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-NR₂ groups (ΔG^{\dagger}_{298}) in the 5-substituted thiazoles were established by variable temperature ¹H n.m.r. spectrometry to be 57.4 kJ mol⁻¹ (5-NO₂), 56.2 (5-COCF₃), 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-5carbaldehydes 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 electronwithdrawing 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-d) substituted amino)thiazoles (hereinafter abbreviated to 2-NR₂-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-NR₂thiazoles 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-NR₂-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 ' the reaction of amines with silicon tetraisothiocyanate⁴ was unsatisfactory for preparing some of the required N,N-disubstituted thioureas and attention was turned to Wallach's route⁵ (later modified⁶) involving addition of hydrogen sulphide to cyanamides. Many N-monoand 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-NR₂-thiazoles (8); as explained earlier ¹ the 4-benzyl compounds (8; R³ = PhCH₂) are more readily obtained *via* the 5-carboxylates (9; R³ = PhCH₂). Condensations involving α -bromo- α -cyanoketones (7) are less satisfactory but three 5-cyano-2-NR₂-thiazoles (10) were prepared in this way. Trifluoroacetylation of the 2-NR₂-thiazoles (8) was remarkably easy and a simple general procedure afforded nineteen 5-trifluoroacetyl-2-NR₂-thiazoles (12) in 85—95% yield. In contrast, nitration presented difficulties.

Nitration of 4-substituted 2-aminothiazoles (R = H, Me, or Bu¹) 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-NR₂-thiazoles are reported to undergo cleavage rather than nitration.¹³

In the present work (Scheme 2) it was found that 4-alkyl-2-NR2-thiazoles are unaffected by 70% nitric acid alone. The 4-alkyl-2-NMe₂ 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 benzylcontaining 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 4aryl-2-NR₂-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-NR₂-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



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Scheme 1. N,N-Disubstituted cyanamides and thioureas, and 5derivatives of 2-(N,N-disubstituted amino)thiazoles. Reagents: i, MgCO₃-H₂O-Et₂O or EtOAc, 5 °C; ii, H₂S-Et₃N-EtOH, 10 °C;

iii, MeI-KOH-Me₂SO; iv, EtOH or Me₂CO or Me₂CO-MgSO₄, heat; v, 6M-HCl, heat; vi, see Scheme 2; vii, (CF₃CO)₂O-C₆H₆, heat

The main spectrometric results are shown in Table 2. With most of the 5-substituted-2-NR₂-thiazoles (10), (11), and (12), splitting of the N-CH¹H n.m.r. signals occurred in the range -3 to -20 °C, and standard treatment ¹⁵ led to the ΔG^{\ddagger} values for rotation of the 2-NR₂ groups. In the amines with R_2 – Me and Ph, Me and CF_3CH_2 , and PhCH₂ and cyclopropyl no splitting was observed. It could be argued that the electronic effects of these groups lower the rotational barrier, but the ΔG^{\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 ΔG^{\ddagger} 32.2 kJ mol⁻¹,¹⁶ and it seems more probable that with these 2-NR2 groups one rotameric form is markedly the more stable and is adopted preferentially over the temperature range studied. The variations in the ΔG^{\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-NR₂ 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-NR₂-compound (11a; R⁵) · H) examined previously, in CHF₂Cl at 60 MHz,¹⁶ ΔG^{\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

$$Bu^{t} N Bu^{t} N$$

$$D_{2}N \int_{S} J^{N} NMe \cdot C_{6}H_{4}NO_{2} - p$$

$$(13) \qquad (14)$$

(8a;
$$R^3 = H$$
, Me, Prⁱ, and Bu^t) \xrightarrow{i} (11a; $R^3 = H$, Me, Prⁱ, and Bu^t)

