N,N-Disubstituted 2-Aminothiazole-5-carboxylates: Preparation and Rotation of Functional Groups

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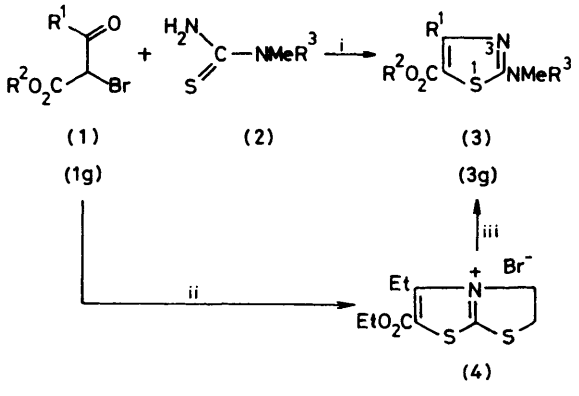
A series of new alkyl *N,N*-disubstituted 2-aminothiazole-5-carboxylates was prepared by condensing α-bromo-β-oxo-esters with *N,N*-disubstituted thioureas. The products exhibit i.r. carbonyl doublets, the higher and lower wavenumber components arising from the carbonyl *O,S-syn*-s-*trans* and *anti*-s-*trans* rotamers respectively. Variable temperature ^{1}H n.m.r. examination showed that the barriers to rotation of the 2-amino-groups are in the range 41—47 kJ mol^{-1}. Further evidence for rotational isomerism of the carboxylate group was provided by ^{13}C n.m.r. study, but the size of its rotational barrier could not be assessed.

The spectrometric work shows that there is strong mesomeric interaction between the carboxylate and amine groups.

Previously it was shown that the i.r. carbonyl doublets of alkyl thiazole-5-carboxylates arise from rotational isomers, and the stronger components (at higher wavenumber) were tentatively assigned to the carbonyl *O,S-syn*-s-*trans* forms.[1] In *N,N*-disubstituted 2-aminothiazole-5-carbaldehydes the aldehyde groups were found to adopt one form (carbonyl *O,S-syn*), and with the *N,N*-dimethyl and *N,N*-benzylmethyl compounds rotation of the 2-amino-groups is associated with high energy barriers.[2] The object of the present work was to study the effects, one on the other, of thiazole-5-carboxylate and *N,N*-disubstituted 2-amine groups with regard to rotational isomerisation and barriers to rotation, and thus to assess the degree of mesomeric interaction between them.

Few 2-(*N,N*-dialkylamino)thiazole-5-carboxylates have been described.[3] The simplest, ethyl 2-morpholino-4-phenylthiazole-5-carboxylate, was obtained from *N*-benzoylthiocarbamoylmorpholine and ethyl chloroacetate[4] but this route did not appear suitable for general development. Condensation of ethyl 2-chloro-3-oxobutanoate with allylthiourea gives the *N*-allyl 5-carboxylate;[5] although acyl chlorides attack the *exo*-nitrogen of this compound forming *N*-acyl-*N*-allyl devivatives,[5] it seemed likely[6] that the use of alkyl halides, as required for the present purposes, would lead to *endo*-*N*-alkyl 5-carboxylates. The direct approach, bromination of β-oxoesters followed by condensation of the α-bromo-derivatives with *N,N*-disubstituted thioureas, was found convenient for preparing the series of esters shown in Scheme 1. (In the four cases where comparisons were made a suspension of magnesium sulphate in acetone was found to be better than ethanol as a medium for the condensations. Subsequently this procedure has been employed effectively for various types of Hantzsch triazole syntheses.) One ester (3g) was also prepared by an alternative approach[7] in which the sulphur atom is derived from Δ^2-thiazoline-2-thiol rather than a substituted thiourea, but the yield was lower and, as observed with dihydrothiazolothiazolium salts lacking the carboxylate group,[2] the route is confined to the formation of 2-dimethylaminothiazoles.

