

Synthesis and Characterisation of some New 2,6-Disubstituted Thiazolo-[3,2-*b*][1,2,4]triazine-3,7-diones

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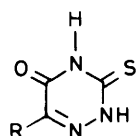
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The addition of dimethyl acetylenedicarboxylate to 3-thioxo-1,2,4-triazin-5-ones afforded in good yield cycloadducts which were characterised by i.r., mass, and ^1H and ^{13}C n.m.r. spectroscopy. On the basis of their ^{13}C chemical shifts and C,H coupling constant measurements the products were identified as 6-substituted (*Z*)-2-(methoxycarbonylmethylene)thiazolo[3,2-*b*][1,2,4]triazine-3,7-diones.

We are interested in the chemistry of heterocyclic compounds containing nitrogen and sulphur atoms for our biological activity studies. In a previous paper¹ we described the addition of acetylenic esters to thioureas. The reaction of substituted thiosemicarbazides with acetylenic esters has been reported² to give 1,3-thiazin-4-one derivatives. With a view to extending the synthetic utility of dimethyl acetylenedicarboxylate (DMAD) to cyclic models of thiosemicarbazides, we have investigated the addition of DMAD to 1,2,4-triazines. We herein report our results.

3-Thioxo-1,2,4-triazin-5-ones (**1a–d**) reacted readily with



(1)

- a; R = H
 b; R = Me
 c; R = CH₂Ph
 d; R = Ph

DMAD in methanol to give the adducts (**2a–d**). The i.r. spectra of (**2**) (Table 1) showed two carbonyl absorptions but no NH bands. Their ^1H n.m.r. spectra [(CD₃)₂SO] (Table 1) exhibited signals corresponding to one methyl ester group at δ 3.90 and a vinyl proton at δ ca. 7.40, besides those of the substituent at C-6;

no signals exchangeable with D₂O were present. These data indicated that a cyclization process had occurred to give a heterocyclic condensed system. The mass spectra of (**2**) (Table 2) showed low intensity (but observable) molecular ion peaks corresponding to 1:1 molar adducts which condensed by MeOH elimination; conventional 'simple' fragmentations, such as loss of OMe and CO₂Me, confirmed the gross structural features. Significant peaks occurred at m/z 212, 144, 116, 86, 85, and 57 (Scheme). In particular, the peak at m/z 212 corresponds to elimination of RCN, thus proving that the 1,2,4-triazine N-1 nitrogen atom was not involved in the addition reaction. Exact mass measurements for the fragment ion at m/z 144 confirmed the composition [C₅H₄O₃S]⁺ showing that the addition involves the sulphur atom. These data were consistent with all four of the possible condensed structures (A, B, C, and D) but were not sufficient to distinguish between them.

A method of distinguishing five- (A and C type) and six-membered (B and D type) adducts from thiols and DMAD, based on the marked differences of the chemical shifts of the carbon atoms in the ^{13}C n.m.r. spectra, has been reported.³ The proton decoupled ^{13}C n.m.r. spectra of our adducts, however, did not show the claimed close similarities in the resonances of the common carbon atoms of the reported³ structures.

Another method⁴ used measurements of three-bond C,H coupling constants to differentiate between the two types of constitutional isomers. Thus it became necessary to carry out a complete analysis of the proton coupled ^{13}C n.m.r. spectra of compounds (**2**). In these spectra [(CD₃)₂SO] (Table 3) the resonances of the methoxy group and vinyl C–H carbon (at ca. 53 and 112 p.p.m., respectively), together with those of the

