Preparation and Chemistry of Some 1,5-Diphenyl-1λ⁴,2,4-thiadiazine 1-Oxides

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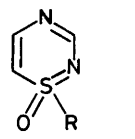
General methods for the preparation of 3-substituted 5-aryl-1λ⁴,2,4-thiadiazine 1-oxides are described. The chemical properties of these new heterocyclic systems have been explored, for example their susceptibility to electrophilic and nucleophilic attack. The 3-bromomethyl derivative can undergo a base-catalysed ring expansion to a seven-membered thiadiazepine; some initial studies at generating fused bicyclic systems from these heterocyclic precursors are also reported.

Although the benzo-fused 1λ⁴,2,4-thiadiazine 1-oxide system[1] has been incorporated into a variety of structures possessing a range of pharmacological properties, including CNS depressant activity,[2] and bronchorespiratory[3] and antihypertensive activities,[4] virtually no work has been carried out on the parent system (**1**). In some preliminary work, Schaffner-Sabba *et al.*[5] reported the synthesis of the oxo derivative (**2**). Because of the potential of such heterocyclic systems in generating new pharmacological leads we have investigated these systems and now report on some methods for their preparation and on some of their chemical properties.

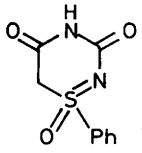
The general scheme envisaged for this work involved the intermediate formation of systems of the type (**3**), followed by condensation across the two nitrogen atoms in order to generate a range of cyclic structures. Formation of the system (**3**) required initial condensation of a nitrile, or its equivalent, with *S*-methyl-*S*-phenylsulphoximide (**4**); Johnson *et al.* have described related condensations with protected forms of the latter compound.[6]

Treatment of compound (**4**) with 2 equiv. of butyl-lithium in tetrahydrofuran (THF) generates the dianion; addition of benzonitrile to this at 0 °C leads to rapid formation of an adduct. Quenching with aqueous sodium chloride produces the enamine (**5**), which slowly loses ammonia by hydrolysis during chromatography to give the ketone (**10**). The ^{1}H NMR and IR spectra of the product (**5**) indicate that the enamine is the preferred tautomer and exists as a single isomer, assigned the (*Z*)-configuration indicated. Acid-catalysed hydrolysis of the enamine (**5**) also produces the ketone (**10**), itself shown by spectral evidence to exist largely in the ketonic form.

By repeating this condensation with a range of substituted benzonitriles a series of substituted enamines (**6**)–(**8**) was prepared; the yields were variable, but in each case only one major enamine isomer appeared to be formed. Compound (**9**) was produced by a similar condensation using *S*-ethyl-*S*-phenylsulphoximide. The enamines were then subjected to a range of condensation reactions in order to generate a heterocyclic system. Thus treatment of the enamines (**5**)–(**9**) with a slight excess of dimethylaminodimethoxymethane (DMF acetal) (**11**) in dimethylformamide (DMF) solution at 80 °C for 30 min afforded the corresponding 5-aryl-1-phenyl-1*H*-1λ⁴,2,4-thiadiazine-1-oxides (**13**)–(**17**) in good yields. That the condensations proceeded so smoothly, under conditions in which no isomerisation of the enamine moiety was detected, lends support to the assignment of the (*Z*)-stereochemistry to the enamines; any (*E*)-isomers would either condense to form polymers or have to isomerise to the (*Z*)-isomer before cyclisation could occur.



(**1**)



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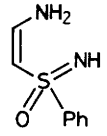
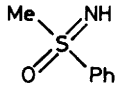
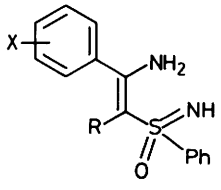


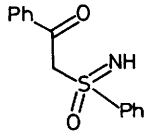
(**3**)



(**4**)



(**10**)

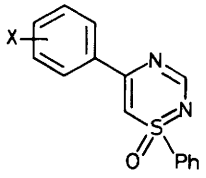


(**5**) X = H, R = H
(**6**) X = 4-Me, R = H
(**7**) X = 4-MeO, R = H
(**8**) X = 2-Cl, R = H
(**9**) X = H, R = Me

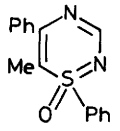
RC(OMe)$_2$NMe$_2$
(**11**) R = H
(**12**) R = Me

The ^{1}H NMR spectra of the derivatives (**13**)–(**16**) showed characteristic absorptions at δ 8.2–8.3 for the C-3 protons and at δ 6.2 for the C-6 protons, with a coupling constant between these in the range of 1.5–1.8 Hz. Condensation of the unsubstituted enamine (**5**) with 1-dimethylamino-1,1-dimethoxyethane (**12**) gave the methyl-substituted derivative (**18**). For (**18**), the proton on the heterocyclic ring appeared as a singlet at δ 6.07, whereas for the isomer (**17**), prepared by the above general method (see Experimental), the proton on the heterocyclic ring occurred at δ 8.07.

