2-(*N,N*-Disubstituted Amino)thiazoles with Electron-withdrawing Groups at Position 5: Preparation and Investigation of Structural Features

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A convenient procedure for preparing *N*-mono- and *N,N*-di-substituted cyanamides from cyanogen bromide has been developed. *N,N*-Disubstituted thioureas, obtained from the cyanamides, were condensed with α-bromo-α-cyano-ketones to give 5-cyano-2-(*N,N*-disubstituted amino)thiazoles and with α-bromo-ketones to give 2-(*N,N*-disubstituted amino)thiazoles. Substitution in the latter products afforded 5-trifluoroacetyl- and 5-nitro-2-(*N,N*-disubstituted amino)thiazoles; nitration is greatly facilitated by the presence of a 4-aryl group.

The average values of the barriers to rotation of the 2-NR_2 groups ($\Delta G^{\ddagger}_{298}$) in the 5-substituted thiazoles were established by variable temperature ^{1}H n.m.r. spectrometry to be 57.4 kJ mol^{-1} (5-NO_2), 56.2 (5-$COCF_3$), and 51.5 (5-CN). I.r. examinations showed that the 5-trifluoroacetyl compounds adopt one rotational form preferentially; this is probably the carbonyl *O,S-syn*-conformation.

Previous studies of 2-(*N,N*-disubstituted amino)thiazole-5-carbaldehydes [1] and -5-carboxylates [2] have given information about the rotational barriers of their 2-amino groups and the conformational preferences of their 5-substituents. The object of the present work was to extend the range of electron-withdrawing substituents at position 5 and to vary more widely the groups attached to the exocyclic nitrogen atom. It was hoped that this would extend the knowledge about structural features such as the degree of mesomeric interaction between the 2-amino group and various 5-substituents attached to the thiazole nucleus.

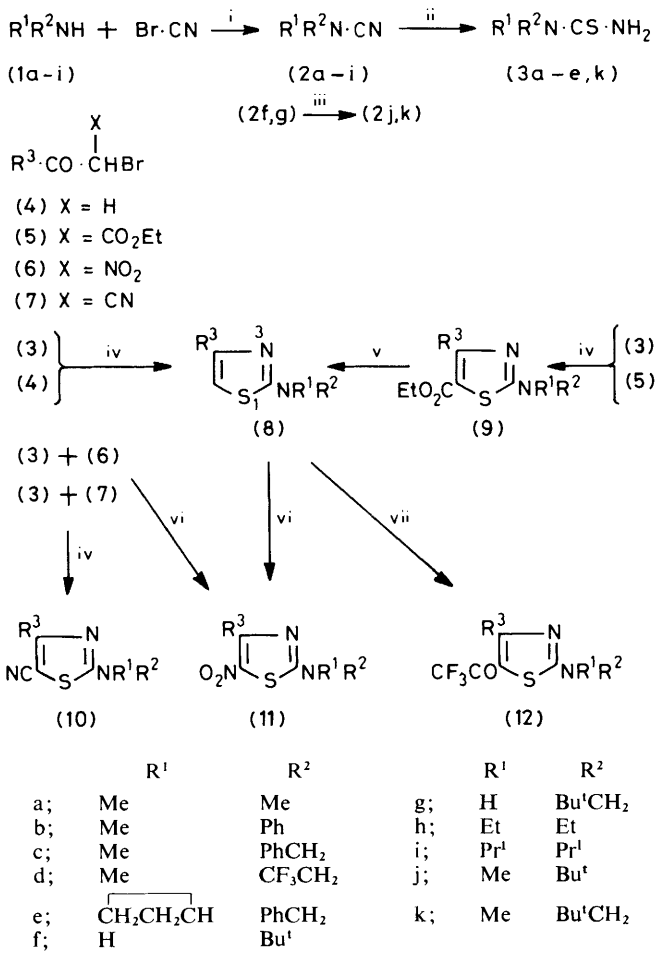
The preparative work, summarised in Schemes 1 and 2, was aimed at producing three series of 2-(*N,N*-disubstituted amino)thiazoles (hereinafter abbreviated to 2-NR_2-thiazoles), *viz.*, the 5-cyano (10), 5-nitro (11), and 5-trifluoroacetyl (12) derivatives. It was intended to study only a selection of the compounds arising from all the possible combinations of the R^1, R^2, and R^3 groups in Scheme 1; those prepared are listed in Table 1. Before the present work several 5-nitro-2-NR_2-thiazoles lacking 4-substituents and a few with 4-substituents were known, but only two 5-cyano compounds had been described and there appeared to be no record of a 5-trifluoroacetyl-2-NR_2-thiazole.[3] While it seemed likely that the 5-nitro and 5-trifluoroacetyl compounds could be obtained by electrophilic substitution of the parent thiazoles (8), no convenient method for introducing the cyano group suggested itself. Thus the plan was to produce the thiazoles (8) and the 5-cyano derivatives (10) by Hantzsch syntheses, and for these a range of *N,N*-disubstituted thioureas was required.

As explained earlier [1] the reaction of amines with silicon tetraisothiocyanate [4] was unsatisfactory for preparing some of the required *N,N*-disubstituted thioureas and attention was turned to Wallach's route [5] (later modified [6]) involving addition of hydrogen sulphide to cyanamides. Many *N*-mono- and *N,N*-di-substituted cyanamides were first obtained from amines using bromine and potassium cyanide (a method which fails with aromatic amines),[7] and in an even earlier method cyanogen bromide was treated with an excess (at least 2 equiv.) of the amine; [5] both methods have been used subsequently.[8] More recently [9] the *N*-monosubstituted cyanamides have been prepared more efficiently from equivalent amounts of primary amines and cyanogen bromide in the presence of a base (anhydrous sodium carbonate). In the present work a study of various bases and solvent combinations led to an efficient general procedure (Scheme 2) for converting primary and secondary amines into cyanamides (yields 80—90%) which is more convenient than the published routes to some of the known amines (*e.g.*, *N*-t-butylcyanamide [10]).