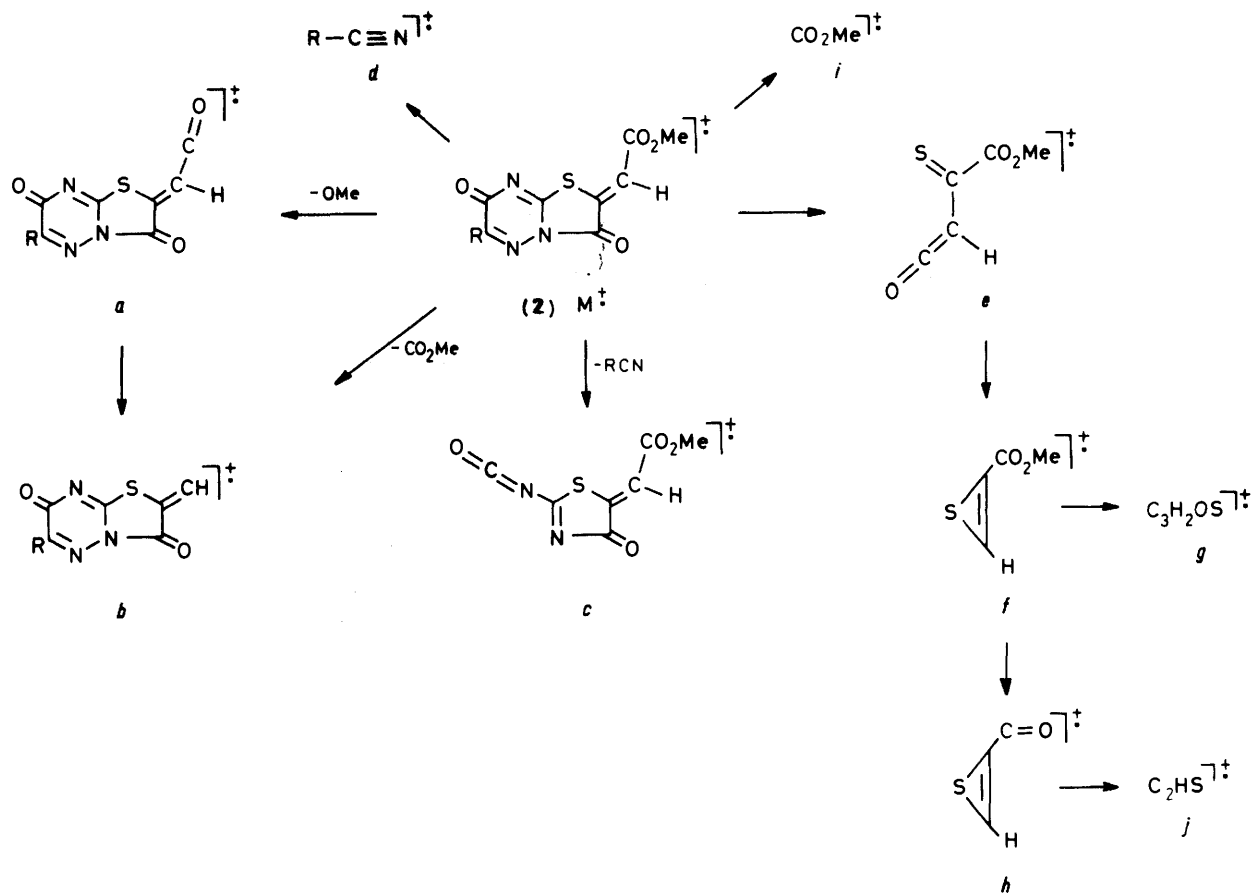
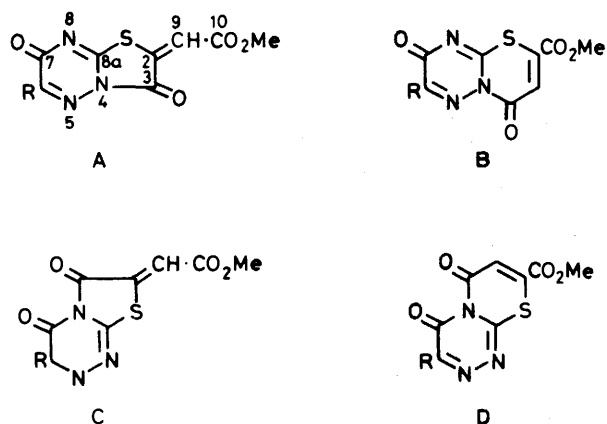
Table 1. Spectroscopic data for 3-thioxo-1,2,4-triazin-5-one-DMAD adducts (**2**)