(8a;
$$\mathbf{R}^3 = \mathbf{Ph}$$
, $\mathbf{C}_6\mathbf{H}_4\mathbf{Br}$ -*p*, and $\mathbf{C}_6\mathbf{H}_4\mathbf{OMe}$ -*p*) $\xrightarrow{\Pi}$
(11a; $\mathbf{R}^3 = \mathbf{Ph}$, $\mathbf{C}_6\mathbf{H}_4\mathbf{Br}$ -*p*, and $\mathbf{C}_6\mathbf{H}_4\mathbf{OMe}$ -*p*)

$$(8c; R^{3} = C_{6}H_{4}Br-p) \xrightarrow{ii} (11c; R^{3} = C_{6}H_{4}Br-p)$$

$$(8b; R^{3} = Bu^{t}) \xrightarrow{i} (13) + (14)$$

$$(8c; R^{3} = Me) \xrightarrow{i} (11c; R^{3} = Me) \xrightarrow{iii} (3c) + (6; R^{3} = Me)$$

$$(8a; R^{3} = PhCH_{2}) \xrightarrow{i} (11a; R^{3} = PhCH_{2}) \xrightarrow{iv} (8a; R^{3} = PhCH_{2})$$

$$(8c; R^3 = Pr^i) \xrightarrow{i} (11c; R^3 = Pr^i) \xleftarrow{iv} (8c; R^3 = Pr^i)$$

Scheme 2. Preparation of 5-nitro derivatives of 2-(N,N-disubstituted amino)thiazoles. Reagents: i, 70% HNO₃-H₂SO₄ at 20 °C; ii, 70% HNO₃ at 5 °C; iii, Me₂CO, heat; iv, NO₂+BF₄-MeCN or tetrahydrothiophene 1,1-dioxide



" Ref. 1. " Ref. 2. " Ref. 16, $\Delta G^{\ddagger}_{150}$ in CHF₂Cl at 60 MHz.

Scheme 3. Barriers to rotation of 2-NR2 groups in compounds of types (10), (11), and (12); rotational isomerism in compounds of type (12)

average ΔG^{\ddagger} values for different types of 5-substituted 2-NR₂-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 ΔG^{\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-COCF₃, and 5-CO₂Et types. This point also emerges from the correspondence between the ΔG^{\ddagger} values and the σ_{P}^{-} constants of the 5-substituents for which figures are available (NO₂, 1.27; CHO, 1.13; CN, 1.00; CO₂Et, 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 ¹⁹F 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 4substituents. 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 ΔG^{\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 4substituent 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 MgCO₃ (4 g) in H₂O–Et₂O (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 Et₂O, and distillation gave *neopentylcyanamide* (12.7 g). A similar yield was obtained when EtOAc was used in place of Et₂O. 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 Me₂SO (65 ml) containing neopentylcyanamide (2g) (8.2 g) and the stirring was continued for 1 h. Dilution with water, isolation with Et₂O, 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 H₂S was bubbled through a solution of N-methyl-N-neopentylcyanamide (2k) (5.6 g) and Et₃N (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 CH₂Cl₂. 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 PrⁱOH. 4-Methyl-2-(N-methyl-N-neopentylamino)thiazole (8k; $R^3 = Me$).—A solution of chloroacetone (2.2 ml) in Me₂CO (5 ml) was added during 10 min to a solution of the thiourea (3k) (4.05 g) in Me₂CO (25 ml) which was boiling under reflux, and the boiling was continued for 2 h. The solution was poured into 2M-H₂SO₄, washed with Et₂O, and basified with 18M-NH₃. Isolation with Et₂O and distillation of the product gave the *thiazole* (8k; $R^3 = Me$) (4.3 g). A similar yield was obtained when anhydrous MgSO₄ was present during the condensation; ² the use of EtOH in place of Me₂CO led to a lower yield (75%). Similarly obtained were the *thiazoles* (8e; $R^3 = Pr^i$ and C₆H₄Br-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-phenylpropanoate² (5; $R^3 = Ph$) with the thiourea (3d) using a suspension of anhydrous MgSO₄ in dry Me₂CO² 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 h¹ 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 Et₂O (300 ml) ¹⁸ was collected and dissolved in H₂O-Et₂O (60 ml; 1 : 5). Br₂ (60 g) was added to the stirred mixture during 45 min. The addition of ice-H₂O (50 g), basification with Na₂CO₃, and isolation with Et₂O gave an oil (7 g) shown by ¹H n.m.r. to contain 1-bromo-1-cyanopropan-2-one (7; R³ = 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 SiO₂ (100 g). Light petroleum-Et₂O (9 : 1) eluted the 5-cyanothiazole (10a; R³ = Me) (0.75 g). Similarly obtained was the 5-cyano-2-(N-methyl-N-phenylamino)thiazole (10b; R³ = Me) (55% from 1-bromo-1-cyanopropan-2-one).

