688

* For details of the Supplementary publications Scheme see Notices to Authors, No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1981, Index issue.

Acknowledgement

We thank Dr. C. K. Prout for the use of facilities in the Chemical Crystallography Laboratory, Oxford University.

References

1 L. Forlani, P. De Maria, and A. Fini, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1156.
2 P. T. Kaye, C. H. Patterson, R. Macrae, and G. D. Meakins, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1631, and earlier papers.
3 L. Forlani, L, Lunazzi, and A. Medici, *Tetrahedron Lett.*, 1977, 4525.
4 A. Dorlars and K. Kaemmerer, Belgian Patent 612,839 (1962) (*Chem. Abstr.*, 1963, **59**, 2831).
5 O. Wallach, *Chem. Ber.*, 1899, **32**, 1872.
6 F. Kurzer, *Org. Synth.*, Coll. Vol. IV, p. 180.
7 R. J. Neville and J. J. McGee, *Can. J. Chem.*, 1963, **41**, 2123.
8 H. Ohtsuka, H. Toyofuku, T. Miyasaka, and K. Arakawa, *Chem. Pharm. Bull. Jpn.*, 1935, **23**, 3234.
9 C. K. Bradsher and W. J. Jones, *Recl. Trav. Chim.*, 1968, **87**, 274.
10 G. W. Anderson and M. R. Davis, *J. Am. Chem. Soc.*, 1945, **67**, 2197.
11 Leading references to work on heterocyclic aldehydes are given in ref. 2.
12 P. T. Kaye, D.Phil. Thesis, Oxford, 1979.
13 W. A. Thomas, *Ann. Rev. NMR Spectrosc.*, 1968, **1**, 43.
14 M. Davis, R. Lakhan, and B. Ternai, *J. Org. Chem.*, 1976, **41**, 3591.
15 L. Lunazzi, D. Macciantelli, and G. Cerioni, *J. Chem. Soc., Perkin Trans.* 2, 1976, 1791.
16 R. F. Dietrich, G. L. Kenyon, J. E. Douglas, and P. A. Kollman, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1592.
17 F. G. Riddell and D. A. R. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1973, 587.
18 Figures quoted in ref. 16.
19 J. P. Declercq, G. Germain, R. Touillaux, and M. Van Meersche, *Acta Crystallogr., Sect. B*, 1981, **37**, 1296.
20 B. L. Trus and R. E. Marsh, *Acta Crystallogr., Sect. B*, 1973, **29**, 2298.
21 R. Celikel, A. J. Geddes, and B. Sheldrick, *Cryst. Struct. Commun.*, 1978, **7**, 683.
22 H. Bock and K. L. Kompa, *Z. Anorg. Chem.*, 1964, **332**, 238.
23 F. D. Stewart, U.S. Patent 2,547,772 (1951) (*Chem. Abstr.*, 1951, **45**, 6344).
24 M. Gaudry and A. Marquet, *Org. Synth.*, 1976, **55**, 24.
25 E. H. Kroeker and S. M. McElvain, *J. Am. Chem. Soc.*, 1934, **56**, 1171.

Received 14*th June* 1982; ***Paper*** 2/985