Hantzsch condensations between various α-bromo-ketones (4) and the thioureas (3a—e) and (3k) gave the parent 2-NR_2-thiazoles (8); as explained earlier [1] the 4-benzyl compounds (8; R^3 = $PhCH_2$) are more readily obtained *via* the 5-carboxylates (9; R^3 = $PhCH_2$). Condensations involving α-bromo-α-cyanoketones (7) are less satisfactory but three 5-cyano-2-NR_2-thiazoles (10) were prepared in this way. Trifluoroacetylation of the 2-NR_2-thiazoles (8) was remarkably easy and a simple general procedure afforded nineteen 5-trifluoroacetyl-2-NR_2-thiazoles (12) in 85—95% yield. In contrast, nitration presented difficulties.

Nitration of 4-substituted 2-aminothiazoles (R = H, Me, or Bu^t) occurs at 20 °C in a medium consisting of 70% nitric acid and an excess of 70—98% sulphuric acid.[11] It appears that 2-nitroaminothiazoles are formed initially and that these isomerise to 5-nitro-2-amino compounds in an acid-catalysed process at a rate determined by the strength of the sulphuric acid; whether the 5-nitro-2-amino derivatives are also produced directly in a competing reaction is not clear. 2-Dimethylamino-, 2-piperidino-, and 2-morpholino-thiazole are satisfactorily nitrated at position 5 by mixed acid,[12] but other 2-NR_2-thiazoles are reported to undergo cleavage rather than nitration.[13]

In the present work (Scheme 2) it was found that 4-alkyl-2-NR_2-thiazoles are unaffected by 70% nitric acid alone. The 4-alkyl-2-NMe_2 compounds are smoothly converted into their 5-nitro derivatives (11a) by mixed acids, but when a benzyl group is present at position 4 or on the exocyclic nitrogen extensive decomposition occurs. Nitration of two benzyl-containing thiazoles (8a; R^3 = $PhCH_2$) and (8c; R^3 = Pr^i) was accomplished, in low yield, using nitronium tetrafluoroborate. In the 4-t-butyl-*N*-methyl-*N*-phenylaminothiazole (8b; R^3 = Bu^t) the phenyl ring is the more readily nitrated. An unexpected result, not previously reported, is that 4-aryl-2-NR_2-thiazoles are efficiently nitrated at position 5 by cold 70% nitric acid alone, and with this type the presence of a benzyl group does not lead to complications. Further work is being carried out on the comparison between 4-alkyl- and 4-aryl-2-NR_2-thiazoles in other electrophilic substitutions. One 5-nitro derivative (11c; R^3 = Me) was obtained by a Hantzsch condensation; another possible approach, treatment of 2-bromo-5-nitrothiazoles with amines, is unsatisfactory for secondary amines containing bulky groups.[14]

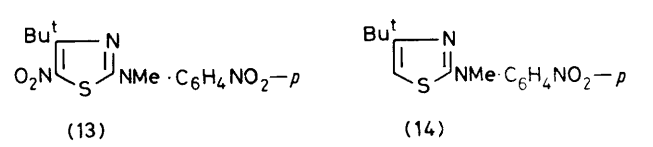


	R¹	R²		R¹	R²
a;	Me	Me	g;	H	Bu^tCH_2
b;	Me	Ph	h;	Et	Et
c;	Me	$PhCH_2$	i;	Pr^i	Pr^i
d;	Me	CF_3CH_2	j;	Me	Bu^t
e;	CH_2CH_2CH	$PhCH_2$	k;	Me	Bu^tCH_2
f;	H	Bu^t			

R^3 = H, Me, $PhCH_2$, Pr^i, Bu^t, Ph, C_6H_4Br-*p*, or C_6H_4OMe-*p*

Scheme 1. *N,N*-Disubstituted cyanamides and thioureas, and 5-derivatives of 2-(*N,N*-disubstituted amino)thiazoles. *Reagents:* i, $MgCO_3$–H_2O–Et_2O or EtOAc, 5 °C; ii, H_2S–Et_3N–EtOH, 10 °C; iii, MeI–KOH–Me_2SO; iv, EtOH or Me_2CO or Me_2CO–$MgSO_4$, heat; v, 6M-HCl, heat; vi, see Scheme 2; vii, $(CF_3CO)_2O$–C_6H_6, heat

The main spectrometric results are shown in Table 2. With most of the 5-substituted-2-NR_2-thiazoles (10), (11), and (12), splitting of the *N*–C*H* ^{1}H n.m.r. signals occurred in the range −3 to −20 °C, and standard treatment [15] led to the $\Delta G^{\ddagger}$ values for rotation of the 2-NR_2 groups. In the amines with R_2 = Me and Ph, Me and CF_3CH_2, and $PhCH_2$ and cyclopropyl no splitting was observed. It could be argued that the electronic effects of these groups lower the rotational barrier, but the $\Delta G^{\ddagger}$ values would have to be below *ca.* 38 kJ mol^{-1} to account for the absence of splitting at −90 °C. This is unlikely since 2-dimethylaminothiazole (no 5-substituent) has $\Delta G^{\ddagger}$ 32.2 kJ mol^{-1},[16] and it seems more probable that with these 2-NR_2 groups one rotameric form is markedly the more stable and is adopted preferentially over the temperature range studied. The variations in the $\Delta G^{\ddagger}$ values of the members of the different types, (10), (11), and (12), are small. Thus, as with 5-aldehydes [1] and 5-carboxylates,[2] the nature of the 4-substituent and the 2-NR_2 groups has little effect on the barrier to rotation, and since the variations are less than the possible errors in the values further discussion is unwarranted. [For the one 5-nitro-2-NR_2-compound (11a; R^5 = H) examined previously, in CHF_2Cl at 60 MHz,[16] $\Delta G^{\ddagger}$ was found to be 51.9 kJ mol^{-1} at 241.5 K. The present study gives a value of 53.8 mol^{-1} at this temperature.] Scheme 3 shows the