5-Cyano-2-dimethylamino-4-t-butylthiazole (10a; $R^3 = Bu^1$). —A solution of Br_2 (0.4 ml) in CHCl₃ (5 ml) was added during 10 min to a stirred solution of 1-cyano-3,3-dimethylbutan-2one (1.5 g) in CHCl₃ (15 ml). After 45 min the solution was washed with aq. Na₂CO₃, dried, and evaporated to give an oil (2.42 g) shown by ¹H n.m.r. to contain 1-bromo-1-cyano-3,3dimethylbutan-2-one (7; $R^3 = Bu^1$) (91%). Condensation of this oil with N,N-dimethylthiourea (1.18 g) gave the 5-cyanothiazole (10a; $R^3 = Bu^1$) (1.1 g) which was purified by sublimation at 100 °C/1 mmHg.

5-Nitrothiazoles. 2-Dimethylamino-5-nitro-4-t-butylthiazole (11a; $R^3 cices Bu^t$).—Nitric acid (70%; 0.82 ml) was added in drops to a vigorously stirred solution of 2-dimethylamino-4-tbutylthiazole (1.9 g) in H₂SO₄ (10 ml) at 5 °C. The solution was stirred at 20 °C for 3 h, poured into ice-H₂O (80 g), and neutralised with 18M-NH₃. The precipitate was collected and crystallised from MeOH to give the 5-nitrothiazole (11a; $R^3 cices Bu^t$) (1.6 g). Similarly obtained were the 5-nitrothiazoles (11a; $R^3 cices H$, Me, and Prⁱ), 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; R³ Bu⁴) (1.5 g) in H₂SO₄ (20 ml) at 0 °C. After 2 h at 0 °C, workup as in the foregoing experiment gave material which was chromatographed on SiO₂ (100 g). Light petroleum–Et₂O (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; R³ – Bu⁴) (0.67 g). Light petroleum-

