Spectrometric and Chemical Studies of 5-Acyl- and 5-Nitroso-2-(*N,N*-disubstituted Amino)thiazoles

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The conformational preferences of 2-(*N,N*-disubstituted amino)thiazoles having a 4-substituent (R^1) and a 5-acyl group (R^2CO) have been established by i.r. spectrometry and a crystallographic examination. In solution the compounds with R^2 = aryl and R^1 = Me or aryl exist predominantly or entirely in the carbonyl *O,S-anti* arrangement; for those with R^1 = aryl and R^2 = Me the *syn* rotamer is the main form but a small amount (*ca.* 15%) of the *anti* rotamer is present.

Nitrosation of 4-aryl-2-dimethylaminothiazoles gives 5-nitroso derivatives, and these are probably the first authentic nitrosothiazoles. The barrier to rotation of the dimethylamino group is unexpectedly high ($\Delta G^{\ddagger}_{298}$ = 69 kJ mol^{-1}), exceeding even that of the 5-trifluoroacetyl analogues.

The first part of this work is concerned with stereochemical features arising from rotation of the acyl group in 5-acyl-2-(*N,N*-disubstituted amino)thiazoles; the second part deals with the preparation of 5-nitroso analogues and the barrier to rotation of their 2-dimethylamino groups.

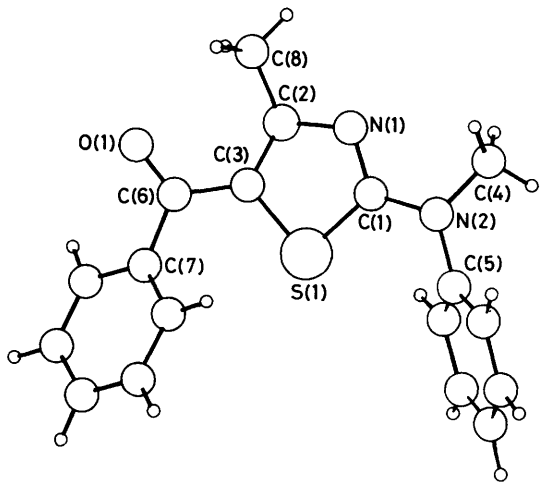
The conformational preferences of 5-acetyl-2-(*N,N*-disubstituted amino)thiazoles, unsubstituted or with methyl, t-butyl or phenyl groups at the position 4, were examined in an earlier study[1] using i.r. and *X*-ray methods. While the 4-H and 4-Ph compounds, in solution, exist predominantly as the carbonyl *O,S-syn* rotamers (structure as in Table 2) the 4-Bu^t compounds adopt the *O,S-anti* arrangement, and with the 4-Me derivatives both forms, of approximately equal stability, are present. These results established a useful general relationship for the rotational isomers of 5-acetyl compounds, namely, that the *anti* forms have i.r. CO stretching bands at higher wavenumbers than those of the *syn* rotamers. The investigation has now been extended to the 5-MeCO compounds with substituted phenyl groups at position 4, and the 5-ArCO compounds[2a] with methyl or aromatic groups at position 4 (see Table 2). Interest was mainly in the comparison between isomeric pairs in which the R^1 and R^2 groups are interchanged.

It transpired that the i.r. results, in isolation, could not be interpreted unambiguously and, therefore, to provide a firm basis one of the 5-ArCO compounds (**1c**) was examined crystallographically. The structure (Table 1) adopted represents a compromise between the tendencies to maximise mesomeric interaction and to avoid steric interference. Of the groups attached to the carbonyl function the 2-aminothiazole system is the more electron-releasing; the CO group is thus rotated less from the plane of the thiazole nucleus (11°) than from that of the phenyl ring (34°), and the bond from the carbonyl group to the thiazole nucleus (1.460 Å) is shorter than that to the phenyl ring (1.491 Å). The *N*-phenyl group is directed towards the sulphur atom, as in other 2-(*N*-methylanilino)thiazoles;[1,3] that one orientation is markedly the more stable is confirmed by the lack of splitting of the *N*-Me ^{1}H n.m.r. signals of compounds (**1a—c**) at temperatures down to −90 °C. [In contrast the α-protons of the hexahydroazepine ring in compounds (**2a—c**) become non-equivalent at *ca.* −20 °C (source frequency 90 MHz).] For the present purpose the salient feature is that compound (**1c**) exists in the *anti* arrangement with the carbonyl group and the thiazole ring almost coplanar.