(8a; R^3 = H, Me, Pr^i, and Bu^t) —i→ (11a; R^3 = H, Me, Pr^i, and Bu^t)

(8a; R^3 = Ph, C_6H_4Br-*p*, and C_6H_4OMe-*p*) —ii→ (11a; R^3 = Ph, C_6H_4Br-*p*, and C_6H_4OMe-*p*)

(8c; R^3 = C_6H_4Br-*p*) —ii→ (11c; R^3 = C_6H_4Br-*p*)

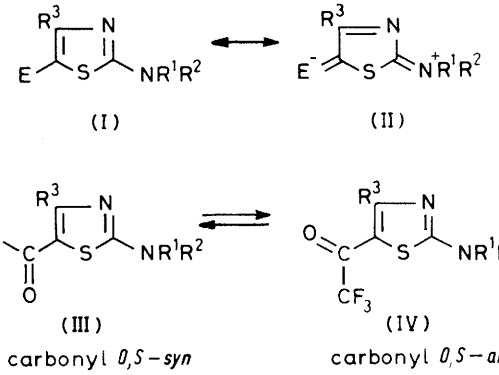
(8b; R^3 = Bu^t) —i→ (13) + (14)

(8c; R^3 = Me) —i→ (11c; R^3 = Me) ←iii— (3c) + (6; R^3 = Me)

(8a; R^3 = $PhCH_2$) —i→ (11a; R^3 = $PhCH_2$) ←iv— (8a; R^3 = $PhCH_2$)

(8c; R^3 = Pr^i) —i→ (11c; R^3 = Pr^i) ←iv— (8c; R^3 = Pr^i)

Scheme 2. Preparation of 5-nitro derivatives of 2-(*N,N*-disubstituted amino)thiazoles. *Reagents:* i, 70% HNO_3–H_2SO_4 at 20 °C; ii, 70% HNO_3 at 5 °C; iii, Me_2CO, heat; iv, $NO_2^+BF_4^-$–MeCN or tetrahydrothiophene 1,1-dioxide



E	NO_2	$COCF_3$	CHO [a]	CN	CO_2Et [b]	H
Number of compounds	11	13	6	2	11	1
Average $\Delta G^{\ddagger}_{298}$(kJ mol^{-1})	57.4	56.2	52.5	51.5	44.2	32.2 [c]

[a] Ref. 1. [b] Ref. 2. [c] Ref. 16, $\Delta G^{\ddagger}_{150}$ in CHF_2Cl at 60 MHz.

Scheme 3. Barriers to rotation of 2-NR_2 groups in compounds of types (10), (11), and (12); rotational isomerism in compounds of type (12)

average $\Delta G^{\ddagger}$ values for different types of 5-substituted 2-NR_2-thiazoles. For comparison with these the figure for the rotational barrier of 2-dimethylaminothiazole should be increased slightly, probably (in line with the 5-nitro derivative) to *ca.* 36 kJ mol^{-1}. A mesomeric effect is seen to operate in all types, and increasing $\Delta G^{\ddagger}$ values can be equated with larger contributions of the dipolar canonical forms (II). The lack of sensitivity towards the size of the 4-substituent implies that mesomerism is not appreciably inhibited by steric interactions which might be expected to arise in form (II) of the 5-NO_2,

5-$COCF_3$, and 5-CO_2Et types. This point also emerges from the correspondence between the $\Delta G^{\ddagger}$ values and the σ_P^- constants of the 5-substituents for which figures are available (NO_2, 1.27; CHO, 1.13; CN, 1.00; CO_2Et, 0.68).

Interpretation of the i.r. bands of the 5-trifluoroacetyl derivatives (12) is not straightforward. These compounds show doublets (*h*, higher, and *l*, lower wavenumber bands) which may be ascribed to the presence of the rotational isomers (III) and (IV) (Scheme 3), but the *l*-bands are so weak as to preclude precise curve resolution. [The exceptional behaviour of compound (12a; R^3 = H) in MeCN probably arises from the incursion of Fermi resonance.] That the ^{19}F n.m.r. signals remain as sharp singlets on cooling the solutions to −90 °C does not necessarily argue against the presence of rotamers. Although the i.r. bands lie in narrow wavenumber ranges the nature of the 4-substituent has somewhat different effects on the *h*- and *l*-bands. Reasoning as before [2,17] suggests that the predominant rotamers, giving the *h*-bands, have the carbonyl *O,S-syn*-arrangement (III). There may appear to be a contradiction between the interpretation of the i.r. data and that of the n.m.r. results with regard to the effects of 4-substituents. Thus it has been argued that the nature of the 4-substituent does have a discernible influence on the position of the CO band of the trifluoroacetyl group but not on its $\Delta G^{\ddagger}$ value. This apparent conflict arises from the different degrees of accuracy with which the results are obtained. A small change in the CO position caused by altering the 4-substituent is readily observed but the corresponding change in the rotational barrier is likely to be smaller than the statistical error of the n.m.r. examination.