The unsubstituted derivative (**5**) was also subjected to other condensation reactions. With chloro[7] or bromo triethyl ortho-



(13) X = H
(14) X = 4-Me
(15) X = 4-MeO
(16) X = 2-Cl



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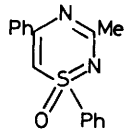

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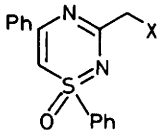
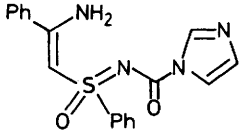


(19) X = Cl
(20) X = Br



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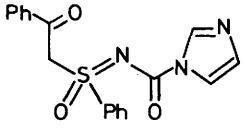

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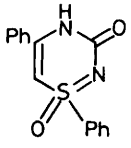

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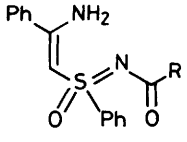
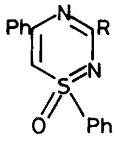


(24) R = CH_2Cl
(25) R = CH_2Ph
(26) R = CO_2Me
(27) R = $(CH_2)_2CO_2Me$
(28) R = CF_3
(29) R = Ph
(30) R = 2-MeC_6H_4
(31) R = 4-$MeOC_6H_4$
(32) R = 2-furyl



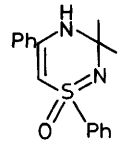
(33) R = CH_2Ph
(34) R = CO_2Me
(35) R = $(CH_2)_2CO_2Me$
(36) R = CF_3
(37) R = Ph
(38) R = 2-MeC_6H_4
(39) R = 4-$MeOC_6H_4$
(40) R = 2-furyl
(41) R = NH_2

acetate[8] condensation occurred smoothly to produce the corresponding halomethyl-1λ⁴,2,4-thiadiazines (**19**) and (**20**), the substituted methyl group providing a handle suitable for further elaboration (see below). *N,N*-Carbonyldi-imidazole in dichloromethane at room temperature initially reacted with compound (**5**) at the more nucleophilic sulphoximide nitrogen to give the acylated product (**21**), in which the enamino group was still present. Careful acid-catalysed hydrolysis of the latter, at room temperature with 2M hydrochloric acid, produced the ketone (**22**), whilst heating of (**21**) in Dowtherm A at 180 °C for 2 h effected the desired cyclisation to the oxo compound (**23**). The cyclic product (**23**) could also be prepared directly, in 79% yield, from the enamine (**5**) and the carbonyldi-imidazole, without isolation of the intermediate (**22**), by heating the reaction mixture directly. A similar two-step reaction was observed on treatment of the enamine (**5**) with a series of acid chlorides and anhydrides (Table), initial reaction occurring on the sulphoximide nitrogen atom. Cyclisation of the derived acyl intermediates (**24**)–(**32**) to the thiadiazines (**19**) and (**33**)–(**40**) could be effected in either of two ways, either by treatment with sodium hydroxide in ethanol or by heating in xylene at reflux in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). The latter method was more universally applicable as it did not cause side reactions such as hydrolysis of the sulphoximide-amide linkage or other functions present.

Finally, with cyanogen bromide, the enamine (**5**) reacted to give the 3-amino derivative (**41**), and with 2,2-dimethoxypropane, in the presence of catalytic toluene-4-sulphonic acid, the 3,3-dimethyldihydrothiadiazine (**42**) was obtained.

The above condensations gave access to a range of new 3-, 5-, and 6-substituted thiadiazine-1-oxides, generally obtained as stable crystalline compounds. Proton chemical shifts for the simpler systems have been referred to above; the ^{13}C chemical shifts for the C-3 and C-6 atoms in the simple derivative (**13**) occur at δ 156.5 and 89.0 respectively. The high field associated with position 6 indicates a relatively high electron density at this position so it was of interest to study the behaviour of some representative thiadiazine 1-oxide systems towards electrophilic attack. Previously Schaffner-Sabba *et al.*[5] have reported that compound (**43**) can be brominated and nitrated at position 6, whilst Ikeda *et al.*[9] have described bromination of the thiazine (**44**) at C-6 and nitration to give a 4,6-dinitro derivative.

The thiadiazines (**13**) and (**23**) react rapidly with bromine in chloroform to give the 6-bromo derivatives (**45**) and (**48**),



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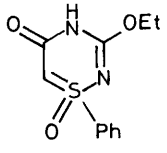

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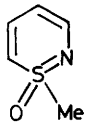

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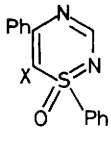
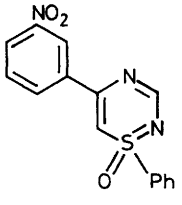


(45) X = Br
(46) X = SPh
(47) X = EtOCO

(48)



(49)

Table. 3-Substituted thiadiazines *via* acylation/cyclisation.

