Cyclic Sulphones. Part XIX.[1] Reactions of the 1,2,6-Thiadiazine 1,1-Dioxide System with Some Electrophiles

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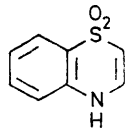
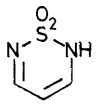
Three 3,5-disubstituted 1,2,6-thiadiazine 1,1-dioxides have been shown to react with a number of electrophiles affording 4-substituted products. Halogenation, nitrosation, azo-coupling, and Mannich and Vilsmeier reactions have been performed, and nitration was also successful provided that the substrates were *N*-methylated. *N*-Methylation was conveniently performed with diazomethane. The behaviour of this heterocyclic sulphone is strikingly analogous to that of 2-pyrimidone.

EVIDENCE has been provided recently[1,2] that heterocycles incorporating a sulphonyl or a carbonyl group in an unsaturated electron-rich cyclic framework show striking similarities in their structural features. With respect to reactivity, we have shown previously[3] that 4*H*-1,4-benzothiazine 1,1-dioxide (1) reacts with a number of electrophiles giving 2-substitution products: this behaviour is analogous to that of 4-quinolone. With the sulphonyl–carbonyl analogy in mind, we have investigated the behaviour of three derivatives of 1,2,6-thiadiazine 1,1-dioxide (2) towards a number of electrophiles and have found that this system reacts analogously to 2-pyrimidone (3), giving 4-substituted products.

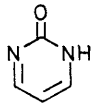
3,5-Dimethyl- and 3,5-diphenyl-2*H*-1,2,6-thiadiazine 1,1-dioxides (4) and (5) are readily available from sulphamide and acetylacetone and dibenzoylmethane, respectively.[4-6] 3-Methyl-5-phenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (6) was analogously prepared from benzoylacetone.



(1)



(2)



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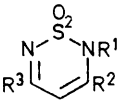
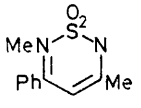




(4) R^1 = H, R^2 = R^3 = Me (10)
(5) R^1 = H, R^2 = R^3 = Ph
(6) R^1 = H, R^2 = Me, R^3 = Ph
(7) R^1 = R^2 = R^3 = Me
(8) R^1 = Me, R^2 = R^3 = Ph
(9) R^1 = R^2 = Me, R^3 = Ph

3,5-Dimethyl-2*H*-1,2,6-thiadiazine (4) is reported to be acidic (pK_a 3·27);[4,5] accordingly, methylation readily occurs with diazomethane and affords the same *N*-methyl derivative (7) as obtained by the action of methyl iodide or methyl sulphate in basic media. Compound (5) behaves analogously. Compound (6) gives a mixture of the two isomeric *N*-methyl derivatives (9) and (10); of these, the former predominates and has been obtained isomerically pure by fractional crystallisation. The structural assignment to compounds (9) and (10) is based upon the following observation. The ^{1}H n.m.r. spectrum of 3,5-diphenyl-2*H*-1,2,6-thiadiazine (5) shows the signal due to the *ortho*-protons of the *two* phenyl groups as the low-field AA' part of an AA'BB'C system: in the ^{1}H n.m.r. spectrum of (8) only *one* phenyl group still shows this pattern, the protons of the other, which is close to the methylated nitrogen atom, giving rise to a pseudo-singlet. Since in the more abundant *N*-methylated product from (6) the *ortho*-protons of the phenyl group resonate at low field, as in the precursor, whereas in the less abundant isomer protons of the phenyl group resonate as a pseudo-singlet, we conclude that in the former methylation has occurred on the nitrogen atom close to the methyl group.

In the ^{1}H n.m.r. spectra of products originating from the action of electrophiles on substrates (4)—(8) the signal due to the olefinic proton H-4 is no longer present, thus confirming that substitution occurs at this position.