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

		B.p. [Bath	Ке	ound (%) squires (?)	(°	
Compound	M.p. (°C)	mmHg]	ပ၂	H	z	Molecular formula
N-Methyl-N-(2,2,2-trifluoroethyl)cyanamide (2d)		4950/15	lm)	z 138.040 + 138.040	96	
N-Benzyl-N-cyclopropylcyanamide (2e)		94—96/0.1	76.4 76.7	7.1	16.2 16.3)	$C_{11}H_{10}N_2$
Neopentylcyanamide (2g)		7273/13	(64.1	10.8	25.0 24 9)	$C_6H_{12}N_2$
N-Methyl-N-t-butylcyanamide (2j)		7071/15	64.0 64.0	10.8	24.8 24.8	C ₆ H ₁₂ N ₂
N-Methyl-N-neopentylcyanamide (2k)		32—33/0.1	66.8 66.8 66.6	11.2	22.2) 22.2)	$C_7H_{14}N_2$
(2a)," (2b)," (2c, h, i), (2f) " N-Methyl-N-(2,2,2-trifluoroethyl)thiourea (3d)	157158		22.4	4.4	17.5	C ₃ H ₇ F ₃ N ₂ S
N-Benzyl-N-cyclopropylthiourea (3e)	127—128		63.8 63.8	t 80 o 7 0 t	13.4	$C_{11}H_{12}N_2S$
N-Methyl-N-neopentylthiourea (3k)	156—157		(04.0 52.4 (52.4	0.0 10.2 10.1	17.5 17.5 17.5	C ₇ H ₁₆ N ₂ S
(3a, b), ⁶ $(3c)$ ^e 4-Methyl-2-(<i>N</i> -methyl- <i>N</i> -neopentylamino)thiazole (8k; $\mathbb{R}^3 = \mathbb{M}e$)		54—56/0.25	lui lui	211.861 z	10	$C_{10}H_{18}N_2S$
4-Benzyl-2-[<i>N</i> -methyl- <i>N</i> -(2,2,2-trifluoroethyl)amino]thiazole (8d; $\mathbb{R}^3 = \mathbb{PhCH}_2$)		9092/0.05		2286.075 + 786.075	28	C ₁₃ H ₁₃ F ₃ N ₂ S
2-(<i>N</i> -Benzyl- <i>N</i> -cyclopropylamino)-4-isopropylthiazole (8e; $R^3 = Pr^i$)		114116/0.4	70.3	7.2	10.0 10.0	$C_{16}H_{20}N_2S$
2-(<i>N</i> -Benzyl- <i>N</i> -cyclopropylamino)-4-(4-bromophenyl)thiazole (8e; $\mathbb{R}^3 = \mathbb{C}_6 \mathbb{H}_4 \mathbb{B} r$ - <i>p</i>)	92—93		59.1 59.1	4.5	(5.01 4.1 (* 1	$C_{19}H_{17}BrN_2S$
$[(8a; R^3 = H), (8a, b, c; R^3 = Me), (8a, c; R^3 = PhCH_2), (8a, c; R^3 = Pr^i), (8a, b, c; R^3 = Bu^i), (8a, c, e; R^3 = C, H_3Br-p), (8a, c; R^3 = C, H_4Br-p)]/(8a; R^3 = Ph)^g$			7.66)) t		
Ethyl 4-benzyl-2-[<i>N</i> -methyl- <i>N</i> -(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)	C16H17F3N2O2S
5-Cyano-2-dimethylamino-4-methylthiazole (10a; $\mathbf{R}^3 = \mathbf{Me}$)	70—71			z 167.051 + 167.051	(21) (71)	C,H,N,S
5-Cyano-4-methyl-2-(<i>N</i> -methyl- <i>N</i> -phenylamino)thiazole (10b; $\mathbb{R}^3 = \mathbb{M}e$)	88—89		62.6	4.8	18.5 18.3	C12H11N3S
5-Cyano-2-dimethylamino-4-t-butylthiazole (10a; $\mathbb{R}^3 = \mathbb{C}_6 \mathbb{H}_4 \mathbb{B}r_2$)	5455		53.3 53.3 (53.4	272	20.2 20.1)	C ₁₀ H ₁₅ N ₃ S
(11a; $R^3 = H$) ^{<i>n</i>} 2-Dimethylamino-4-methyl-5-nitrothiazole (11a; $R^3 = Me$)	142—143		38.7	4.7 4.8	22.3	C ₆ H ₉ N ₃ O ₂ S
2-(N-Benzyl-N-methylamino)-4-methyl-5-nitrothiazole (11c; $R^3 = Me$)	61—62		54.5	5.1	15.8	C12H13N3O2S
4-Benzyl-2-dimethylamino-5-nitrothiazole (11a; $R^3 = PhCH_2$)	126128		54.8	5.1	15.9	C ₁₂ H ₁₃ N ₃ O ₂ S
2-Dimethylamino-4-isopropyl-5-nitrothiazole (11a; $\mathbf{R}^{3} = \mathbf{P}^{1}$)	8183		44.5	0.9 9	19.4	C ₆ H ₁₃ N ₃ O ₂ S
2-(N-Benzyl-N-methylamino)-4-isopropyl-5-nitrothiazole (11c; $R^3 = Pr^1$)	77—78			² 291.104	14 (I)	C14H17N3O2S