Experimental

Since most of the preparative work involved application of general procedures these are illustrated by examples and the products obtained by each procedure are then specified. The characterisation of new compounds and leading references to known compounds are given in Table 2.

Neopentylcyanamide (2g).—Neopentylamine (11.7 g) was added during 30 min to a stirred dispersion of $MgCO_3$ (4 g) in H_2O–Et_2O (50 ml; 1 : 9) containing BrCN (14.4 g) at at 5 °C, and the stirring was continued for 1 h at 20 °C. Dilution with water, isolation with Et_2O, and distillation gave *neopentylcyanamide* (12.7 g). A similar yield was obtained when EtOAc was used in place of Et_2O. The cyanamides (2a—i) were thus obtained, yields 80—90%.

N-*Methyl*-N-*neopentylcyanamide* (2k).—MeI (9.2 ml) was added during 10 min to a vigorously stirred suspension of finely powdered KOH (6.5 g) in Me_2SO (65 ml) containing neopentylcyanamide (2g) (8.2 g) and the stirring was continued for 1 h. Dilution with water, isolation with Et_2O, and distillation gave N-*methyl*-N-*neopentylcyanamide* (7.8 g). Similarly obtained was N-*t-butyl*-N-*methylcyanamide* (2j) (87%).

N-*Methyl*-N-*neopentylthiourea* (3k). —Dry H_2S was bubbled through a solution of *N*-methyl-*N*-neopentylcyanamide (2k) (5.6 g) and Et_3N (12 ml) in EtOH (14 ml) at 10 °C for 2 h, and the mixture was filtered. The precipitate crystallised from EtOH to give N-*methyl*-N-*neopentylthiourea* (3k) (3.6 g). Evaporation of the filtrate gave material which was dissolved in CH_2Cl_2. The solution was boiled with active charcoal, filtered, and evaporated. Crystallisation of the residue gave a second batch of product (1.7 g), m.p. 152—154 °C. Products thus obtained were the thioureas (3a—e) and (3k), yields 65—80% after crystallisation from EtOH or Pr^iOH.

4-*Methyl*-2-(N-*methyl*-N-*neopentylamino*)*thiazole* (8k; R^3 = Me).—A solution of chloroacetone (2.2 ml) in Me_2CO (5 ml) was added during 10 min to a solution of the thiourea (3k) (4.05 g) in Me_2CO (25 ml) which was boiling under reflux, and the boiling was continued for 2 h. The solution was poured into 2M-H_2SO_4, washed with Et_2O, and basified with 18M-NH_3. Isolation with Et_2O and distillation of the product gave the *thiazole* (8k; R^3 = Me) (4.3 g). A similar yield was obtained when anhydrous $MgSO_4$ was present during the condensation; [2] the use of EtOH in place of Me_2CO led to a lower yield (75%). Similarly obtained were the *thiazoles* (8e; R^3 = Pr^i and C_6H_4Br-*p*), yields 70—88%.

4-*Benzyl*-2-[N-*methyl*-N-(2,2,2-*trifluoroethyl*)*amino*]*thiazole* (8d; R^3 = $PhCH_2$).—Condensation of ethyl 2-bromo-3-oxo-3-phenylpropanoate [2] (5; R^3 = Ph) with the thiourea (3d) using a suspension of anhydrous $MgSO_4$ in dry Me_2CO [2] gave *ethyl* 4-*benzyl*-2-[N-*methyl*-N-(2,2,2-*trifluoromethyl*)*amino*]-*thiazole*-5-*carboxylate* (9d; R^3 = $PhCH_2$) (80%). Hydrolysis and decarboxylation of this ester by boiling under reflux with 6M-HCl for 6 h^1 afforded the *thiazole* (8d; R^3 = $PhCH_2$) (76%).

5-*Cyano*-2-*dimethylamino*-4-*methylthiazole* (10a; R^3 = Me). —The precipitate obtained by treating MeCN (25 g) with Na (8 g) suspended in dry Et_2O (300 ml) [18] was collected and dissolved in H_2O–Et_2O (60 ml; 1 : 5). Br_2 (60 g) was added to the stirred mixture during 45 min. The addition of ice-H_2O (50 g), basification with Na_2CO_3, and isolation with Et_2O gave an oil (7 g) shown by ^1H n.m.r. to contain 1-bromo-1-cyanopropan-2-one (7; R^3 = Me) (95%). Condensation of this oil (1.2 g) with *N,N*-dimethylthiourea (0.88 g) under the standard conditions gave material which was purified by chromatography on SiO_2 (100 g). Light petroleum–Et_2O (9 : 1) eluted the 5-*cyanothiazole* (10a; R^3 = Me) (0.75 g). Similarly obtained was the 5-*cyano*-2-(N-*methyl*-N-*phenylamino*)*thiazole* (10b; R^3 = Me) (55% from 1-bromo-1-cyanopropan-2-one).

5-*Cyano*-2-*dimethylamino*-4-*t-butylthiazole* (10a; R^3 = Bu^t). —A solution of Br_2 (0.4 ml) in $CHCl_3$ (5 ml) was added during 10 min to a stirred solution of 1-cyano-3,3-dimethylbutan-2-one (1.5 g) in $CHCl_3$ (15 ml). After 45 min the solution was washed with aq. Na_2CO_3, dried, and evaporated to give an oil (2.42 g) shown by ^1H n.m.r. to contain 1-bromo-1-cyano-3,3-dimethylbutan-2-one (7; R^3 = Bu^t) (91%). Condensation of this oil with *N,N*-dimethylthiourea (1.18 g) gave the 5-*cyanothiazole* (10a; R^3 = Bu^t) (1.1 g) which was purified by sublimation at 100 °C/1 mmHg.