Compound	R	$\nu_{\text{C=O}}/\text{cm}^{-1}$	$\nu_{\text{C=O}}/\text{cm}^{-1}$	$\lambda_{\text{max.}}/\text{nm}$	$\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$		
					Vinyl (1 H, s)	CO ₂ Me (3 H, s)	R
(2a)	H	1 760	1 600	233	7.40	3.90	8.17 (1 H, s)
		1 705	1 551	303			
				332			
(2b)	Me	1 760	1 598	234	7.37	3.90	2.30 (3 H, s)
		1 698	1 560	305			
				332			
(2c)	CH ₂ Ph	1 760	1 580	232	7.38	3.90	4.07 (2 H, s)
		1 680	1 545	293			
				332			
(2d)	Ph	1 752	1 585	227	7.43	3.90	7.50–8.30 (5 H, m)
		1 695	1 535	262			
				318			

Table 2. Characteristic mass spectral peaks of 3-thioxo-1,2,4-triazin-5-one-DMAD adducts (2)*

Compd.	R	M^{++}	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>	<i>f</i>	<i>g</i>	<i>h</i>	<i>i</i>	<i>j</i>	
(2a)	H	m/z	239	208	180	212	27	144	116	86	85	59	57
		(I%)	(3)	(6)	(3)	(62)	(62)	(61)	(100)	(32)	(64)	(35)	(40)
(2b)	Me	m/z	253	222	194	212	41	144	116	86	85	59	57
		(I%)	(2)	(4)	(9)	(50)	(6)	(48)	(100)	(27)	(59)	(28)	(40)
(2c)	CH ₂ Ph	m/z	329	298	239	212	117	144	116	86	85	59	57
		(I%)	(52)	(3)	(3)	(13)	(56)	(27)	(100)	(30)	(73)	(39)	(37)
(2d)	Ph	m/z	315	284	256	212	103	144	116	86	85	59	57
		(I%)	(6)	(2)	(14)	(13)	(72)	(31)	(100)	(33)	(80)	(50)	(58)

*Intensities as % of the base peak.

**Scheme.** Mass spectral fragmentations of the adducts (2) (all transitions are metastable supported)

substituent at C-6, were assigned on the basis of their characteristic chemical shifts and one-bond C,H coupling constants. The six other signals, without one-bond interactions, were attributed to sp^2 quaternary carbons. The resonance of the C-6 carbon atom, bearing the substituent, was easily identified owing to the large *ipso* SCS effect;⁵ e.g. replacement of the proton by a methyl group shifts the C-6 signal downfield by 8.75 p.p.m.

Within the series, the resonances values of the remaining signals displayed close similarities and the assignment was made by multiplicity arguments. The signal at 158.91–159.80 p.p.m. was assigned to the C-7 carbonyl carbon atom, because its multiplicity varied depending on the substituent at C-6; as a result of three-bond interactions, it appeared as a doublet, quartet, triplet, or singlet when R was H, Me, CH₂Ph, or Ph, respectively.

Table 3. ^{13}C N.m.r. data for 3-thioxo-1,2,4-triazin-5-one-DMAD adducts (**2**) in $(\text{CD}_3)_2\text{SO}$; chemical shifts (multiplicity, coupling constant)*

Carbon	(2a ; R=H)	(2b ; R=Me)	(2c ; R=CH ₂ Ph)	(2d ; R=Ph)
C-2	136.19 (s)	136.35 (s)	136.39 (s)	136.30 (s)
C-3	158.03 (d, 5.4)	158.04 (d, 6.0)	158.11 (d, 4.9)	158.07 (d, 6.2)
C-6	144.52 (<i>d</i> , 195.8)	153.27 (q, 7.3)	153.90 (t, 7.4)	149.21 (t, 4.0)
C-7	159.25 (d, 7.3)	159.80 (q, 2.5)	159.21 (t, 2.2)	158.91 (s)
C-8a	166.24 (s)	165.97 (s)	166.10 (s)	165.00 (s)
C-9	122.34 (<i>d</i> , 174.9)	122.21 (<i>d</i> , 174.8)	122.10 (<i>d</i> , 174.8)	122.41 (<i>d</i> , 175.1)
C-10	165.61 (q, 4.0)	165.64 (q, 3.9)	165.60 (q, 4.1)	165.62 (q, 4.0)
OMe	53.23 (<i>q</i> , 148.8)	53.23 (<i>q</i> , 148.8)	53.19 (<i>q</i> , 148.8)	53.20 (<i>q</i> , 148.4)
R: -CH ₃		17.40 (<i>q</i> , 130.5)		
-CH ₂ -			36.41 (<i>t</i> , 126.4)	
C-1'			135.34†	131.14†
C-2',6'			129.19 (<i>d</i> , 160.9)†	129.12 (<i>d</i> , 161.7)†
C-3',5'			128.44 (<i>d</i> , 160.9)†	128.43 (<i>d</i> , 162.8)†
C-4'			126.86 (<i>d</i> , 158.9)†	131.44 (<i>d</i> , 162.7)†