The main spectrometric characteristics of the esters (3) are summarised in Table 1. Rotational isomerism of the ester group is established by the i.r. results, the main trends of which are similar to those reported for thiazole-5-carboxylates



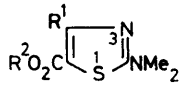
	R^1	R^2	R^3		R^1	R^2	R^3
a;	H	Et	Me	h;	Pr	Et	Me
b;	Me	Me	Me	i;	Pr^i	Et	Me
c;	Me	Et	Me	j;	Bu^t	Et	Me
d;	Me	Et	Ph	k;	Ph	Et	Me
e;	$PhCH_2$	Et	Me	l;	C_6H_4Me-*p*	Me	Me
f;	$PhCH_2$	Et	$PhCH_2$	m;	C_6H_4OMe-*p*	Et	Me
g;	Et	Et	Me	n;	C_6H_4Br-*p*	Et	Me

Scheme 1. Preparative work. *Reagents:* i, EtOH or Me_2CO–$MgSO_4$, heat; ii, Δ^2-thiazoline-2-thiol–$HCO{\cdot}NMe_2$, 20 °C; iii, Me_2NH–H_2O–EtOH, 20 °C

Table 1. I.r. and n.m.r. absorptions of 2-aminothiazole-5-carboxylates (3)

The i.r. work was carried out as described previously.[a] The positions (in cm^{-1} at 303 K) of the components of doublets are followed, in parentheses, by their percentage areas. Enthalpy differences (ΔH^0/kJ mol^{-1}) between the forms giving rise to the doublets were obtained using solutions in CS_2 over the range 204—303 K and are in the direction (form with higher cm^{-1}) ⟶ (form with lower cm^{-1}). The ^1H n.m.r. signals (δ values at 305 K) of NCH_3 groups are for solutions in $CDCl_3$. The $\Delta G^{\ddagger}$ values (kJ mol^{-1}, statistical error ±4 kJ mol^{-1}, obtained using solutions in CD_2Cl_2 over the range 180—305 K, are the activation energies for rotation about the C(2)–N bond at 298 K. The ^{13}C n.m.r. signals (δ values) are for solutions in CD_2Cl_2, examined at 22.6 MHz over the range 189—305 K. For signals which broaden at low temperature the positions are followed, in parentheses, by their half-height widths (Hz).

	I.r. CO region					^1H N.m.r.	
	In CCl_4		In MeCN				
Compd.					ΔH^0	NCH_3	$\Delta G^{\ddagger}$
(3a)	1 703 (100)		1 696 (100)			3.10	47
(3b)	1 710 (77)	1 689 (23)	1 703 (69)	1 681 (31)	1.8	3.10	47
(3c)[b]	1 704 (73)	1 685 (27)	1 697 (67)	1 676 (33)		3.14	46
(3d)	1 707 (74)	1 689 (26)	1 699 (67)	1 679 (33)		3.51	
(3e)	1 706 (72)	1 686 (28)	1 698 (65)	1 677 (35)	1.9	3.04	44
(3f)	1 706 (73)	1 685 (27)	1 698 (64)	1 676 (36)		2.99	44
(3g)[b]	1 704 (78)	1 684 (22)	1 697 (71)	1 674 (29)	1.6	3.10	46
(3h)	1 705 (80)	1 683 (20)	1 697 (72)	1 673 (28)	1.5	3.12	45
(3i)[b]	1 707 (84)	1 673 (16)	1 699 (78)	1 670 (22)	1.7	3.14	43
(3j)[c]	1 709 (94)	1 667 (6)	1 702 (90)	1 662 (10)		3.12	41
(3k)	1 717 (68)	1 684 (32)	1 710 (62)	1 677 (38)		3.14	42
(3l)[b]	1 722 (67)	1 690 (33)	1 715 (62)	1 681 (38)	2.1	3.11	41
(3m)	1 709 (65)	1 681 (35)	1 703 (61)	1 674 (39)	1.5	3.10	42
(3n)	1 712 (69)	1 685 (31)	1 705 (63)	1 676 (37)	2.0	3.14	42



		^{13}C N.m.r.								
Compd.	Temp. (K)	R^1		R^2		CO	NMe_2		C(2)	C(4)	C(5)
(3b)	305	17.7		51.4		171.6	40.0		162.9	161.0 (3.2)	109.4 (3.1)
(3b)	189	17.3		51.2		169.1	41.1	38.7	161.1	159.3 (11.5)	107.1 (14.5)
(3c)	305	17.7		60.3	14.5	171.4	39.8		162.4	160.6 (3.1)	109.3 (3.1)
(3c)	189	17.1		59.8	14.1	169.0	40.1	38.4	161.1	159.3 (8.0)	107.7 (11.5)
(3j)	305	36.8	29.3	60.6	14.6	171.7	39.8		169.9	162.1 (3.1)	107.8 (3.1)
(3j)	189	35.7	27.2	60.0	13.9	170.9	40.2	37.6	168.8	161.1 (3.1)	107.1 (3.2)

[a] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1959. [b] I.r. CO overtone region (CCl_4): compound (3c) 3 386 (77), 3 350 (23); compound (3g) 3 387 (75), 3 347 (25); compound (3i) 3 386 (78), 3 328 (22); compound (3l) 3 424 (70), 3 359 (30). [c] Additional bands at 1 688 cm^{-1} (9% of total area) in CCl_4 and at 1 687 cm^{-1} (11% of total area) in MeCN.