Reagent	Intermediate	Product	Overall yield (%)	M.p. (°C)	% Found (required) C	H	N	S
$ClCH_2COCl$	(**24**)	(**19**)	76	99–100	*a*			
$PhCH_2COCl$	(**25**)	(**33**)	50	127–128	73.4 (73.7	5.1 5.1	7.8 7.8	8.9 8.9)
MeO_2COCl	(**26**)	(**34**)	50	99–101	62.5 (62.6	4.4 4.3	8.7 8.6	9.9 9.8)
$MeO_2(CH_2)_2COCl$	(**27**)	(**35**)	51	100–101	64.2 (64.4	5.1 5.1	8.0 7.9	9.0 9.0)
$(CF_3CO)_2O$	(**28**)	(**36**)	77	136–137	57.1 (57.1	3.4 3.3	8.3 8.3	9.6 9.5)
PhCOCl	(**29**)	(**37**)	66	112–113	73.3 (73.2	4.7 4.7	8.1 8.1	9.3 9.3)
$2\text{-}MeC_6H_4COCl$	(**30**)	(**38**)	63	100–101	73.7 (73.7	5.1 5.1	7.8 7.8	9.0 8.9)
$4\text{-}MeOC_6H_4COCl$	(**31**)	(**39**)	64	124–126	70.6 (70.6	4.9 4.9	7.5 7.5	8.6 8.6)
2-FurylCOCl	(**32**)	(**40**)	43	160–161	68.1 (68.2	4.3 4.2	8.4 8.4	9.6 9.6)

[a] See Experimental.

respectively. The rapid rate of bromination suggested an addition-elimination process rather than a direct electrophilic substitution and this suggestion was reinforced when it was observed that the thiadiazine (**13**) was unreactive towards acetyl nitrate. Under more forcing conditions, using a nitric–sulphuric acid mixture, mono-nitration did occur but the product was found to be nitrated in the 5-phenyl substituent. The nitro-product, obtained in 70% yield, was shown to be the *meta*-nitrated product (**49**). Presumably under these strong acid conditions the thiadiazine ring is protonated and behaves as a deactivating substituent for the pendant phenyl group. The position of nitration was indicated by the appearance of a low-field *ortho*-proton at δ 8.75 and confirmed by an NOE experiment, in which irradiation of the 6-H signal shows an enhancement of the signals due to the *ortho*-positions in both of the pendant phenyl rings, including the signal at δ 8.75.

The bromine atom in the thiadiazine (**45**) could be displaced with certain nucleophiles, such as sodium thiophenate in DMF, in this case yielding the sulphide (**46**). Treatment of the bromo compound with butyl-lithium, in the presence of tetramethylethylenediamine (TMEDA), gave the 6-lithio derivative, which could be quenched, for example, with ethyl chloroformate to give the corresponding 6-ethoxycarbonyl derivative (**47**). Although some direct exchange of the 6-H proton in the unsubstituted thiadiazine (**13**) was observed with lithium diiodopropylamide, as evidenced by deuterium incorporation, this was not as efficient as metallation of the bromo compound.

Some further reactions of the 3-oxothiadiazine (**23**) were also studied. Thus alkylation with methyl iodide, using potassium carbonate in DMF as base, afforded two isomeric products, in the ratio 96:4. The major isomer was the 4-methyl compound (**50**), whereas the minor product was the *O*-methylated compound (**53**); the ^1H NMR spectrum of the former showed the *N*-methyl group at δ 3.22, and of the latter the *O*-methyl group at δ 4.05. Further confirmation of this assignment was obtained by an X-ray crystallographic determination on compound (**50**).[10] With increasingly bulky alkylating agents, the oxygen alkylation product is favoured; thus with ethyl iodide a 3:2 ratio of the *O*-ethyl product (**54**) to the *N*-ethyl product (**51**) was formed, whilst use of isopropyl iodide gave only the *O*-alkylated product (**55**). Allyl bromide also gave a mixture of the *O*- and *N*-allylated products (**56**) and (**52**) respectively, but on treatment with palladium acetonylacetonate at 200 °C, the *O*-alkylated isomer was completely converted into the *N*-alkylated product. Thus *O*-alkylation must be the kinetically controlled process.

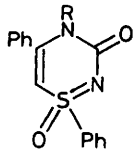
Treatment of the oxothiadiazine (**23**) with phosphorus oxychloride at reflux gave the imino chloride (**57**), which could be readily hydrolysed back to starting material under basic aqueous conditions thus indicating potential displacement by nucleophiles. Accordingly a number of nucleophilic displacements were carried out to give derivatives (**53**)–(**61**) (see Experimental for details). Reaction of the chloride (**57**) with sodium hydrosulphide gave what appeared to be the thione (**62**) rather than the tautomeric mercaptan. This was shown by the ^1H NMR signal at δ 11.87 assigned as an NH rather than SH signal, which is usually observed in the region δ 1–2.