5-*Nitrothiazoles*. 2-*Dimethylamino*-5-*nitro*-4-*t-butylthiazole* (11a; R^3 = Bu^t).—Nitric acid (70%; 0.82 ml) was added in drops to a vigorously stirred solution of 2-dimethylamino-4-t-butylthiazole (1.9 g) in H_2SO_4 (10 ml) at 5 °C. The solution was stirred at 20 °C for 3 h, poured into ice-H_2O (80 g), and neutralised with 18M-NH_3. The precipitate was collected and crystallised from MeOH to give the 5-*nitrothiazole* (11a; R^3 = Bu^t) (1.6 g). Similarly obtained were the 5-nitrothiazoles (11a; R^3 = H, Me, and Pr^i), yields 60—70%.

Nitric acid (70%; 0.57 ml) was added to a stirred solution of 2-(*N*-methyl-*N*-phenylamino)-4-t-butylthiazole (8b; R^3 = Bu^t) (1.5 g) in H_2SO_4 (20 ml) at 0 °C. After 2 h at 0 °C, work-up as in the foregoing experiment gave material which was chromatographed on SiO_2 (100 g). Light petroleum–Et_2O (9 : 1) eluted the *dinitro compound* (13) (0.61 g). Repetition of the experiment using less nitric acid (70%; 0.20 ml) gave a mixture which was chromatographed. Light petroleum eluted starting material (8b; R^3 = Bu^t) (0.67 g). Light petroleum–

Table 1. Characterisation of new compounds and leading references to known compounds

Compound	M.p. (°C)	B.p. [Bath temp. (°C)/ mmHg]	Found (%) Requires (%) C	H	N	Molecular formula
N-Methyl-*N*-(2,2,2-trifluoroethyl)cyanamide (2d)		49—50/15	*m/z* 138.0406 (M^+ 138.0405)			
N-Benzyl-*N*-cyclopropylcyanamide (2e)		94—96/0.1	76.4 (76.7	7.1 7.0	16.2 16.3)	$C_{11}H_{10}N_2$
Neopentylcyanamide (2g)		72—73/13	64.1 (63.9	10.8 10.6	25.0 24.9)	$C_6H_{12}N_2$
N-Methyl-*N*-t-butylcyanamide (2j)		70—71/15	64.0 (63.9	10.8 10.6	24.8 24.9)	$C_6H_{12}N_2$
N-Methyl-*N*-neopentylcyanamide (2k)		32—33/0.1	66.8 (66.6	11.2 11.2	22.2 22.2)	$C_7H_{14}N_2$
(2a),[a] (2b),[b] (2c, h, i),[c] (2f) [d]						
N-Methyl-*N*-(2,2,2-trifluoroethyl)thiourea (3d)	157—158		22.4 (22.5	4.4 4.4	17.5 17.5)	$C_3H_7F_3N_2S$
N-Benzyl-*N*-cyclopropylthiourea (3e)	127—128		63.8 (64.0	6.8 6.8	13.4 13.6)	$C_{11}H_{12}N_2S$
N-Methyl-*N*-neopentylthiourea (3k)	156—157		52.4 (52.4	10.2 10.1	17.5 17.5)	$C_7H_{16}N_2S$
(3a, b),[b] (3c) [c]						
4-Methyl-2-(*N*-methyl-*N*-neopentylamino)thiazole (8k; R^3 = Me)		54—56/0.25	*m/z* 198.1191 (M^+ 198.1191)			$C_{10}H_{18}N_2S$
4-Benzyl-2-[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]thiazole (8d; R^3 = $PhCH_2$)		90—92/0.05	*m/z* 286.0758 (M^+ 286.0758)			$C_{13}H_{13}F_3N_2S$
2-(*N*-Benzyl-*N*-cyclopropylamino)-4-isopropylthiazole (8e; R^3 = Pr^i)		114—116/0.4	70.3 (70.5	7.2 7.4	10.0 10.3)	$C_{16}H_{20}N_2S$
2-(*N*-Benzyl-*N*-cyclopropylamino)-4-(4-bromophenyl)thiazole (8e; R^3 = C_6H_4Br-*p*)	92—93		59.1 (59.2	4.5 4.5	7.4 7.3)	$C_{19}H_{17}BrN_2S$
[(8a; R^3 = H), (8a, b, c; R^3 = Me), (8a, c; R^3 = $PhCH_2$), (8a, c; R^3 = Pr^i), (8a, b, c; R^3 = Bu^t), (8a, c, e; R^3 = C_6H_4Br-*p*), (8a, c; R^3 = C_6H_4OMe-*p*)],[f] (8a; R^3 = Ph) [g]						
Ethyl 4-benzyl-2-[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]thiazole-5-carboxylate (9d; R^3 = $PhCH_2$)	72—74		53.5 (53.6	4.7 4.8	7.8 7.8)	$C_{16}H_{17}F_3N_2O_2S$
5-Cyano-2-dimethylamino-4-methylthiazole (10a; R^3 = Me)	70—71		*m/z* 167.0517 (M^+ 167.0517)			$C_7H_9N_3S$
5-Cyano-4-methyl-2-(*N*-methyl-*N*-phenylamino)thiazole (10b; R^3 = Me)	88—89		62.6 (62.8	4.8 4.8	18.5 18.3)	$C_{12}H_{11}N_3S$
5-Cyano-2-dimethylamino-4-t-butylthiazole (10a; R^3 = C_6H_4Br-*p*)	54—55		53.3 (53.4	7.2 7.2	20.2 20.1)	$C_{10}H_{15}N_3S$
(11a; R^3 = H) [h]						
2-Dimethylamino-4-methyl-5-nitrothiazole (11a; R^3 = Me)	142—143		38.7 (38.5	4.7 4.8	22.3 22.4)	$C_6H_9N_3O_2S$
2-(*N*-Benzyl-*N*-methylamino)-4-methyl-5-nitrothiazole (11c; R^3 = Me)	61—62		54.5 (54.7	5.1 5.0	15.8 16.0)	$C_{12}H_{13}N_3O_2S$
4-Benzyl-2-dimethylamino-5-nitrothiazole (11a; R^3 = $PhCH_2$)	126—128		54.8 (54.7	5.1 5.0	15.9 16.0)	$C_{12}H_{13}N_3O_2S$
2-Dimethylamino-4-isopropyl-5-nitrothiazole (11a; R^3 = Pr^i)	81—83		44.5 (44.6	6.0 6.1	19.4 19.5)	$C_8H_{13}N_3O_2S$
2-(*N*-Benzyl-*N*-methylamino)-4-isopropyl-5-nitrothiazole (11c; R^3 = Pr^i)	77—78		*m/z* 291.1041 (M^+ 291.1041)			$C_{14}H_{17}N_3O_2S$