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2-Dimethylamino-5-nitro-4-t-butylthiazole (11a; $\mathbb{R}^3 = \mathbb{B}u^t$)	126127	47.2 (47.2	6.7 6.55	18.5 18.3)	C ₉ H ₁₅ N ₃ O ₂ S
2-[N-Methyl-N-(4-nitrophenyl)amino]-5-nitro-4-t-butylthiazole (13)	121123	49.9	4.9 4.8	16.7	C14H16N4O4S
2-[N-Methyl-N-(4-nitrophenyl)amino]-4-t-butylthiazole (14)	133134	57.8 57.8	4.0 5.95	14.5	$C_{14}H_{17}N_3O_2S$
2-Dimethylamino-5-nitro-4-phenylthiazole (11a; $R^3 = Ph$)	136138	53.2	6.0 4.6	14.4)	C ₁₁ H ₁₁ N ₃ O ₂ S
4-(4-Bromophenyl)-2-dimethylamino-5-nitrothiazole (11a; $R^3 = C_6H_4Br_p$)	205206	40.5 40.5	3.2 2.2 -	16.9) 12.6	C ₁₁ H ₁₀ BrN ₃ O ₂ S
2-(N-Benzyl-N-methylamino)-4-(4-bromophenyl)-5-nitrothiazole (11c; $R^3 = C_8H_4Br_p$)	132133	50.7 50.7 50.5	3.6 3.6	10.2	C ₁₇ H ₁₄ BrN ₃ O ₂ S
2-Dimethylamino-4-(4-methoxyphenyl)-5-nitrothiazole (11a; $R^3 = C_6H_4OMe_P$)	169171	51.4 51.4	0.0 7.4 7.4	15.1 15.1	C ₁₂ H ₁₃ N ₃ O ₃ S
2-Dimethylamino-5-triftuoroacetylthiazole (12a; $R^3 = H$)	7879	37.2	3.1	12.6	C,H,F ₃ N ₂ OS
2-Dimethylamino-4-methyl-5-trifluoroacetylthiazole (12a; $R^3 = Me$)	9597	(1, 5) 40,4	3.8 3.8	(c.71	C ₈ H ₉ F ₃ N ₂ OS
4-Methyl-2-(<i>N</i> -methyl- <i>N</i> -phenylamino)-5-triftuoroacetylthiazole (12b; $R^3 = Me$)	7778	52.0 52.0	8.0. 6.0 1	9.0 9.0	C ₁₃ H ₁₁ F ₃ N ₂ OS
2-(<i>N</i> -Benzyl- <i>N</i> -methylamino)-4-methyl-5-triftuoroacetylthiazole (12c; $R^3 = Me$)	7475	53.5 53.5	. 6. 6	(8.8 0	C ₁₄ H ₁₃ F ₃ N ₂ OS
4-Methyl-2-(<i>N</i> -methyl- <i>N</i> -neopentylamino)-5-triftuoroacetylthiazole (12k; $R^3 = Me$)	103104	(1927) (1927) (1927)	4.7 7.8.7	(9.5 9.5	$C_{12}H_{17}F_3N_2OS$
4-Benzyl-2-dimethylamino-5-trifluoroacetylthiazole (12a; $R^3 = PhCH_2$)	92—94	53.3	8. . . 4	(C.9 8.7	C ₁₄ H ₁₃ F ₃ N ₂ OS
4-Benzyl-2-(<i>N</i> -benzyl- <i>N</i> -methylamino)-5-triftuoroacetylthiazole (12c; $R^3 = PhCH_2$)	7374	6.13 61.3	4 4 7 0 4	(6.9 0.7 2.0	$C_{20}H_{17}F_3N_2OS$