Whereas 3,5-dimethylthiadiazine 1,1-dioxide (4) reacts readily with bromine to give compound (11), the diphenyl derivative (5) is resistant to this reagent. Chlorination, however, occurs easily to give the chloro-compound (16): the 3-methyl-5-phenylthiadiazine 1,1-dioxide (6) is analogously chlorinated to give (21).

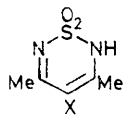
The thiadiazine 1,1-dioxides (4) and (5) undergo the azo-coupling reaction with benzene- and *p*-nitrobenzene-diazonium chlorides to give the azo-compounds (12), (13), and (17).

Nitrous acid attacks both the thiadiazine 1,1-dioxides (4) and (5): the product (14) from the former is brownish in the solid state but develops a blue-green colour in solution, whereas the product (18) from the latter is a white crystalline powder. The nitroso-forms (14) and (18) would be expected to be in equilibrium with the corresponding hydroxyimino-forms (27) and (28), respectively. Upon treatment with diazomethane the nitroso-compound (14) is readily methylated; ^{1}H n.m.r. analysis of the product strongly suggests the methoxyimino-structure (29) (see Experimental section).

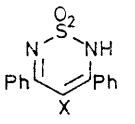
The Mannich reaction with formaldehyde and morpholine on the substrates (4) and (5) leads to the morpholinomethyl derivatives (15) and (19), respectively: these are better described as inner salts of the thiadiazinyl anion and the morpholinium cation (see ^{1}H n.m.r. spectra; Table 2).

[1] Part XVIII, G. Pagani, *J.C.S. Perkin II*, 1974, 1392.
[2] Part XVII, G. Pagani, *J.C.S. Perkin II*, 1974, 1389.
[3] G. Pagani and S. Bradamante, *Tetrahedron Letters*, 1968, 1041.
[4] E. F. Degering and J. E. Wilson, *J. Org. Chem.*, 1952, **17**. 339.
[5] J. B. Wright, *J. Org. Chem.*, 1964, **29**, 1905.
[6] A. M. Roe and J. B. Harbridge, *Chem. and Ind.*, 1965, 182.

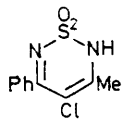
The action of formaldehyde and hydrochloric acid in the cold on the thiadiazine 1,1-dioxide (4) does not give the 4-chloromethyl-3,5-dimethyl-2*H*-1,2,6-thiadiazine,



(11) X = Br
(12) X = N=NPh
(13) X = N=N·C$_6$H$_4$·NO$_2$-*p*
(14) X = NO
(15) X = CH$_2$Mph

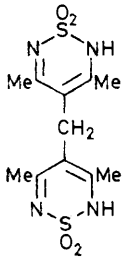


(16) X = Cl
(17) X = N=NPh
(18) X = NO
(19) X = CH$_2$Mph
(20) X = CHO



(21)

Mph = morpholino



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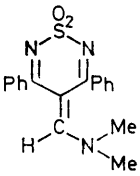

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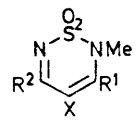
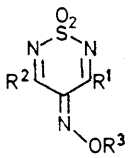


(24) R^1 = R^2 = Me, X = Br
(25) R^1 = R^2 = Me, X = NO$_2$
(26) R^1 = R^2 = Ph, X = NO$_2$



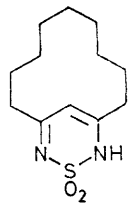
(27) R^1 = R^2 = Me, R^3 = H
(28) R^1 = R^2 = Ph, R^3 = H
(29) R^1 = R^2 = R^3 = Me

but leads instead to the bisthiadiazinylmethane derivative (22), identified by analytical and mass spectral data.

The Vilsmeier reaction on the thiadiazine 1,1-dioxide (5) afforded the *NN*-dimethylaminomethylene derivative (23) as a white crystalline solid: this enamine could be hydrolysed in acidic media to the formyl derivative (20).