2-Dimethylamino-5-nitro-4-t-butylthiazole (11a; R^3 = Bu^t)	126—127	47.2	6.7	18.5	$C_9H_{15}N_3O_2S$
		(47.2	6.55	18.3)	
2-[*N*-Methyl-*N*-(4-nitrophenyl)amino]-5-nitro-4-t-butylthiazole (13)	121—123	49.9	4.9	16.7	$C_{14}H_{16}N_4O_4S$
		(50.0	4.8	16.7)	
2-[*N*-Methyl-*N*-(4-nitrophenyl)amino]-4-t-butylthiazole (14)	133—134	57.8	5.95	14.5	$C_{14}H_{17}N_3O_2S$
		(57.7	5.8	14.4)	
2-Dimethylamino-5-nitro-4-phenylthiazole (11a; R^3 = Ph)	136—138	53.2	4.6	17.0	$C_{11}H_{11}N_3O_2S$
		(53.0	4.45	16.9)	
4-(4-Bromophenyl)-2-dimethylamino-5-nitrothiazole (11a; R^3 = C_6H_4Br-*p*)	205—206	40.5	3.2	12.6	$C_{11}H_{10}BrN_3O_2S$
		(40.3	3.1	12.8)	
2-(*N*-Benzyl-*N*-methylamino)-4-(4-bromophenyl)-5-nitrothiazole (11c; R^3 = C_6H_4Br-*p*)	132—133	50.7	3.6	10.2	$C_{17}H_{14}BrN_3O_2S$
		(50.5	3.5	10.4)	
2-Dimethylamino-4-(4-methoxyphenyl)-5-nitrothiazole (11a; R^3 = C_6H_4OMe-*p*)	169—171	51.4	4.6	15.1	$C_{12}H_{13}N_3O_3S$
		(51.6	4.7	15.0)	
2-Dimethylamino-5-trifluoroacetylthiazole (12a; R^3 = H)	78—79	37.2	3.1	12.6	$C_7H_7F_3N_2OS$
		(37.5	3.15	12.5)	
2-Dimethylamino-4-methyl-5-trifluoroacetylthiazole (12a; R^3 = Me)	95—97	40.4	3.8	11.6	$C_8H_9F_3N_2OS$
		(40.3	3.8	11.7)	
4-Methyl-2-(*N*-methyl-*N*-phenylamino)-5-trifluoroacetylthiazole (12b; R^3 = Me)	77—78	52.0	3.9	9.0	$C_{13}H_{11}F_3N_2OS$
		(52.0	3.7	9.3)	
2-(*N*-Benzyl-*N*-methylamino)-4-methyl-5-trifluoroacetylthiazole (12c; R^3 = Me)	74—75	53.5	4.2	8.8	$C_{14}H_{13}F_3N_2OS$
		(53.5	4.2	8.9)	
4-Methyl-2-(*N*-methyl-*N*-neopentylamino)-5-trifluoroacetylthiazole (12k; R^3 = Me)	103—104	48.7	5.8	9.5	$C_{12}H_{17}F_3N_2OS$
		(49.0	5.8	9.5)	
4-Benzyl-2-dimethylamino-5-trifluoroacetylthiazole (12a; R^3 = $PhCH_2$)	92—94	53.3	4.1	8.7	$C_{14}H_{13}F_3N_2OS$
		(53.5	4.2	8.9)	
4-Benzyl-2-(*N*-benzyl-*N*-methylamino)-5-trifluoroacetylthiazole (12c; R^3 = $PhCH_2$)	73—74	61.3	4.3	7.0	$C_{20}H_{17}F_3N_2OS$
		(61.5	4.4	7.2)	
4-Benzyl-2-[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]-5-trifluoroacetylthiazole (12d; R^3 = $PhCH_2$)	112—114	46.9	3.0	7.3	$C_{15}H_{12}F_6N_2OS$
		(47.1	3.2	7.3)	
2-Dimethylamino-4-isopropyl-5-trifluoroacetylthiazole (12a; R^3 = Pr^i)	70—71	45.3	4.8	10.3	$C_{10}H_{13}F_3N_2OS$
		(45.1	4.9	10.5)	
2-(*N*-Benzyl-*N*-methylamino)-4-isopropyl-5-trifluoroacetylthiazole (12c; R^3 = Pr^i)	48—50	56.3	5.0	8.1	$C_{16}H_{17}F_3N_2OS$
		(56.1	5.0	8.2)	
2-(*N*-Benzyl-*N*-cyclopropylamino)-4-isopropyl-5-trifluoroacetylthiazole (12e; R^3 = Pr^i)	54—56	58.5	5.0	7.7	$C_{18}H_{19}F_3N_2OS$
		(58.7	5.2	7.6)	
4-t-Butyl-2-dimethylamino-5-trifluoroacetylthiazole (12a; R^3 = Bu^t)	92—94	47.3	5.5	9.9	$C_{11}H_{15}F_3N_2OS$
		(47.1	5.4	10.0)	
2-(*N*-Methyl-*N*-phenylamino)-4-t-butyl-5-trifluoroacetylthiazole (12b; R^3 = Bu^t)	77—78	56.3	5.2	8.2	$C_{16}H_{17}F_3N_2OS$
		(56.1	5.0	8.2)	
2-(*N*-Benzyl-*N*-methylamino)-4-t-butyl-5-trifluoroacetylthiazole (12c; R^3 = Bu^t)	76—77	57.3	5.4	7.9	$C_{17}H_{19}F_3N_2OS$
		(57.3	5.4	7.9)	
4-(4-Bromophenyl)-2-dimethylamino-5-trifluoroacetylthiazole (12a; R^3 = C_6H_4Br-*p*)	129—130	41.3	2.5	7.4	$C_{13}H_{10}BrF_3N_2OS$
		(41.2	2.7	7.4)	
2-(*N*-Benzyl-*N*-methylamino)-4-(4-bromophenyl)-5-trifluoroacetylthiazole (12c; R^3 = C_6H_4Br-*p*)	59—60	*m/z* 453.9963			$C_{19}H_{14}BrF_3N_2OS$
		(M^+ 453.9963)			
2-(*N*-Benzyl-*N*-cyclopropylamino)-4-(4-bromophenyl)-5-trifluoroacetylthiazole (12e; R^3 = C_6H_4Br-*p*)	124—125	52.5	3.4	5.7	$C_{21}H_{16}BrF_3N_2OS$
		(52.4	3.4	5.8)	
2-Dimethylamino-4-(4-methoxyphenyl)-5-trifluoroacetylthiazole (12a; R^3 = C_6H_4OMe-*p*)	127—129	50.8	3.9	8.5	$C_{14}H_{13}F_3N_2O_2S$
		(50.9	4.0	8.5)	
2-(*N*-Benzyl-*N*-methylamino)-4-(4-methoxyphenyl)-5-trifluoroacetylthiazole (12c; R^3 = C_6H_4OMe-*p*)	71—73	59.1	4.5	6.8	$C_{20}H_{17}F_3N_2O_2S$
		(59.1	4.2	6.9)	