To assess the possible advantage of using F.T. i.r. spectrometry in the present work two compounds (**1a**) and (**1b**) from the earlier study[1] were re-examined. There is good agreement between the results, but the improved data-processing facilities reveal the presence of a minor CO band, not detected previously, in the 4-phenyl compound (**1b**). The capabilities of high-resolution i.r. spectrometry, even with solution spectra, are illustrated by the results with the isotopic mixture (**1l**)[2b] (last entry in Table 2): the absorptions of the CH_3CO and CD_3CO groups can be detected separately in the bands arising from both stereochemical forms.

Replacement of the 2-(*N*-methylanilino) group in compounds

Table 1. Crystallographic results (standard deviations in parentheses) for compound (**1c**)



Planes [*and atoms contained*]

1 Thiazole
[S(1)–C(1)–N(1)–C(2)–C(3)]
2 Carbonyl
[C(3)–C(6)–C(7)–O(1)]
3 C-Phenyl
[aromatic ring containing C(7)]
4 *Exo* N
[C(1)–C(4)–C(5)–N(2)]
5 *N*-Phenyl
[aromatic ring containing C(5)]

Dihedral angles (°) *between planes*

Planes 1—2	168.86(2)
Planes 1—3	135.99(3)
Planes 1—4	8.43(3)
Planes 1—5	108.36(2)
Planes 2—3	34.09(2)
Planes 4—5	114.34(3)

Bond lengths (Å)

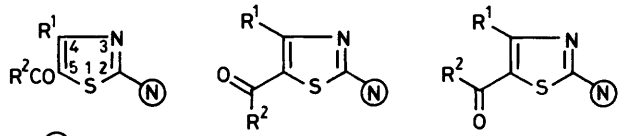
S(1)–C(1)	1.729(2)
C(1)–N(1)	1.313(2)
N(1)–C(2)	1.370(2)
C(2)–C(3)	1.374(3)
C(3)–S(1)	1.750(2)
C(1)–N(2)	1.357(2)
N(2)–C(4)	1.454(3)
N(2)–C(5)	1.433(2)
C(2)–C(8)	1.497(2)
C(3)–C(6)	1.460(2)
C(6)–O(1)	1.226(2)
C(6)–C(7)	1.491(3)

Perpendicular distances (Å)

C(8)–plane 1	−0.0099(2)
N(2)–plane 4	−0.006(3)

Table 2. Infrared CO bands of 5-acyl-2-(*N*,*N*-disubstituted amino)-thiazoles

The positions of bands (cm^{-1} at 303 K) are followed, in parentheses, by their percentage areas