Some of these products were examined for further chemical transformations. For example, when the hydrazine product (**59**) was heated with DMF dimethyl acetal (**11**) at 105 °C in xylene in the presence of catalytic toluene-4-sulphonic acid a condensation product formed, identified as the [1,2,4]triazolo[3,4-*c*][1λ⁴,2,4-thiadiazine (**63**). Under milder conditions, *viz.* 60 °C in the absence of acid, this reaction afforded an intermediate, shown to be the amidine (**64**); on heating at 105 °C the latter afforded the bicyclic system (**63**). ^1H NMR spectroscopy ruled out the isomeric structure (**65**) for the intermediate.

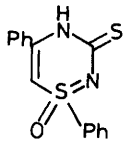
One feature of the sulphoximide group not yet exploited is its known ability to exist as optical antipodes.[6] A brief examination of the incorporation of the optically active forms into some of the cyclic systems, described as racemates above, was therefore made.

Optically pure (+)-*S*-methyl-*S*-phenylsulphoximide, (+)-(**4**), and its antipode, (−)-(**4**) were prepared by the method described by Johnson and Schroek,[11] and absolute configurations assigned as (*R*) and (*S*) respectively. Condensation of both compounds with benzonitrile, to give the intermediate enamines, was followed directly by condensation with DMF dimethyl acetal to give the optically active thiadiazines, (*R*)-(**13**) and (*S*)-(**13**); the former showed a negative rotation, $[\alpha]_D$ −120.7°, and the latter a positive rotation, $[\alpha]_D$ +119.4°.

One final series of reactions was performed on the halo-substituted thiadiazines (**19**) and (**20**). The synthesis of these derivatives was described above. As anticipated the halo-



(50) R = Me
(51) R = Et
(52) R = $CH_2CH{=}CH_2$



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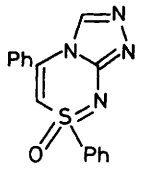

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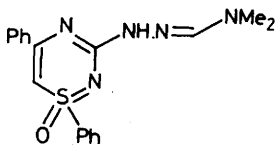

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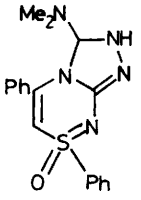

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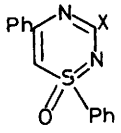
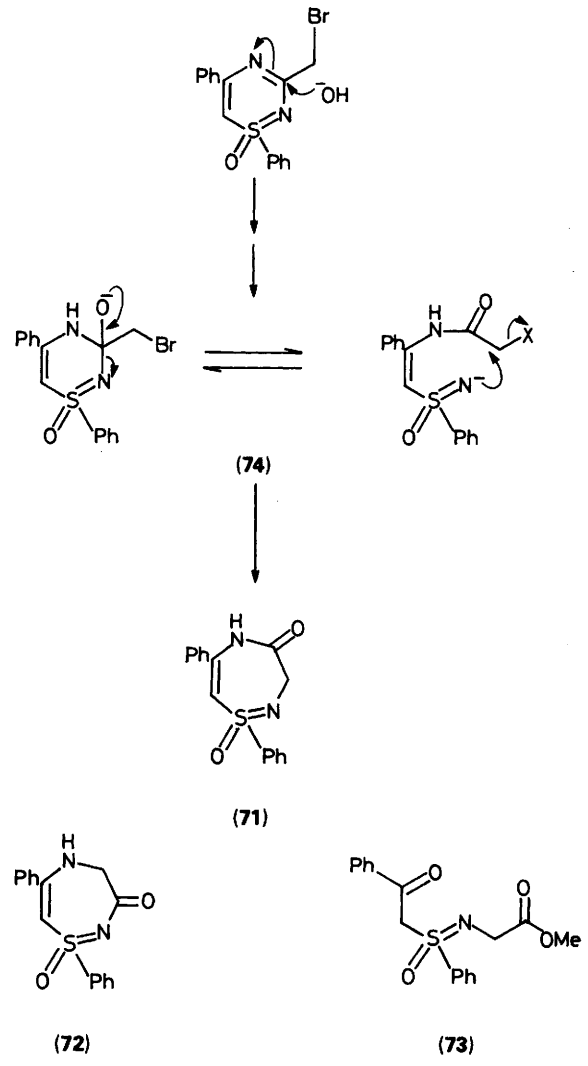