[a] Ref. 7. [b] Ref. 5. [c] Ref. 8. [d] Ref. 10. [e] W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, 1953, **18**, 779. [f] Ref. 1. [g] M. Sélim, M. Sélim, O. Tétu, G. Drillen, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1965, 3527. [h] Ref. 12.

Table 2. ^{1}H N.m.r. and i.r. absorptions of 5-derivatives of 2-(*N*,*N*-disubstituted amino)thiazoles

The ^{1}H n.m.r. signals (δ values at 305 K) are for solutions in $CDCl_3$. The $\Delta G^{\ddagger}$ values (kJ mol^{-1}, statistical error ±3 kJ mol^{-1}), obtained at a source frequency of 90 MHz using solutions in CD_2Cl_2 over the range 183—305 K, are the activation energies for rotation about the C(2)–N bond at 298 K. I.r. work was carried out as described previously;[a] band positions are in cm^{-1} at 303 K. The weaker components of doublets are shown in parentheses; their areas are generally 3—10% of those of the stronger components in CCl_4 and 5—15% in MeCN

Compd.	R^3	^{1}H N.m.r. N–CH_3	N–CH_2	$\Delta G^{\ddagger}$
(10a)	Me	3.12		52
(10b)	Me	3.52		*b*
(10a)	Bu^t	3.09		51
(11a)	H	3.20		56
(11a)	Me	3.16		57
(11c)	Me	3.06	4.73	56
(11a)	$PhCH_2$	3.13		58

Compd.	R^3	^{1}H N.m.r. N–CH_3	N–CH_2	$\Delta G^{\ddagger}$
(11a)	Pr^i	3.18		58
(11c)	Pr^i	3.07	4.77	56
(11a)	Bu^t	3.15		57
(11a)	Ph	3.20		58
(11a)	C_6H_4Br-*p*	3.18		59
(11c)	C_6H_4Br-*p*	3.10	4.78	59
(11a)	C_6H_4OMe-*p*	3.21		58