Although it is apparent that nitric acid attacks the thiadiazine 1,1-dioxide system, the products were in our hands too unstable for purification. However, successful nitration experiments could be performed with the *N*-methylated thiadiazine 1,1-dioxides (7) and (8), giving the nitro-derivatives (15) and (26), respectively. Bromination of (7) to (24) also occurs readily. However, *N*-methylation of the thiadiazine system apparently prevents the attack of weak electrophiles: nitrosation, azo-coupling, and Vilsmeier and Mannich reactions fail.

The 1,2,6-thiadiazine dioxide system thus reacts with a number of electrophiles giving 4-substitution products: this behaviour parallels closely that shown by 2-pyrimidone.[7] However, the tendency of the 2*H*-1,2,6-thiadiazine 1,1-dioxide system to retain its structural type upon treatment with electrophiles can be accounted for either by regarding the system as aromatic or by considering it as a cyclic derivative of the enolic form of a β-diketone.* We attempted to clarify this point through the following approach. We synthesized the nonamethylenethiadiazine dioxide (30) from cyclododecane-1,3-dione in the expectation that any ring current in the heterocycle would affect the chemical shifts of some of the methylene protons in the saturated ring. No evidence for diamagnetic effects was obtained, but the significance of this result is dubious in view of the fact [9] that even the aromatic systems (31) and (32) do not show any marked displacement of the chemical shifts of the protons in the polymethylene chain.



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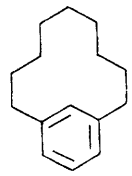
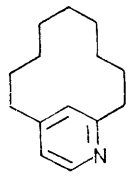


(31)



(32)

EXPERIMENTAL

*3-Methyl-5-phenyl-*2H*-1,2,6-thiadiazine* 1,1-*Dioxide* (6).—A solution of sulphamide (1 g) and benzoylacetone (1·69 g) in ethanol (10 ml) was saturated with hydrogen chloride and refluxed for 12 h. The *precipitate* was collected, washed with ether, and crystallized.

13-Thia-12,14-diazabicyclo[9.3.1]*pentadeca-*1(15),11(12)*-diene* 13,13-*Dioxide* (30).—Cyclododecane-1,3-dione (0·59 g) [10] and sulphamide (0·25 g) in ethanol (10 ml) were treated as above for 3 days. Every 12 h the solution was saturated again with hydrogen chloride. Evaporation left a residue which was crystallized from ethanol–water; the *product* (0·35 g) was finally sublimed at 100° and 0·1 mmHg.

Methylation of 3,5-*Dimethyl- and* 3,5-*Diphenyl-*2H*-1,2,6-thiadiazine* 1,1-*Dioxides*.—(a) *With diazomethane*. A stirred suspension of the thiadiazine (10 mmol) in ether (25—50 ml) was treated with ethereal diazomethane in excess for 6 h. The solvent was evaporated off and the *residue* crystallized (yields 80—90%).

(b) *With methyl iodide*. A stirred solution of the thiadiazine (10 mmol) in acetone (70 ml) was treated with potassium carbonate (5 g) and methyl iodide (50 mmol). After a few h at room temperature the mixture was filtered, the solvent was evaporated off, and the residue was crystallized (yields 70—80%).

(c) *With dimethyl sulphate*. A stirred solution of the thiadiazine sodium salt (10 mmol) in water (20 ml) was treated with dimethyl sulphate (11 mmol) for 12 h at room temperature. The precipitate was washed with 0·1N-sodium hydroxide and crystallized (yields 70—80%).

Methylation of 3-*Methyl-5-phenyl-*2H*-1,2,6-thiadiazine* 1,1-*Dioxide*.—(a) *With diazomethane*. Treatment of the thiadiazine (6) (1·4 g) with diazomethane in ether as above

* Such a consideration applies also to the case of 2-pyrimidone and recalls that ' aromatic behaviour ' may have little to do with ' aromaticity ' (see discussion by Lloyd [8]).

[7] G. W. Kenner and Sir Alexander Todd, in ' Heterocyclic Compounds,' ed. R. C. Elderfield, vol. 6, Wiley, New York, 1957, ch. 7.