4-Benzyl-2-[N-methyl-N-(2,2,2-trifluoroethyl)amino]-5-trifluoroacetylthiazole (12d; $R^3 = PhCH_2$)	112114	(01.) 46.9	3.0 20	(7.1	C ₁₅ H ₁₂ F ₆ N ₂ OS
2-Dimethylamino-4-isopropyl-5-triftuoroacetylthiazole (12a; $R^3 = Pr^i$)	1202	45.3	5.5 8.8	() 10.3	C ₁₀ H ₁₃ F ₃ N ₂ OS
$2-(N-Benzy)-N-methylamino)-4-isopropyl-5-triftuoroacetylthiazole (12c; R^3 = Pr^i)$	4850	(45.1 56.3	5.0	10.5) 8.1	C ₁₆ H ₁₇ F ₃ N ₂ OS
2-(<i>N</i> -Benzyl- <i>N</i> -cyclopropylamino)-4-isopropyl-5-trifluoroacetylthiazole (12e; $R^3 = Pr^4$)	5456	(56.1 58.5	5.0	8.2) 7.7	C ₁₈ H ₁₉ F ₃ N ₂ OS
4-t-Butyl-2-dimethylamino-5-triftuoroacetylthiazole (12a; $R^3 = Bu^t$)	92—94	47.3	5.5	(0./ 9.9	C ₁₁ H ₁₅ F ₃ N ₂ OS
$2-(N-Methyl-N-phenylamino)-4-t-butyl-5-triftuoroacetylthiazole (12b; \mathbb{R}^3 = \mathbb{B}u^t)$	7778	56.3 56.3	5.2 5.2	8.2 8.2	C ₁₆ H ₁₇ F ₃ N ₂ OS
2-(N-Benzyl-N-methylamino)-4-t-butyl-5-trifluoroacetylthiazole (12c; $R^3 = Bu^t$)	7677	57.3	5.4	(7.8 1.9	C ₁₇ H ₁₉ F ₃ N ₂ OS
4-(4-Bromophenyl)-2-dimethylamino-5-triftuoroacetylthiazole (12a; $R^3 = C_6H_4Brp$)	129130	0,0) 1,14 1,12	4. 0. 1 4. 0. 1	6.4	C ₁₃ H ₁₀ BrF ₃ N ₂ OS
2-(N-Benzyl-N-methylamino)-4-(4-bromophenyl)-5-trifluoroacetylthiazole (12c; $R^3 = C_6 H_4 Brp$)	5960	(41.2 m	2/ /z 453.9963 + 452.0023	(4.)	C ₁₀ H ₁₄ BrF ₃ N ₂ OS
2-(N-Benzyl-N-cyclopropylamino)-4-(4-bromophenyl)-5-trifluoroacetylthiazole (12e; $R^3 = C_6 H_4 Br-p$)	124—125	52.5	3.4	5.7	C21H16BrF3N2OS
2-Dimethylamino-4-(4-methoxyphenyl)-5-trifluoroacetylthiazole (12a; $R^3 = C_6H_4OMe-p$)	127	50.8 50.8	3.9 2.6	9.5 8.5	C ₁₄ H ₁₃ F ₃ N ₂ O ₂ S
$2-(N-\text{Benzyl-}N-\text{methylamino})-4-(4-\text{methoxyphenyl})-5-\text{trifluoroacetylthiazole}$ (12c; $R^3 = C_6H_4OMe-p$)	7173	6.0c) 59.1 1.92)	4.5 4.5 2.2	6.8 6.9 (6.9	C20H17F3N2O2S
• Ref. 7. ^h Ref. 5. ^e Ref. 8. ^d Ref. 10. ^e W. G. Finnegan, R. A. Henry, and E. Lieber, <i>J. Org. Chem.</i> , 1953 Soc. Chim. Fr., 1965, 3527. ^h Ref. 12.	, 18 , 779. ^J Ref. 1. ^g M. Sélir	n, M. Sélim,	O. Tétu, G.	Drillen,	and P. Rumpf, Bull.