(1) Ⓝ = N(Me)Ph

(2) Ⓝ = N

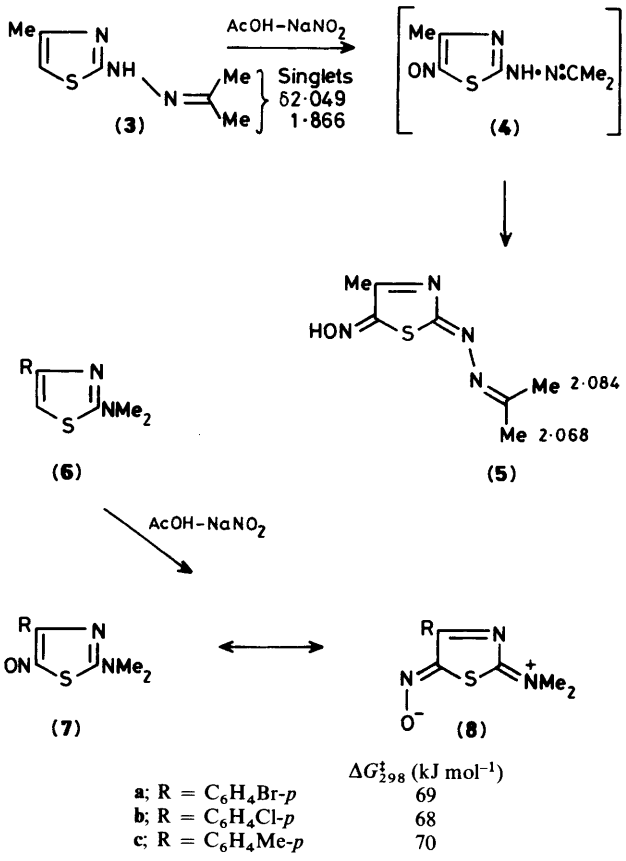
Compd.	R^1	R^2	Solvent	Form *Anti*	Form *Syn*
(1a)[a,b]	Me	Me	CCl_4	1 659(63)	1 635(37)
			MeCN	1 653(41)	1 625(59)
(2a)[a]	Me	Me	CCl_4	1 653(56)	1 628(44)
			MeCN	1 646(36)	1 618(54)
(1b)[b]	Ph	Me	CCl_4	1 667(10)	1 637(90)
(2b)	Ph	Me	CCl_4	1 662(8)	1 634(92)
(1c)	Me	Ph	CCl_4	1 630(100)	
(2c)	Me	Ph	CCl_4	1 627(100)	
(1d)	C_6H_4OMe-*p*	Me	CCl_4	1 662(15)	1 635(85)
			MeCN	1 659(17)	1 627(83)
(1e)	Me	C_6H_4OMe-*p*	CCl_4	1 628(100)	
(1f)	C_6H_4Cl-*p*	Me	CCl_4	1 667(20)	1 638(80)
			MeCN	1 662(18)	1 631(82)
(1g)	Me	C_6H_4Cl-*p*	CCl_4	1 631(100)	
(1h)	C_6H_4OMe-*p*	Ph	CCl_4	1 608(100)	
(1i)	Ph	C_6H_4OMe-*p*	CCl_4	1 618(100)	
(1j)	C_6H_4Cl-*p*	Ph	CCl_4	1 622(100)	
(1k)	Ph	C_6H_4OCl-*p*	CCl_4	1 619(100)	
(1l)[c]	(1:1) CD_3, CH_3 / CH_3, CD_3		CCl_4	1 657, 1 656 (62)	1 634, 1 633 (38)

[a] Overtone region (CCl_4): compound (**1a**) 3 298(68), 3 250 (32); compound (**2a**) 3 287(59), 3 234(41). [b] Ref. 1. [c] Ref. 2*b*.

(**1**) by the more electron-releasing hexahydroazepin-1-yl group [compounds (**2**)] causes a small decrease in wavenumber. Within each of the three sets of ketones (R^1 = Me, R^2 = Ar; R^1 = Ar, R^2 = Me; R^1 = Ar, R^2 = Ar) there is a consistent conformational preference. The main form of the 5-acetyl compounds (R^1 = Ar, R^2 = Me) is the *syn* rotamer[1] and a small amount (*ca.* 15%) of the *anti* rotamer is present. Single CO bands for the isomeric 4-methyl compounds (R^1 = Me, R^2 = Ar) establish that they exist predominantly or entirely in one form which, from the crystallographic work, is identified as the *anti* rotamer. The third set (R^1 and R^2 both aromatic) also have single bands, at positions which show that they too adopt the *anti* arrangement.

Heterocyclic compounds in which both *syn* and *anti* arrangements of an α-formyl or α-acetyl group coplanar with the nucleus are free from strain have an intrinsic preference for the *syn* rotamer[1,4] (probably because this has the carbonyl group and the formal 4,5-double bond in a *transoid* orientation). To attain the planar (acetyl group-thiazole ring) *syn* conformation the 4-Ar-5-MeCO compounds must undergo an out-of-plane twist of the aromatic ring [the dihedral angle is 45° in the 4-phenyl ketone (**1b**)[1]], and the difference in stability between the alternative forms is only *ca.* 4.3 kJ mol^{-1}. Although it was expected that the isomeric 4-Me-5-ArCO compounds would similarly accommodate the *syn* arrangement an over-riding tendency for avoiding proximity of the methyl and aromatic groups appears to prevail, and the *anti* arrangement is adopted. When both the R^1,R^2 groups are aromatic prohibitive $R^1 \cdots R^2$ repulsion is unavoidable in the *syn* form, and the carbonyl group can approach coplanarity with the thiazole ring in only the *anti* rotamer.