[8] D. Lloyd, ' Carbocyclic Non-benzenoid Aromatic Compounds,' Elsevier, Amsterdam, 1966.

[9] S. Bradamante, A. Marchesini, and G. Pagani, *Tetrahedron Letters*, 1971, 671.

[10] K. Shank and B. Eistert, *Chem. Ber.*, 1966, **99**, 1414.

TABLE 1

Physical and analytical data

Compound	M.p. (°C)	Solvent	Found (%) C	H	N	Formula	Required (%) C	H	N
(6)	181	EtOH–H_2O	53·8	4·6	12·6	$C_{10}H_{10}N_2O_2S$	54·05	4·5	12·6
(7)	79 [a]	H_2O							
(8)	174	EtOH	64·6	4·9	9·4	$C_{16}H_{14}N_2O_2S$	64·4	4·7	9·4
(9)	147	EtOH	55·85	5·2	12·0	$C_{11}H_{12}N_2O_2S$	55·9	5·1	11·85
(11)	140	MeOH–H_2O	25·4	3·1	11·8	$C_5H_7BrN_2O_2S$	25·1	2·95	11·7
(12)	165	AcOH	49·5	4·4	20·8	$C_{11}H_{12}N_4O_2S$	50·0	4·6	21·2
(13)	195	AcOH	43·0	3·8	22·6	$C_{11}H_{11}N_5O_4S$	42·7	3·6	22·6
(14)	174 (decomp.)	H_2O	32·1	3·8	21·7	$C_5H_7N_3O_2S$	31·75	3·7	22·2
(15)	213	EtOH–H_2O	45·95	6·5	16·0	$C_{10}H_{17}N_3O_3S$	46·3	6·6	16·2
(16)	187	AcOH	56·2	3·6	8·9	$C_{15}H_{11}ClN_2O_2S$	56·5	3·5	8·8
(17)	184	AcOH	65·0	4·0	14·9	$C_{21}H_{16}N_4O_2S$	64·9	4·15	14·4
(18)	221	EtOH	57·3	3·4	13·45	$C_{15}H_{11}N_3O_3S$	57·5	3·5	13·4
(19)	164	EtOH	62·6	5·5	10·8	$C_{20}H_{21}N_3O_3S$	62·65	5·5	11·0
(20)	223	AcOH–H_2O	62·0	3·9	9·2	$C_{16}H_{12}N_2O_3S$	61·5	3·9	9·0
(21)	140	H_2O	47·1	3·8	11·1	$C_{10}H_9ClN_2O_2S$	46·8	3·5	10·9
(22)	218	H_2O	39·6	5·0	16·7	$C_{11}H_{16}N_4O_4S_2$	39·8	4·85	16·9
(23)	282	EtOH	63·3	5·2	12·8	$C_{18}H_{17}N_3O_2S$	63·7	5·05	12·4
(24)	91	EtOH	28·6	3·65	11·1	$C_6H_9BrN_2O_2S$	28·5	3·6	11·1
(25)	103	EtOH	33·0	4·3	18·9	$C_6H_9N_3O_4S$	32·9	4·1	19·2
(26)	162	EtOH	56·3	3·7	12·2	$C_{16}H_{13}N_3O_4S$	56·0	3·8	12·2
(30)	177	*b*	55·8	8·1	10·8	$C_{12}H_{20}N_2O_2S$	56·2	7·9	10·9

[a] Ref. 6. [b] Sublimed.

gave a precipitate which after two crystallizations from ethanol afforded 2,3-*dimethyl*-5-*phenyl*-2H-1,2,6-*thiadiazine* 1,1-*dioxide* (9) (76%). The ethereal mother liquors contained a 1 : 1 mixture of the two isomeric *N*-methylthiadiazines (9) and (10).

(b) *With methyl iodide.* Treatment of (6) (2 g) with potassium carbonate and methyl iodide as above gave a product (94%), ^{1}H n.m.r. analysis of which showed a ratio of (9) to (10) of *ca.* 5 : 1.