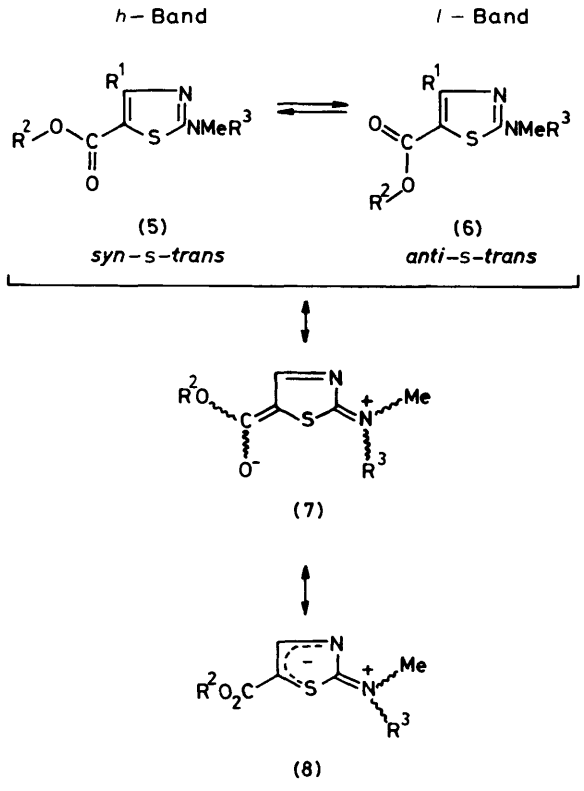
having a hydrogen or a halogen atom at position 2.[1] All but one of the esters exhibit carbonyl doublets; the components of these are designated the *h* (higher wavenumber)- and *l* (lower wavenumber)-bands. (Two of the esters are methyl carboxylates and are therefore expected to have carbonyl absorptions *ca.* 6 cm^{-1} higher than those of the ethyl analogues.) As the 4-substituent is varied along the series Me, Et, Pr, Pr^i, Bu^t the *h*-band is little affected, but moves to slightly higher wavenumber as the substituent becomes branched. This contrasts with the small but regular shifts to lower wavenumber of the *l*-band. Reasoning as before [1] leads to the assignments in Scheme 2, the salient features being that the degree of twist between the planes of the carboxylate group and thiazole ring is greater in the carbonyl *O,S-syn*-s-*trans* form (5) than in the *anti*-s-*trans* form (6), and that the difference is enhanced as the size of the 4-substituent is increased. Thus, increasing electron donation by the substituent moves the *l*-band to lower wavenumber, but with the *h*-band the loss of conjugation accompanying a greater degree of non-planarity and causing a shift to higher wavenumber eventually supervenes. Examination of the parent ester in the present series supports this conclusion. Ester (3a), lacking a 4-substituent, is free to adopt the *syn*-s-*trans* arrangement (5) exclusively; the position of this ester's single band confirms that it is related to the *h*-bands of the doublets. Comparison of the esters having aromatic substituents at position 4 [esters (3k—n)] with, for example, the 4-methyl analogue (3c) shows that the 4-aryl groups increase the wavenumber of the *h*-band but have little effect on the *l*-band. Repulsion between the aromatic and ester groups will be more severe in the *syn*-form (5), where the alkoxy-group is involved, leading to a larger dihedral angle between the two ring systems (and possibly also affecting the out-of-plane twist of the carboxylate group). In this form, then, the aromatic substituents will act mainly to withdraw electrons (−*I* effect).

It appears that thiazole-5-carboxylates with and without 2-dialkylamino-substituents have an inherent tendency, influenced only slightly by solvent polarity, to favour the carbonyl *O,S-syn* conformation (5); although the enthalpy difference between the rotamers is small, this is also the thermochemically more stable form (Table 1). The reason for this general tendency, which is even more marked in the corresponding 5-carbaldehydes,[2,8] is not yet clear.