Scheme 1. Nitrosation of 2-(*N*-monosubstituted and *N*,*N*-disubstituted amino)thiazoles



	$\Delta G^{\ddagger}_{298}$ (kJ mol^{-1})
a; R = C_6H_4Br-*p*	69
b; R = C_6H_4Cl-*p*	68
c; R = C_6H_4Me-*p*	70

There are few reports of compounds formulated as nitrosothiazoles. The status of the earliest representative (2-methylimino-3-nitroso-2,3-dihydrothiazole)[5] is doubtful in view of later work.[6] A yellow (*sic*) product formed by nitrosating 4-phenyl-2-*p*-tolylaminothiazole was represented[7] as the 5-nitroso derivative; reduction gave, in low yield, an unstable amine. Nitrosation of 2-amino- and 2-methylamino-4-phenylthiazole under acid conditions gave salts (presumed to be 5-nitroso compounds) from which small amounts of 5-benzylideneaminothiazoles were obtained by reduction and condensation with benzaldehyde.[8] More recently the ^1H n.m.r. spectra of the yellow products formed by nitrosating four 2-hydrazino-4-methylthiazoles were interpreted as showing that they are tautomeric mixtures of 5-nitrosothiazoles and 5-oximino-2,5-dihydrothiazoles.[9] One of these nitrosations, that of 2-isopropylidenehydrazino-4-methylthiazole (**3**), was repeated here (Scheme 1). Examination of the starting material and product (obtained after purification in 70% yield) at 300 MHz showed an appreciable difference in their isopropylidene signals. This is understandable on the basis of the 5-oximino structure (**5**) (possibly with the assignments indicated), but if the reaction involves only the introduction of a remote 5-nitroso group [structure (**4**)] hardly any effect would be expected. Conversion of the initial products into the more stable 5-oximino compounds probably occurred in all the reported preparations,[7-9] and it is unlikely that an authentic nitrosothiazole had been isolated.

The nitroso-oximino isomerisation would be prevented by disubstitution of the 2-amino group. Nitrosation of several

Table 3. Crystallographic data for compound (**1c**)

Formula	$C_{18}H_{16}N_2OS$
Rel. mol. mass	308.4
Crystal class	Monoclinic
a/Å	10.850(2)
b/Å	13.682(2)
c/Å	11.617(3)
α/°	90
β/°	111.21(2)
Weights	766,855,15,81
γ/°	90
U/Å^3	1 608
Space group	$P2_1/c$
Z	4
D_c/Mg m^{-3}	1.274
F(000)	648
Crystal size/mm	0.25 × 0.5 × 0.75
Radiation	Cu-K_α
μ (cm^{-1})	17.6
(sin θ/λ)$_{max.}$	0.636
Total I^a	4 619
Unique I^b	2 825
n^c	3
R	0.0426
R_w	0.0621
$\Delta_{max.}$/e Å^{-3} ^{d}	0.3

[a] Total number of reflections measured. [b] Number of reflections with intensity significantly above the background intensity. [c] Criterion for recognising observed reflections $I > n\sigma(I)$. [d] Maximum height in final difference electron density synthesis.

4-alkyl-2-dimethylaminothiazoles, *e.g.* (**6**; R = Bu^t), gave green solutions, but after work-up mixtures of colourless products were obtained. However, from the 4-*p*-substituted phenyl analogues (**6a**—**c**) the deep-green nitroso compounds (**7a**—**c**) were obtained as crystalline products. These are stable as solids, and as solutions in non-polar solvents below *ca.* 60 °C; they are unusual in showing two *N*Me ^{1}H n.m.r. signals *at room temperature.*