(53) X = OMe
(54) X = OEt
(55) X = OPr^i
(56) X = $OCH_2CH{=}CH_2$
(57) X = Cl
(58) X = N⟨ ⟩
(59) X = $NHNH_2$
(60) X = SMe
(61) X = SEt
(66) X = CH_2N⟨ ⟩
(67) X = CH_2SPh
(68) X = CH_2SEt
(69) X = CH_2NHMe
(70) X = CH_2OEt

substituent possesses benzylic properties and undergoes ready nucleophilic displacements. Thus, with piperidine the chloride (**19**) rapidly produces the piperidinomethyl derivative (**66**), whilst thiolates produce the corresponding sulphides such as compounds (**67**) and (**68**). The favourable nature of these substitutions led us to examine possible ring expansion reactions by analogy with the work of Cohen and Mahnke,[12] who demonstrated that certain chloromethyl-substituted benzothiadiazines can undergo base-catalysed ring expansions. Whereas treatment of the bromomethyl-substituted thiadiazine (**20**) with methylamine gave only the substitution product (**69**), reaction with sodium hydroxide in aqueous ethanol gave three products, readily separated by column chromatography. The least polar and major product (51% yield) was readily identified as the straight substitution product (**70**), and the intermediate compound the simple ketone (**10**) (8%). The most polar product, isolated in 24% yield, was shown by spectral data to be either the amide (**71**) or its isomer (**72**). Chemical evidence supporting the former structure was obtained by first hydrolysing the rearrangement product with sodium hydroxide and then esterifying the product with diazomethane to produce the ester (**73**).



(74)

(71)

(72)

(73)

Scheme.

None of the simpler sulphoximide (**10**) was formed during this hydrolysis as would be expected from the isomeric substance (**72**), thus ruling out this alternative. A mechanism for the rearrangement, following that of Sternbach for the benzodiazepines[13] and that of Cohen and Mahnke,[12] is outlined in the Scheme. Attempts to perform the ring expansion reaction using the 3-chloromethylthiadiazine (**19**) gave only the hydrolysis product (**10**), suggesting that hydrolytic ring cleavage of the ring-opened intermediate (**74**; X = Cl) is very much faster than displacement of chloride by the sulphoximide nitrogen.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP3-200S spectrophotometer, using, unless otherwise stated, KBr discs. ^{1}H NMR spectra were recorded on a Perkin-Elmer R12 or a Bruker WP-200 spectrometer and are reported in ppm relative to tetramethylsilane (TMS) as internal reference for solutions in deuteriochloroform or as stated. ^{13}C NMR spectra were obtained on the Bruker instrument at 50.13 MHz and are also reported in ppm from TMS. Mass spectra were obtained with a Kratos MS 25 instrument. Microanalytical determinations were carried out by CHN Analysis Ltd of Leicester.

Column chromatography (gravity) was carried out using Merck Kieselgel 60 (0.063–0.20 mm) at substrate to absorbate ratios of 1:100 to 1:30. Flash chromatography (hand bellows) was carried out using Merck TLC-Kieselgel 60H (15 microns) at substrate to absorbate ratios of 1:50 to 1:15. Optical rotations were measured using a model AA-100 polarimeter from Optical Activity Ltd.

Solvents were dried using the methods described by Perrin.[14] Light petroleum refers to the fraction of boiling range 40–60 °C Butyl-lithium in hexane was obtained from Aldrich and standardised just prior to use by titration against biphenylmethanol.[15] *S*-Methyl-*S*-phenylsulphoximide and its ethyl analogue were prepared from the appropriate thioethers from the *N*-toluene-4-sulphonylsulphimide and the *N*-toluene-4-sulphonylsulphoximide *via* established methods.[16] Organic solutions were generally dried over anhydrous magnesium sulphate and evaporated under reduced pressure using a Buchi rotavapor.

S-(2-*Aminostyryl*)-S-*phenylsulphoximide* (**5**).—To a solution of *S*-methyl-*S*-phenylsulphoximide (8.3 g, 0.053 mol) in dry THF (200 ml) at 0 °C under dry nitrogen, was added butyllithium in hexane, (1.4M; 79 ml, 0.11 mol) at a controlled rate to keep the temperature below 10 °C. To the yellow solution was added benzonitrile (15 ml, 0.17 mol) and the mixture stirred at 0 °C for 30 min before the addition of saturated brine and separation of the organic layer. The organic solution was washed with a little water, dried, and evaporated to yield a red oil. Trituration of the oil with light petroleum removed most of the excess of benzonitrile, then the residue was chromatographed through silica gel, using 1:4 ethyl acetate–dichloromethane as eluant, to give the *title compound* (10.5 g, 77%), m.p. 95–96 °C (ether–dichloromethane); ν_{max} 3 420, 3 320, 1 620, 1 550, and 1 495 cm^{-1}; δ_H 3.2 (1 H, br, exchanges with D_2O, NH), 4.95 (1 H, s, 1-H), 6.40 (2 H, br s, exchanges with D_2O, NH_2), 7.3–8.1 (10 H, m, aryl H) (Found: C: 65.4; H, 5.5; N, 10.8; S, 12.3. $C_{14}N_2OS$ requires C, 65.1; H, 5.5; N, 10.8; S, 12.4%).