The results obtained by variable temperature examination

Table 2. Characterisation of new 2-aminothiazole-5-carboxylates

Thiazole-5-carboxylate	M.p. (°C)	Analysis (%) Found C	H	N	Molecular formula	Requires C	H	N
(3a) Ethyl 2-dimethylamino	38—39	47.9	6.1	13.9	$C_8H_{12}N_2O_2S$	48.0	6.0	14.0
(3b) Methyl 2-dimethylamino-4-methyl	64—65	47.8	6.0	14.0	$C_8H_{12}N_2O_2S$	48.0	6.0	14.0
(3c) Ethyl 2-dimethylamino-4-methyl	42—43	50.5	6.6	13.2	$C_9H_{14}N_2O_2S$	50.4	6.6	13.1
(3d) Ethyl 4-methyl-2-(*N*-methyl-*N*-phenylamino)	64—65	60.8	5.8	10.0	$C_{14}H_{16}N_2O_2S$	60.8	5.8	10.1
(3e) Ethyl 4-benzyl-2-dimethylamino	73—75	*m/z* 290.1090			$C_{15}H_{18}N_2O_2S$	M^+ 290.1089		
(3f) Ethyl 4-benzyl-2-(*N*-benzyl-*N*-methylamino)	65—67	68.5	6.0	7.4	$C_{21}H_{22}N_2O_2S$	68.8	6.05	7.6
(3g) Ethyl 2-dimethylamino-4-ethyl	39—41	52.8	6.9	12.0	$C_{10}H_{16}N_2O_2S$	52.6	7.1	12.3
(3h) Ethyl 2-dimethylamino-4-propyl	30—32	54.7	7.6	11.2	$C_{11}H_{18}N_2O_2S$	54.5	7.5	11.6
(3i) Ethyl 2-dimethylamino-4-(1-methylethyl)	59—60	54.3	7.55	11.4	$C_{11}H_{18}N_2O_2S$	54.5	7.5	11.6
(3j) Ethyl 4-t-butyl-2-dimethylamino	72—74	56.1	7.9	10.8	$C_{12}H_{20}N_2O_2S$	56.2	7.9	10.9
(3k) Ethyl 2-dimethylamino-4-phenyl	115—116	61.0	5.6	10.0	$C_{14}H_{16}N_2O_2S$	60.8	5.8	10.1
(3l) Methyl 2-dimethylamino-4-(4-methylphenyl)	128—129	60.6	5.7	9.9	$C_{14}H_{16}N_2O_2S$	60.8	5.8	10.1
(3m) Ethyl 2-dimethylamino-4-(4-methoxyphenyl)	68—69	58.6	6.1	9.0	$C_{15}H_{18}N_2O_3S$	58.8	5.9	9.2
(3n) Ethyl 4-(4-bromophenyl)-2-dimethylamino	88—89	47.3	4.2	7.9	$C_{14}H_{15}BrN_2O_2S$	47.3	4.3	7.9



Scheme 2. Rotamers and canonical forms of 2-aminothiazole-5-carboxylates

of the NCH_3 ^{1}H n.m.r. signals are similar to those reported for the 5-carbaldehydes.[2] At temperatures below *ca.* −30 °C the *N,N*-dimethyl- and the *N*-benzyl-*N*-methyl-amines have two NCH_3 signals with Δν *ca.* 20 Hz (at a source frequency of 90 MHz). The latter amines also show two NCH_2Ph resonances, and in these compounds the two rotamers [represented generally by structure (7; R^3 = $PhCH_2$) in Scheme 2] are present in unequal amounts (*ca.* 7 : 3). No splitting occurred with the *N*-methyl-*N*-phenylamine (3d). Standard treatment[9] of the data led to $\Delta G^{\ddagger}$ values of 41—47 kJ mol^{-1} at 298 K, but the results are not sufficiently accurate to merit consideration of the variations between individual esters. However, as discussed later, it is significant that the range is lower than that (50—55 kJ mol^{-1}) of the 5-carbaldehydes.[2]

The ^{1}H n.m.r. signals of the carboxylate groups showed neither splitting nor appreciable broadening over the temperature range examined (193—309 K in CD_2Cl_2, 173—309 K in CS_2). The ^{13}C n.m.r. spectra of three esters were examined at temperatures down to 189 K. Two of them [(3b) and (3c), Table 1] showed splitting of the NCH_3 signals at *ca.* −20 °C and at very low temperatures the C(4) and C(5) signals broadened. Apparently the rotamers (5) and (6) of these esters have very similar ^{13}C signals but those of C(4) and C(5) are sufficiently different for the detection of rotational isomerism at 189 K. In the case of the 4-t-butyl ester (3j) the NCH_3 signal split but the signals of C(4) and C(5) remained sharp. This accords with the conclusion, from the i.r. study, that ester (3j) exists very largely in one conformation with a marked out-of-plane twist of the carboxylate group.