Rotational barriers in the literature (*e.g.*, Me_2NNO[10] 95.3 kJ mol^{-1}, Me_2NCHO[11] 87.8, $Me_2NC_6H_4NO$-*p*[12] 50.6, $Me_2NC_6H_4CHO$-*p*[13] 45.1) suggested that 5-nitrosothiazoles should have values somewhat, but not greatly, higher than those of the corresponding 5-carbaldehydes[3] in which $\Delta G^{\ddagger}_{298}$ for rotation about the C(2)–N bond is *ca.* 53 kJ mol^{-1}. The values found for the 5-nitroso compounds (near 69 kJ mol^{-1}, Scheme) are much higher, and exceed even those of the related 5-trifluoroacetyl- and 5-nitro-thiazoles (56 and 57.5 kJ mol^{-1}, respectively).[14] This outcome is surprising, but there is little quantitative information about the nitroso group's electronic effects (for example, a σ-value is not available), and it may be that in certain structural environments the nitroso group exerts an extremely strong $-M$ effect. The present results establish that the dipolar canonical, presumably the *O,S-syn* form (**8**), makes an unusually large contribution to the structure of 2-amino-5-nitrosothiazoles; that this canonical is the counterpart of the 5-oximino structure [as in (**5**)] favoured by nitroso compounds which are free to isomerise may be significant.

Experimental

Crystallographic Work.—The determination was carried out as described in ref. 3; a complete account is given elsewhere,[15] and the customary crystallographic material is available from the Cambridge Crystallographic Data Centre.* The results, in standard form, are shown in Tables 3 and 4.

Table 4. Atomic co-ordinates for compound (**1c**)

Atom	x/a	y/b	z/c
S(1)	0.455 2(5)	0.106 4(4)	−0.200 1(4)
C(1)	0.289 1(2)	0.104 4(1)	−0.221 3(2)
C(2)	0.375 1(2)	0.137 0(1)	−0.022 1(2)
C(3)	0.491 0(2)	0.134 5(1)	−0.044 5(2)
C(4)	0.056 3(2)	0.102 0(2)	−0.352 1(2)
C(5)	0.231 5(2)	0.059 7(2)	−0.436 0(2)
C(6)	0.289 2(2)	−0.029 2(2)	−0.435 1(2)
C(7)	0.323 8(3)	−0.056 5(2)	−0.534 3(3)
C(8)	0.299 6(3)	0.005 8(2)	−0.633 2(2)
C(9)	0.242 8(4)	0.094 2(2)	−0.632 8(2)
C(10)	0.207 1(3)	0.122 0(2)	−0.535 8(2)
C(11)	0.625 0(2)	0.144 6(2)	0.045 7(2)
C(12)	0.739 5(2)	0.150 6(1)	0.003 9(2)
C(13)	0.736 2(2)	0.200 0(2)	−0.101 3(2)
C(14)	0.847 9(2)	0.203 8(2)	−0.133 3(2)
C(15)	0.962 4(2)	0.158 0(2)	−0.060 2(3)
C(16)	0.967 0(2)	0.114 0(2)	0.046 1(3)
C(17)	0.857 4(2)	0.107 9(2)	0.079 5(2)
C(18)	0.362 4(2)	0.152 0(2)	0.100 8(2)
N(1)	0.261 5(2)	0.122 1(1)	−0.122 2(1)
N(2)	0.194 9(2)	0.088 3(1)	−0.334 1(2)
O(1)	0.644 8(2)	0.147 8(2)	0.156 5(1)

Spectrometric Work.—I.r. spectra of solutions in dry solvents were recorded at 303 K on a Perkin-Elmer 1750 Fourier Transform spectrometer (at a spectral slit-width of 0.5 cm^{-1}) operating with a 3700 Professional Computer. ^{1}H N.m.r. spectra, apart from those in Scheme 1, were recorded at 90 MHz. Chemical shifts refer to solutions in $CDCl_3$ at 305 K. Rotational barriers (statistical errors ± 3 kJ mol^{-1}) were obtained by examining solutions in CD_2Cl_2 over the range 180—310 K and processing the results as described in ref. 3.