By a similar method were prepared: S-(2-*amino*-4′-*methylstyryl*)-S-*phenylsulphoximide* (**6**), from the sulphoximide (**4**) and 4-methylbenzonitrile, as an oil (68%), ν_{max}(film) 3 495, 3 290, 1 625, 1 545, and 1 515 cm^{-1}; δ_H 2.35 (3 H, s, Me), 2.95 (1 H, s, exchanges with D_2O, NH), 5.0 (1 H, s, 1-H), 6.52 (2 H, br s, exchanges with D_2O, NH_2), 7.0–8.2 (9 H, m, aryl H).

S-(2-*Amino*-4′-*methoxystyryl*)-S-*phenylsulphoximide* (**7**), from from the sulphoximide (**4**) and 4-methoxybenzonitrile, as an oil (61%), ν_{max}(film) 3 420, 3 310, 1 620, 1 545, and 1 510 cm^{-1}; δ_H 3.0 (1 H, br s, exchanges with D_2O, NH), 3.8 (3 H, s, MeO), 4.9 (1 H, s, 1-H), 6.4 (2 H, br s, exchanges with D_2O, NH_2), 6.9–8.0 (9 H, m, aryl H).

S-(2-*Amino*-2′-*chlorostyryl*)-S-*phenylsulphoximide* (**8**), from the sulphoximide (**4**) and 2-chlorobenzonitrile, as an oil (29%), ν_{max}(film) 3 410, 3 320, 1 620, 1 555, and 1 450 cm^{-1}; δ_H 2.8 (1 H, exchanges with D_2O, NH), 4.65 (1 H, s, 1-H), 6.4 (2 H, br s, exchanges with D_2O, NH_2), 7.0–8.1 (9 H, m, aryl H).

S-(2-*Amino*-1-*methylstyryl*)-S-*phenylsulphoximide* (**9**), from *S*-ethyl-*S*-phenylsulphoximide and benzonitrile, as an oil (43%), ν_{max}(film) 3 420, 3 320, 1 615, 1 570, and 1 445 cm^{-1}; δ_H 1.6 (3 H, s, Me), 3.3 (1 H, br s, exchanges with D_2O, NH), 6.35 (2 H, br s, exchanges with D_2O, NH_2), 7.3–8.2 (10 H, m, aryl H).

S-*Benzoylmethyl*-S-*phenylsulphoximide* (**10**).—To a solution of the aminostyrene (**5**) (250 mg, 1 mmol) in ethanol (20 ml) was added hydrochloric acid (6M; 1 ml), and the solution warmed to 50 °C. Removal of the solvent, neutralisation of the residue with aqeuous sodium hydrogen carbonate and extraction with dichloromethane gave the *title compound* (210 mg, 84%), m.p. 77–79 °C (ether); ν_{max} 3 300, 3 060, 1 685, 1 600, 1 450, 1 285, and 1 245 cm^{-1}; δ_H 3.7 (1 H, br s, exchanges with D_2O, NH), 4.74 (2 H, br s, CH_2), 7.2–8.1 (10 H, m, aryl H) (Found: C, 64.6; H, 5.1; N, 5.3; S, 12.1. $C_{14}H_{13}NO_2S$ requires C, 64.8; H, 5.1; N, 5.4; S, 12.4%).

1,5-*Diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**13**).—To a solution of the styrene (**5**) (2 g, 7.7 mmol) in dry dimethylformamide was added DMF dimethyl acetal (**11**) (1 g, 8.5 mmol), and the mixture heated at 80 °C for 15 min before cooling and diluting with ethyl acetate (25 ml). The organic solution was washed with water, dried with magnesium sulphate, and evaporated to yield an oil which crystallised on trituration with ether to yield the *title thiadiazine* (1.67 g, 6.2 mmol, 80%), m.p. 110–111 °C; ν_{max} 1 590, 1 540, 1 500, 1 455, and 1 410 cm^{-1}; δ_H 6.2 (1 H, d, *J* 1.8 Hz, 6-H), 7.2–8.0 (10 H, m, aryl H), 8.3 (1 H, d, *J* 1.8 Hz, 3-H) (Found: C, 67.2; H, 4.6; N, 10.3; S, 11.7. $C_{15}H_{12}N_2OS$ requires C, 67.1; H, 4.5; N, 10.4; S, 11.9%).

By a similar method the following were also prepared: 5-(4-*methylphenyl*)-1-*phenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**14**) (74%), m.p. 103–104 °C; ν_{max} 1 543, 1 450, 1 415, 1 395, 1 240, and 1 220 cm^{-1}; δ_H 2.38 (3 H, s, Me), 6.2 (1 H, d, *J* 1.5 Hz, 6-H), 7.1–8.0 (9 H, m, aryl H), 8.25 (1 H, d, *J* 1.5 Hz, 3-H) (Found: C, 67.8; H, 5.0; N, 9.9; S, 11.3. $C_{16}H_{14}N_2OS$ requires C, 68.1; H, 5.0; N, 9.9; S, 11.4%).