The drop of *ca.* 20 cm^{-1} of the CO bands (of both rotamers) caused by introducing the *N,N*-disubstituted amino-group at position 2 of triazole-5-carboxylates provides clear evidence for the involvement of canonical (7) (Scheme 2). With 5-carbaldehydes the decrease is somewhat bigger (*ca.* 25 cm^{-1}).[8] This difference and the higher $\Delta G^{\ddagger}$ figures (rotation of the 2-amino-group) of the aldehydes are reasonably attributed to the expected greater contribution of the dipolar canonical form corresponding to structure (7) in the case of aldehydes. However, the $\Delta G^{\ddagger}$ values are not very sensitive to the nature of the electron-withdrawing group (*cf.* 52 kJ mol^{-1} for 2-dimethylamino-5-nitrothiazole[10]) and there may be a sizeable contribution from canonical forms represented by structure (8) with the negative charge delocalised around the ring. The relative importance of the contributions by canonical forms (7) and (8) could be assessed from the value of the barrier to rotation of the carboxylate group, but the present work gives no information about this feature.

Experimental

The β-oxo-esters required for this work (see Scheme 1) were brominated by the procedure developed earlier.[1] ^{1}H N.m.r. examination of the products (which were not further purified or fully characterised) showed them to be the α-bromo-derivatives (1) containing <6% of impurities. The addition of these derivatives to solutions of *N,N*-disubstituted ureas[2] (2) in EtOH, boiling under reflux, as described previously[1]

gave the 2-aminothiazole-5-carboxylates (3) (64—73%), characterised by the material in Table 2.

Four esters, (3e), (3f), (3i), and (3j), were also prepared as in the following example. $MgSO_4$ (dried at 250 °C; 10 g) was suspended in a solution of *N,N*-dimethylthiourea (4 g) in dry Me_2CO (75 ml). The mixture was boiled under reflux, and ethyl 2-bromo-3-oxo-4-phenylbutanoate (1e) (purity 95%; 11.5 g) was added during 45 min. Evaporation, basification with 18M-NH_4OH, and extraction with $CHCl_3$ gave the ester (3e) (9.0 g after crystallisation from EtOH–hexane), m.p. 69—72 °C, and 73—75 °C after sublimation of a portion at 0.02 mmHg. The yields obtained by this procedure and the earlier condensations in EtOH were: ester (3e), 81 and 67%; (3f), 78 and 68%; (3i), 75 and 64%; (3j), 85 and 73%.

Alternative Route to Ethyl 2-Dimethylamino-4-ethylthiazole-5-carboxylate (3g).—A solution of ethyl 2-bromo-3-oxopentanoate (1g) (3.37 g) and Δ^2-triazoline-2-thiol (1.82 g) in $HCO.NMe_2$ (6 ml) was kept at 20 °C for 3 h. The crystalline material was collected, washed with Et_2O, and recrystallised from EtOH to give *2-ethoxycarbonyl-3-ethyl-5,6-dihydrotriazolo*[2,3-b]*thiazolium bromide* (4) (3.5 g), m.p. 186—187 °C (Found: C, 36.9; H, 4.3; N, 4.3. $C_{10}H_{14}BrNO_2S_2$ requires C, 37.0; H, 4.35; N, 4.3%); δ[$(CD_3)_2SO$] 5.82 (2 H, d of d, 5-H), 4.32 (2 H, q with *J* 7 Hz, OCH_2CH_3), 4.09 (2 H, d of d, 6-H), 3.05 (2 H, q with *J* 7 Hz, CH_2CH_3), 1.28 (3 H, t with *J* 7 Hz, OCH_2CH_3), and 1.18 (3 H, t with *J* 7 Hz, CH_2CH_3); $\nu_{max.}$ (Nujol) 1 718 cm^{-1}; *m/z* 325 and 323 (M^+, 40%) and 252 (100). 25% Aqueous Me_2NH (0.8 ml) was added to a solution of the foregoing salt (1.16 g) in EtOH (15 ml) at 20 °C. After 4 h the solvent was evaporated off and water (30 ml) was added. Extraction with $CHCl_3$ gave an oil (0.4 g) which was purified by chromatography on SiO_2 (30 g). Elution with $CHCl_3$ afforded the ester (3 g) (0.45 g), m.p. 38—40 °C.

Acknowledgements

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