TABLE 2

^{1}H N.m.r. data (τ values)

Compd.	Solvent	Aromatic	Me	Other
(6)	$(CD_3)_2SO$	1·83—2·55	7·72	3·40 (CH)
(7)	$(CD_3)_2SO$		7·72, 7·85	6·61 (NMe), 4·05 (CH)
(8)	$(CD_3)_2SO$	1·80—2·60		3·09 (CH), 6·65 (NMe)
(9)	$(CD_3)_2SO$	1·85—2·55	7·52	3·25 (CH), 6·50 (NMe)
(10) [a]	$(CD_3)_2SO$	2·30—2·55	7·70	3·80 (CH), 6·76 (NMe)
(11)	$CDCl_3$		7·57	1·80 (NH)
(12)	$(CD_3)_2SO$	2·20—2·70	7·47	
(13)	$(CD_3)_2SO$	1·60—2·50	7·45	
(14)	$(CD_3)_2SO$		7·42, 7·50	
(15)	D_2O–NaOD		7·81	6·63 (CH_2), 6·30, 7·48 (Mph [b])
(16)	$CDCl_3$	2·10—2·60		
(17)	$(CD_3)_2SO$	1·98—3·10		
(18)	$(CD_3)_2SO$	1·90—2·60		
(19)	$(CD_3)_2SO$	2·20—2·70		6·12—6·80, 7·55 (Mph [b] and CH_2)
(20)	$(CD_3)_2SO$	1·80—2·72		0·74 (CHO)
(21)	$CDCl_3$	2·00—2·70	7·50	
(22)	$(CD_3)_2SO$		7·89	6·48 (CH_2)
(23)	$(CD_3)_2SO$	2·00—2·62		6·86, 7·75 (NMe)
(24)	$(CD_3)_2SO$		7·46, 7·51	6·48 (NMe)
(25)	$(CD_3)_2SO$		7·54, 7·63	6·45 (NMe)
(26)	$(CD_3)_2SO$	2·20—2·60		6·75 (NMe)
(30)	$CDCl_3$			3·80 (NH), 4·00 (CH), 7·31—7·68, 8·00—8·95 (CH_2)

[a] As deduced from the spectrum of mixture of (9) and (10). [b] Morpholino.

4-*Chloro*-3,5-*diphenyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (16) *and* 4-*Chloro*-3-*methyl*-5-*phenyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (21).—The chlorine produced by the action of 50% sulphuric acid on a mixture of sodium chlorate (1·06 g) and sodium chloride (1·75 g) was bubbled into a solution of the appropriate thiadiazine (1·8 mmol) in acetic acid (15 ml), which was then refluxed for 2 h. The *precipitate* obtained on cooling was recrystallized (yield 60—70%).

4-*Bromo*-3,5-*dimethyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (11).—Bromine (0·3 ml) was added to an aqueous solution of the thiadiazine (4) (0·8 g), which was then heated at 90° for 20 min. Evaporation left a *residue* which was crystallized (yield 70%).

4-*Bromo*-2,3,5-*trimethyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (24).—Bromine (2·40 mmol) in chloroform (3 ml) was added to a cold (5°) solution of the 2,3,5-trimethyl-2*H*-thiadiazine (7) (2·32 mmol). The solvent was removed at ambient temperature under reduced pressure; the resulting yellow *oil* slowly crystallized (74%).

3,5-*Dimethyl*- *and* 3,5-*Diphenyl*-4-*morpholinomethyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxides* [(15) *and* (19)].—A solution (38%) of formaldehyde in water (5·05 mmol) and morpholine (5·05 mmol) were added to a solution of the thiadiazine (4) or (5) (5 mmol) in ethanol (15 ml). Upon heating (2 min) a *solid* separated; this was washed with ethanol and crystallized (yield 93—95%).

4-*Phenylazo*- *and* 4-p-*Nitrophenylazo*-3,5-*dimethyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxides* [(12) *and* (13)].—A cold (0°) solution of the diazonium chloride (5 mmol), prepared according to standard procedures, was added to a solution of the thiadiazine (4) (5 mmol) in water (10 ml). The *solid* which separated was washed with water and crystallized.