5-(4-*Methoxyphenyl*)-1-*phenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**15**) (57%), m.p. 102–104 °C; ν_{max} 1 605, 1 540, 1 519, 1 400, 1 250, and 1 220 cm^{-1}; δ_H 3.8 (3 H, s, MeO), 6.15 (1 H, d, *J* 1.2 Hz, 6-H), 6.9–8.0 (9 H, m, aryl H), 8.2 (1 H, d, *J* 1.2 Hz, 3-H) (Found: C, 64.4; H, 4.8; N, 9.3; S, 10.7. $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4; S, 10.7%).

5-(2-*Chlorophenyl*)-1-*phenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**16**) (79%), m.p. 85–87 °C; ν_{max} 1 540, 1 480, 1 450, 1 400, 1 336, and 1 240 cm^{-1}; δ_H 6.15 (1 H, d, *J* 1.5 Hz, 6-H), 7.1–7.9 (9 H, m, aryl H), 8.2 (1 H, d, *J* 1.5 Hz, 3-H) (Found: C, 59.6; H, 3.7; N, 9.2; S, 10.7; Cl, 11.7. $C_{15}H_{11}ClN_2OS$ requires C, 59.6; H, 3.7; N, 9.2; S, 10.6; Cl, 11.7%).

6-*Methyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**17**) (74%), from *S*-(2-amino-4′-methylstyryl)-*S*-phenylsulphoximide (**9**), m.p. 105–106 °C; ν_{max} 1 555, 1 495, 1 475, 1 445, and 1 390 cm^{-1}; δ_H 1.9 (3 H, s, Me), 7.2–8.0 (10 H, m, aryl H), 8.07 (1 H, s, 3-H) (Found: C, 68.2; H, 5.1; N, 9.9; S, 11.2. $C_{16}H_{14}N_2OS$ requires C, 68.1; H, 5.0; N, 9.9; S, 11.4%).

3-*Methyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**18**) (86%), from the aminostyrene (**5**) and the acetal (**12**), m.p. 103–104 °C; ν_{max} 1 580, 1 530, 1 490, 1 455, 1 415, and 1 365 cm^{-1}; δ_H 2.48 (3 H, s, Me), 6.07 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 67.8; H, 5.0; N, 9.8; S, 11.3. $C_{16}H_{14}N_2OS$ requires C, 68.1; H, 5.0; N, 9.9; S, 11.4%).

3-*Chloromethyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**19**).—*Method A*. To a solution of the enamine (**5**) (1.55 g, 6 mmol) in DMF (30 ml) was added triethyl orthochloroacetate (1.41 g, 7.2 mmol) and the mixture stirred at 50 °C for 1 h. After dilution with ethyl acetate (100 ml) and washing with water, the organic solution was dried ($MgSO_4$) and evaporated to give the *title thiadiazine* (0.85 g, 45%), m.p. 99–100 °C (from ether); ν_{max} 1 535, 1 460, 1 450, 1 240, 1 200, and 1 100 cm^{-1}; δ_H 4.45 (2 H, s, CH_2Cl), 6.2 (1 H, s, 6-H), 7.2–8.1 (10 H, m, aryl H) (Found: C, 60.8; H, 4.2; N, 8.8; S, 10.2; Cl, 11.3. $C_{16}H_{13}ClN_2OS$ requires C, 60.7; H, 4.1; N, 8.8; S, 10.1; Cl, 11.2%).

Method B. To a solution of the enamine (**5**) (2.6 g, 10 mmol) in dichloromethane (50 ml) was added triethylamine (2.0 g, 20 mmol) and then, dropwise over 10 min, chloroacetyl chloride (1.1 g, 10 mmol). After stirring the mixture at room temperature for 30 min, the organic solution was washed with water, dried and evaporated to give an oil (3.1 g). Without further purification this oil was dissolved in ethanol (80 ml), aqueous sodium hydroxide (2M, 14 ml) added, and the mixture stirred for 10 min. A heavy white precipitate formed, which was collected

and dried to give the title thiadiazine, m.p. and mixed m.p. 99–100 °C with spectral properties identical with those of the material described above.

3-*Bromomethyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**20**).—This was prepared in the manner described under method A for compound (**19**), using triethyl orthobromoacetate. The *title material* (65%) showed m.p. 93–94 °C (from ether); ν_{max} 1 580, 1 530, 1 495, 1 460, 1 385, and 1 240 cm^{-1}; δ_H 4.34 (2 H, br s, CH_2Br), 6.14 (1 H, s, 6-H), 7.3–8.1 (1 H, m, aryl H) (Found: C, 53.4; H, 3.7; N, 7.8; S, 8.8, Br, 22.1. $C_{16}H_{13}N_2OS$ requires C, 53.2; H, 3.6; N, 7.8; S, 8.9; Br, 22.1%).