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

The ¹H n.m.r. signals (δ values at 305 K) are for solutions in CDCl₃. The ΔG^{\ddagger} values (kJ mol⁻¹, statistical error ± 3 kJ mol⁻¹), obtained at a source frequency of 90 MHz using solutions in CD₂Cl₂ 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 CCl₄ and 5–15% in MeCN

		¹ H N.m.r.						¹ H N.m.r.		
Compd.	R ³	N-CH ₃	$N - CH_2$	ΔG^{\ddagger}	Compd.	F	٤ ³	N-CH ₃	N-CH ₂	ΔG^{\ddagger}
(10a)	Me	3.12		52	(11a)	Pri		3.18		58
(10b)	Me	3.52		b	(11c)	Pri		3.07	4.77	56
(10a)	But	3.09		51	(11a)	But		3.15		57
(11a)	Н	3.20		56	(11a)	Ph		3.20		58
(11a)	Me	3.16		57	(11a)	C ₆ H₄	Br-p	3.18		59
(11c)	Me	3.06	4.73	56	(11c)	C₀H₄	Br-p	3.10	4.78	59
(11a)	PhCH₂	3.13		58	(11a)	C ₆ H ₄	OMe-p	3.21		58
							I.:	r. CO regio		
		'H N.m.r.			CCl ₄			MeCN		
Compd.	R ³	N-CH	N^-CH_2	ΔG^{\ddagger}		~	~ <u> </u>	<i>с</i>		
(12a)	н	3.26		57		1 673	(1 648)	1	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	е		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	l 658	(1 634)
(12c)	Pr ⁱ		4.92	f		1 671	(1 645)	1	658	(1 635)
(12a)	Buʻ	3.19		55		1 672	(1 641)]	661	(1 631)
(12b)	But	3.60		b		1 674	(1 644)	1	i 663	(1 633)
(12c)	Bu ^t	3.09	4.82	56		1 672	(1 642)	1	661	(1 632)
(12a)	C ₆ H₄Br- <i>p</i>	3.22		57		1 679	(1 645)	1	669	(1 636)
(12c)	C ₆ H₄Br-p	3.12	4.83	57		1 679	(1 646)	1	669	(1 637)
(12e)	C ₆ H₄Br- <i>p</i>		4.92	f		1 680	(1 646)	1	669	(1 635)
(12a)	C ₆ H ₅ OMe- <i>p</i>	3.16		56		1 674	(1 641)	1	663	(1 631)
(12c)	C ₆ H₄OMe- <i>p</i>	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 ΔG^{\ddagger} . ^e No splitting of N^-CH_3 singlet or N^-CH_2 quartet. ^f No splitting of N^-CH_2 cmultiplet (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-2one ¹⁹ (0.65 g) was added during 10 min to a mixture of CCl₄ (20 ml) and H₂O (5 ml) containing Br₂ (0.29 ml) which was stirred vigorously at 0 °C. After a further 30 min more CCl₄ (20 ml) was added. The organic layer was washed with H₂O, dried, and evaporated to give an oil (0.61 g) shown by ¹Hn.m.r. to contain 1-bromo-1-nitropropan-2-one (6; R³ = Me) (93%). Condensation of this oil with N-benzyl-N-methylthiourea (0.63 g) gave the 5-nitrothiazole (11c; R³ = Me) (0.45 g) which was purified by adsorption on SiO₂ and elution with Et₂O.

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 H₂O was added. Isolation with CHCl₃ gave material which was chromatographed on SiO₂ (50 g). Light petroleum–Et₂O (7:3) eluted a product (0.11 g) which, from a ¹H n.m.r. examination, is considered to be 2-dimethyl-

amino-4-(4-nitrobenzyl)thiazole. CHCl₃ 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-H₂O (80 ml) and basified with 18M-NH₃. 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-Nmethylamino)-4-methylthiazole (0.74 g) and trifluoroacetic anhydride (1 ml) in dry C₆H₆ (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 Na₂CO₃. Isolation with Et₂O 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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