Compd.	R^3	^{1}H N.m.r. N–CH_3	N–CH_2	$\Delta G^{\ddagger}$	I.r. CO region: CCl_4		MeCN	
(12a)	H	3.26		57	1 673	(1 648)	1 665	(1 646)[c]
(12a)	Me	3.17		56	1 672	(1 646)	1 663	(1 638)
(12b)	Me	3.58		*b*	1 674	(1 648)	1 666	(1 640)
(12c)	Me	3.09	4.80	55	1 672	(1 646)	1 663	(1 635)
(12k)	Me	3.18	3.40	*d*	1 670	(1 645)	1 659	(1 635)
(12a)	$PhCH_2$	3.13		57	1 671	(1 647)	1 662	(1 638)
(12c)	$PhCH_2$	3.03	4.76	58	1 671	(1 648)	1 663	(1 638)
(12d)	$PhCH_2$	3.15	4.25	*e*	1 676	(1 651)	1 668	(1 642)
(12a)	Pr^i	3.20		56	1 670	(1 643)	1 660	(1 634)
(12c)	Pr^i	3.08	4.82	56	1 670	(1 644)	1 658	(1 634)
(12c)	Pr^i		4.92	*f*	1 671	(1 645)	1 658	(1 635)
(12a)	Bu^t	3.19		55	1 672	(1 641)	1 661	(1 631)
(12b)	Bu^t	3.60		*b*	1 674	(1 644)	1 663	(1 633)
(12c)	Bu^t	3.09	4.82	56	1 672	(1 642)	1 661	(1 632)
(12a)	C_6H_4Br-*p*	3.22		57	1 679	(1 645)	1 669	(1 636)
(12c)	C_6H_4Br-*p*	3.12	4.83	57	1 679	(1 646)	1 669	(1 637)
(12e)	C_6H_4Br-*p*		4.92	*f*	1 680	(1 646)	1 669	(1 635)
(12a)	C_6H_5OMe-*p*	3.16		56	1 674	(1 641)	1 663	(1 631)
(12c)	C_6H_4OMe-*p*	3.08	4.80	55	1 675	(1 641)	1 663	(1 640)

[a] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1959. [b] No splitting of N–CH_3 singlet. [c] Area 67% of that of the stronger band (at 1 665 cm^{-1}). [d] The N–CH_3 and N–CH_2 singlets split at 263 K but overlap prevents evaluation of $\Delta G^{\ddagger}$. [e] No splitting of N–CH_3 singlet or N–CH_2 quartet. [f] No splitting of N–CH_2 singlet or N–$CHCH_2CH_2$ multiplet (at δ 2.59).

Et_2O (9 : 1) eluted the *nitro compound* (14) (0.75 g) followed by the dinitro compound (13) (0.11 g).

2-(N-*Benzyl*-N-*methylamino*)-4-*methyl*-5-*nitrothiazole* (11c; R^3 = Me).—The sodio derivative of 1-nitropropan-2-one [19] (0.65 g) was added during 10 min to a mixture of CCl_4 (20 ml) and H_2O (5 ml) containing Br_2 (0.29 ml) which was stirred vigorously at 0 °C. After a further 30 min more CCl_4 (20 ml) was added. The organic layer was washed with H_2O, dried, and evaporated to give an oil (0.61 g) shown by ^{1}Hn.m.r. to contain 1-bromo-1-nitropropan-2-one (6; R^3 = Me) (93%). Condensation of this oil with *N*-benzyl-*N*-methylthiourea (0.63 g) gave the *5-nitrothiazole* (11c; R^3 = Me) (0.45 g) which was purified by adsorption on SiO_2 and elution with Et_2O.

4-*Benzyl*-2-*dimethylamino*-5-*nitrothiazole* (11a; R^3 = $PhCH_2$).—$NO_2^+BF_4^-$ (0.4 g) was added to a stirred solution of 4-benzyl-2-dimethylaminothiazole (0.5 g) in dry MeCN (5 ml). After 30 min H_2O was added. Isolation with $CHCl_3$ gave material which was chromatographed on SiO_2 (50 g). Light petroleum–Et_2O (7 : 3) eluted a product (0.11 g) which, from a ^{1}H n.m.r. examination, is considered to be 2-dimethylamino-4-(4-nitrobenzyl)thiazole. $CHCl_3$ eluted the *5-nitrothiazole* (11a; R^3 = $PhCH_2$) (0.31 g). Repetition of the experiment using tetrahydrothiophene 1,1-dioxide as solvent gave the product (11a; R^3 = $PhCH_2$) in lower yield (22%). Similar nitration of 2-(*N*-benzyl-*N*-methylamino)-4-isopropylthiazole (8c; R^3 = Pr^i) in tetrahydrothiophene 1,1-dioxide gave the *5-nitrothiazole* (11c; R^3 = Pr^i) (18%).

2-(N-*Benzyl*-N-*methylamino*)-4-(4-*bromophenyl*)-5-*nitrothiazole* (11c; R^3 = C_6H_4Br-*p*).—2-(*N*-Benzyl-*N*-methylamino)-4-(4-bromophenyl)thiazole (0.8 g) was added during 15 min to nitric acid (70%; 15 ml) which was stirred at 5 °C. After a further 10 min the solution was poured into ice–H_2O (80 ml) and basified with 18M-NH_3. Isolation with EtOAc gave the *5-nitrothiazole* (11c; R^3 = C_6H_4Br-*p*) (0.79 g). Similarly obtained were the *5-nitrothiazoles* (11a; R^3 = Ph, C_6H_4Br-*p*, and C_6H_4OMe-*p*), yields 80—90%.

2-(N-*Benzyl*-N-*methylamino*)-4-*methyl*-5-*trifluoroacetylthiazole* (12c; R^3 = Me).—A solution of 2-(*N*-benzyl-*N*-methylamino)-4-methylthiazole (0.74 g) and trifluoroacetic anhydride (1 ml) in dry C_6H_6 (2 ml) was boiled gently under

reflux for 4 h. (If the boiling is vigorous most of the anhydride remains in the condenser.) The solution was poured into H_2O and basified with Na_2CO_3. Isolation with Et_2O gave the 5-*trifluoroacetylthiazole* (12c; R^3 = Me) (1.01 g). Similarly obtained were the nineteen 5-*trifluoroacetylthiazoles* listed in Table 2, yields 85—95%.

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