* Chemical shifts in p.p.m. downfield from SiMe₄; multiplicities in italics for one-bond interactions; coupling constants in Hz. † Excessive overlaps occurred for the other coupling constants not listed.

The signals of the other four quaternary carbons appeared as two singlets at 136.19–136.39 and 165.00–166.24 p.p.m., together with a doublet (J 4.9–6.2 Hz) at 158.03–158.11 and a quartet (J 3.9–4.1) at 165.60–165.64 p.p.m. Obviously the quartet was attributed to the ester carbonyl carbon which experiences coupling with the OMe protons.

The two singlets with long-range interactions ($J \leq 1.2$ Hz) were assigned to the C-2 and C-8a carbon atoms since neither is able to give rise to a doublet with a large long-range coupling constant. In fact, in all of the structures considered, the C-2 carbon atom always has a geminal C,H coupling constant and the C-8a carbon atom could experience only four-bond interactions: both coupling constants values are known to be small.^{6,7} Of these two signals, the one at *ca.* 136 p.p.m. was attributed to the C-2 carbon atom and the other at lower field to the C-8a carbon; the deshielding of the latter arises from its chemical environment since it is either bridged by and/or bonded to three heteroatoms.

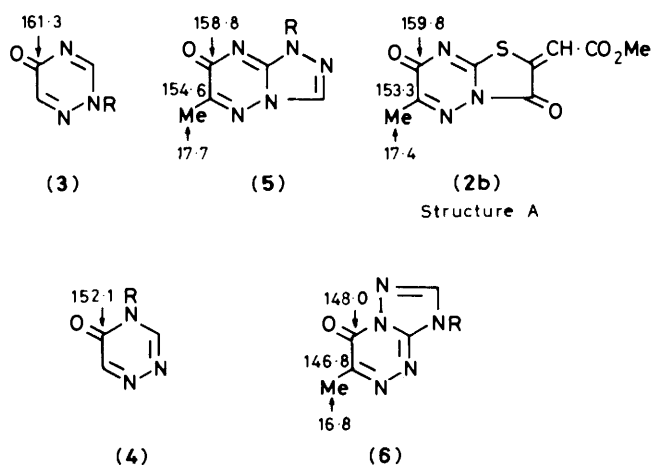
Consequently, the remaining doublet at *ca.* 158 p.p.m. must be for the C-3 carbonyl carbon atom. The coupling constant value of this resonance (J 4.9–6.2 Hz) may be explained exclusively in terms of three-bond C,H coupling with the vinyl proton (only present in the A and C structures) in the *cis* configuration. It agrees with the values observed for α,β -unsaturated esters both ring open or cyclic; it is reported^{7–11} that these compounds exhibit $^2J_{\text{CO,H}}$ 0.6–2.5 Hz, $^3J_{\text{CO,H(cis)}}$

4.3–7.5 Hz, $^3J_{\text{CO,H(trans)}}$ 11.5–14.3 Hz. In addition, the absence of vicinal $^3J_{\text{C,H}}$ coupling in the signal of the ester carbonyl carbon, expected for a six-membered ring structure, ruled out both B and D possibilities.

An immediate decision between structures C and A in favour of the latter can be reached by comparison of the ^{13}C chemical shifts for our products with those of similar compounds having a 1,2,4-triazine nucleus. Daunis *et al.*¹² have shown that in a 1,2,4-triazinone ring structure the chemical shift for the carbonyl carbon is markedly affected by the nature of the adjacent nitrogen (pyridine type in our structure A and pyrrole type in our structure C). The reported chemical-shift values of 1,2,4-triazinones (**3**) and (**4**) and 1,2,4-triazinone condensed systems (**5**) and (**6**) are compared with the values of our compounds (**2**) (see Figure). Since the values found for adducts from 3-thioxo-1,2,4-triazin-5-ones (**1**) and DMAD fit well with structure A, compounds (**2**) are identified as 6-substituted (*Z*)-2-(methoxycarbonylmethylene)thiazolo[3,2-*b*][1,2,4]-triazine-3,7-diones.