3,5-*Diphenyl*-4-*phenylazo*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (17).—Benzenediazonium chloride (5 mmol) in water (1 ml) was added to a solution of 3,5-diphenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (5) (5 mmol) in tetrahydrofuran (100 ml). Hydrochloric acid was then added and the *solid* was collected and crystallized.

Nitrosation of 3,5-*Dimethyl*-1,2,6-*thiadiazine* 1,1-*Dioxide*.—Sodium nitrite (3·3 mmol) in water (0·5 ml) was added to a slightly acidic cold (0°) aqueous solution (10 ml) of

3,5-dimethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (3 mmol): after 12 h at 0°, the solution was extracted with ethyl acetate (4 × 30 ml): the extracts were dried and evaporated under reduced pressure. The product reacted with an excess of ethereal diazomethane to give material showing ^{1}H n.m.r. signals in accord with structure (29): τ [$(CD_3)_2CO$] 7·51 (CH_3), 7·40 (CH_3), and 5·62 (OMe).

Nitrosation of 3,5-*Diphenyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide*.—Sodium nitrite (5 mmol) in water (1 ml) was added to a solution of 3,5-diphenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (5) (5 mmol) in tetrahydrofuran (100 ml); a few drops of 36% hydrochloric acid were then added with stirring. The solvent was removed under reduced pressure at room temperature and the residue was crystallized (yield 60%).

Vilsmeier Reaction of 3,5-*Diphenyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide*.—Phosphoric trichloride (1·1 mmol) was added to a solution of the thiadiazine (5) (1 mmol) in dimethylformamide (2 ml). The mixture was heated at 50° for 12 h, then cooled and diluted with water (20 ml); the solid was collected and crystallized to give 4-*dimethylaminomethylene*-3,5-*diphenyl*-1,2,6-*thiadiazine* 1,1-*dioxide* (23) (73·6%). This product (0·1 g) was hydrolysed upon heating its solution in dilute acetic acid (20 ml) in the presence of two drops of 20% hydrochloric acid to give 4-*formyl*-3,5-*diphenyl*-2H-1,2,6-*thiadiazine* 1,1-*dioxide* (20) (80%).

2,3,5-*Trimethyl*-4-*nitro*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (25).—A solution of nitric acid (*d* 1·48; 1·5 ml) in acetic anhydride (2 ml) was slowly added to a cold (0°) and stirred solution of the 2,3,5-trimethyl-2*H*-1,2,6-thiadiazine (7) (600 mg) in the same solvent (5 ml). The temperature was raised to 25 °C during 4 h; the solution was then poured onto crushed ice. The *solid* was filtered off and crystallized (65%). Lower yields were obtained (20%) by using, under the same conditions, anhydrous copper nitrate as the nitrating agent.

2-*Methyl*-4-*nitro*-3,5-*diphenyl*-2H-1,2,6-*thiadiazine* 1,1-*Dioxide* (26).—Nitration was performed as above in acetic anhydride with a large excess of nitrating agent (8 : 1); the mixture was heated at 40° for 8 h.

4,4′-*Methylenebis*-(3,5-*dimethyl*-2H-1,2,6-*thiadiazine*) *Bis*-1,1-*dioxide* (22).—Aqueous formaldehyde (38%; 7·7 mmol) was added to a cold (0°) solution of 3,5-dimethyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (4) (7 mmol) in 36% hydrochloric acid; hydrogen chloride was then bubbled through the solution, with the temperature maintained at 0 °C. After 2 h the solution was neutralized with sodium hydrogen carbonate and evaporated under reduced pressure. The residue was taken up in methanol and a few drops of hydrochloric acid, and the solution was filtered and evaporated; the *product* was crystallized from water. The mass spectrum showed no molecular ion, but two peaks of equal intensity at *m/e* 172 and 160 were apparent.

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