Preparative Work.—A solution of $NaNO_2$ (0.45 g) in water (20 ml) was added during 20 min to a solution of 2-isopropylidenehydrazino-4-methylthiazole[9] (**3**) (1.02 g) in 10M HCl (0.65 ml)–water (20 ml) which was stirred at 2 °C. The cooling bath was removed, and the mixture was stirred for 2 h. The insoluble material was collected and dried to give a yellow solid (1.05 g) which, after two crystallisations from EtOH, afforded 5-hydroxyimino-2-isopropylidenehydrazono-2,3-dihydrothiazole (**5**) (0.78 g), m.p. 204—210 °C (decomp.) [lit.,[9] 210—213 °C (decomp.)]; $\nu_{max.}$(Nujol) 1 635 cm^{-1} (C=N); *m/z* (chemical ionization) 199 [$(M + 1)^+$, 100%] and 198 (21).

4-*Aryl*-2-*dimethylaminothiazoles* (**6**).—Treatment of *p*-bromo-, *p*-chloro-, and *p*-methyl-phenacyl bromide with *N,N*-dimethylthiourea in Me_2CO (boiling under reflux for 2 h) by the general procedure[14] gave the 4-*p*-bromophenylthiazole[3] (**6a**) (82%), δ 3.04 (s, 6 H, NMe_2), 4-p-*chlorophenyl*-2-*dimethylaminothiazole* (**6b**) (79%), m.p. 59—60 °C (from MeOH) (Found: C, 55.2; H, 4.6; N, 11.8. $C_{11}H_{11}ClN_2S$ requires C, 55.3; H, 4.6; N, 11.7%); δ 6.61 (1 H, s, 5-H) and 3.06 (s, 6 H, NMe_2); and 2-*dimethylamino*-4-p-*tolylthiazole* (**6c**) (83%), m.p. 67—68 °C (from MeOH) (Found: C, 66.1; H, 6.3; N, 12.6. $C_{12}H_{14}N_2S$ requires C, 66.0; H, 6.5; N, 12.8%); δ 6.59 (1 H, s, 5-H) and 3.03 (s, 6 H, NMe_2).

4-*Aryl*-5-*nitrosothiazoles* (**7**).—A solution of $NaNO_2$ (0.81 g) in water (10 ml) was added during 15 min to a solution of the 4-*p*-bromophenylthiazole (**6a**) (1.72 g) in AcOH (20 ml) which

* See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1988, Issue 1.

was stirred at 2 °C. After a further 5 min, the mixture was diluted with ice–water (25 ml), basified (Na_2CO_3), and extracted with $CHCl_3$. Removal of solvent at 20 °C/15 mmHg gave a green solid (1.65 g) which was stirred with dry $CHCl_3$ (25 ml) at 40 °C for 10 min. Filtration, and storage of the filtrate at 2 °C for 2 days gave large green crystals. Recrystallisation afforded 4-p-*bromophenyl*-2-*dimethylamino*-5-*nitrosothiazole* (**7a**) (1.21 g), m.p. 146—147 °C (Found: C, 42.4; H, 3.3; N, 13.3. $C_{11}H_{10}BrN_3OS$ requires C, 42.3; H, 3.2; N, 13.5%); δ[$CDCl_3$–$(CD_3)_2SO$] 3.20 and 3.49 (two s, each 3 H, NMe_2); *m/z* 313 and 311 (M^+, 38%) and 44 (100); $\lambda_{max.}$(EtOH) 428 nm (ε 1930).

Similarly, the thiazoles (**6b**) and (**6c**) gave 4-p-*chlorophenyl*-2-*dimethylamino*-5-*nitrosothiazole* (**7b**) (61%), m.p. 139—141 °C (Found: C, 49.1; H, 3.9; N, 15.5. $C_{11}H_{10}ClN_3OS$ requires C, 49.3; H, 3.8; N, 15.7%); δ[$CDCl_3$–$(CD_3)_2SO$] 3.25 and 3.54 (NMe_2); $\lambda_{max.}$(EtOH) 428 nm (ε 3 200); and 2-*dimethylamino*-5-*nitroso*-4-p-*tolylthiazole* (**7c**) (69%), m.p. 155—156 °C [from $CHCl_3$–light petroleum (b.p. 60—80 °C)] (Found: C, 58.1; H, 5.2; N, 16.9. $C_{12}H_{13}N_3OS$ requires C, 58.3; H, 5.3; N, 17.0%); δ 2.42 (3 H, s, CH_3Ar) and 3.19 and 3.47 (NMe_2); *m/z* 247 (M^+, 8%) and 59 (100).

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