Experimental

M.p.s were determined on a Büchi-Tottoli capillary apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as Nujol mulls and u.v. spectra for methanolic solutions with a Perkin-Elmer model 200 spectrophotometer (methanol was dried with magnesium and distilled). ^1H N.m.r. spectra were recorded at 60 MHz on a Varian EM-360 instrument with SiMe₄ as internal standard as $(\text{CD}_3)_2\text{SO}$ solutions. ^{13}C N.m.r. spectra at natural abundance were recorded at 20 MHz on a Varian FT-80A pulsed Fourier transform spectrometer in $(\text{CD}_3)_2\text{SO}$ solutions. The chemical shifts were measured from the central solvent peak and converted to the SiMe₄ scale by using the difference of 39.60 p.p.m. between $(\text{CD}_3)_2\text{SO}$ and SiMe₄. The magnitude of all $J_{\text{C,H}}$ values have been taken from proton gated decoupled spectra. Mass spectra were run on a JEOL-JMS-O1SG-2 double-focusing mass spectrometer operating with an electron-beam energy of 75 eV and an accelerating voltage of 10 kV. Exact mass measurements, performed at 15 000 resolving power, were carried out to an accuracy of ± 10 p.p.m. of the theoretical value. Metastable peaks were detected by the accelerating voltage-scanning method. T.l.c. for confirming compound purity utilized 0.25 mm silica gel plates (Merck) with fluorescent indicator and ethyl acetate–benzene (7:3) or ethyl acetate–methanol (8:2) solvent systems. The 6-substituted 3-thioxo-1,2,4-triazin-5-ones (**1a–d**) were prepared by a literature

**Figure.**

method;¹³ their purity was checked by t.l.c. and they were identified on the basis of their spectroscopic properties.

General Procedure for Preparation of 6-Substituted (Z)-2-(Methoxycarbonylmethylene)thiazolo[3,2-b][1,2,4]triazine-3,7-diones (2)—A solution of DMAD (0.12 mol) in warm methanol (10 ml) was gently added to a stirred warm methanolic solution of (1) (0.1 mol). The mixture was stirred at room temperature for 20 min and then set aside overnight during which time crystals separated. The resulting crude mass was collected, washed with warm methanol, and recrystallized from ethyl acetate. Two recrystallizations were sufficient to produce analytically pure samples of (2). Spectral data of products are given in Tables 1—3. Analytical data are listed below.

(Z)-2-Methoxycarbonylmethylenethiazolo[3,2-b][1,2,4]triazine-3,7-dione (**2a**) (52%); colourless crystals, m.p. 230—231 °C (Found: C, 40.3; H, 2.2; N, 17.45; S, 13.2. C₈H₅N₃O₄S requires C, 40.16; H, 2.10; N, 17.57; S, 13.38%).

(Z)-6-Methyl-2-methoxycarbonylmethylenethiazolo[3,2-b][1,2,4]triazine-3,7-dione (**2b**) (78%); colourless crystals, m.p. 210—211 °C (Found: C, 42.75; H, 2.85; N, 16.45; S, 12.5. C₉H₇N₃O₄S requires C, 42.68; H, 2.78; N, 16.60; S, 12.64%).

(Z)-6-Benzyl-2-methoxycarbonylmethylenethiazolo[3,2-b][1,2,4]triazine-3,7-dione (**2c**) (49%); colourless crystals, m.p. 206—207 °C (Found: C, 54.8; H, 3.4; N, 12.65; S, 12.75. C₁₅H₁₁N₃O₄S requires C, 54.71; H, 3.37; N, 12.76; S, 9.72%).

(Z)-6-Phenyl-2-methoxycarbonylmethylenethiazolo[3,2-b][1,2,4]triazine-3,7-dione (**2d**) (55%); colourless crystals, m.p. 201—202 °C (Found: C, 53.5; H, 3.0; N, 13.0; S, 10.15. C₁₄H₉N₃O₄S requires C, 53.33; H, 2.87; N, 13.33; S, 10.15%).

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