S-(2-*Aminostyryl*)-N-(N′-*imidazocarbonyl*)-S-*phenylsulphoximide* (**21**).—To a solution of the enamine (**5**) (6.5 g, 25 mmol) in chloroform (100 ml) was added *N*,*N*′-carbonyldiimidazole (6.1 g, 38 mmol) and the solution stirred for 4 h before evaporation of the solvent. The residue was chromatographed, using 1:5 ethyl acetate–dichloromethane as eluant, to give the *product* (6.8 g, 77%), m.p. 170–171 °C (from chloroform), ν_{max} 3 420, 3 300, 1 680, 1 650, 1 370, and 1 285 cm^{-1}; δ_H 5.2 (1 H, s, vinyl H), 6.3 (2 H, br s, NH_2), 7.0 (1 H, s, imidazole H), 7.3–8.1 (11 H, m, aryl and imidazole H), 8.25 (1 H, s, imidazole H) (Found: C, 61.2; H, 4.6; N, 15.8; S, 9.1. $C_{18}H_{16}N_4O_2S$ requires C, 61.3; H, 4.6; N, 15.9; S, 9.1%).

Hydrolysis of (**21**).—To a solution of the enamine (**21**) (200 mg) in ethanol (20 ml) was added dilute HCl (2M; 4 ml), and the solution stirred for 10 min at room temperature before adding an aqueous solution of sodium hydrogen carbonate (2M; 20 ml). The mixture was extracted with dichloromethane and the organic extract was dried and evaporated to give S-(*benzoylmethyl*)-N-(N′-*imidazocarbonyl*)-S-*phenylsulphoximide* (**22**) (180 mg, 90%), m.p. 106–108 °C (from ether); ν_{max} 1 686, 1 370, 1 287, 1 235, 1 192, and 1 020 cm^{-1}; δ_H 5.16 and 5.35 (2 H, ABq, *J* 12 Hz, CH_2CO), 7.01 (1 H, s, imidazole 4-H), 7.4–8.2 (12 H, m, aryl and imidazole H) (Found: C, 61.3; H, 4.3; N, 11.8; S, 9.2. $C_{18}H_{15}N_3O_3S$ requires C, 61.2; H, 4.3; N, 11.9; S, 9.1%).

3-*Oxo*-1,5-*diphenyl*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**23**).—The enamine (**21**) (6.4 g, 18 mmol) was suspended in Dowtherm A (70 ml) and heated at 200 °C for 1 h. After cooling to room temperature, ether (210 ml) was added and the crystalline solid collected by filtration, and washed with a little ether and chloroform to give the *title product* (4.5 g, 87%). A sample, recrystallised from methanol, showed m.p. 304–305 °C; ν_{max} 3 170, 1 650, 1 600, 1 575, 1 295, and 1 235 cm^{-1}; δ_H [$(CD_3)_2SO$] 6.5 (1 H, s, 6-H), 7.7–8.0 (10 H, m, aryl H), 10.8 (1 H, br s, exchanges with D_2O, 4-H) (Found: C, 63.3; H, 4.3; N, 9.9; S, 11.2. $C_{15}H_{12}N_2O_2S$ requires C, 63.3; H, 4.3; N, 9.9; S, 11.3%).

3-*Amino*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**41**).—To a solution of the enamine (**5**) (2.58 g, 10 mmol) in DMF (25 ml) at 10 °C was added cyanogen bromide (1.15 g, 11 mmol) and the mixture stirred for 1 h before warming to 50 °C and stirring at this temperature for a further 1 h. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate to give the crude product, which was directly purified by chromatography, using 1:4 ethyl acetate–dichloromethane as eluant, to give the *title thiadiazine* (0.6 g, 21%), m.p. 169–170 °C (from chloroform–ether); ν_{max} 3 430, 3 295, 1 630, 1 540, 1 475, and 1 445 cm^{-1}; δ_H 2.45 (0.4 H, br s, exchanges with D_2O, 4-H), 5.65 (1.6 H, br s, exchanges with D_2O, NH), 5.75 (1 H, s, 6-H), 7.2–8.0 (10 H, m, aryl H) (Found: C, 63.5; H, 4.7; N, 14.7; S, 11.2. $C_{15}H_{13}N_2OS$ requires C, 63.6; H, 4.6; N, 14.8; S, 11.3%).

3,4-*Dihydro*-3,3-*dimethyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**42**).—A solution of the enamine (**5**) (1 g, 3.9 mmol) in 2,2-dimethoxypropane (10 ml) containing toluene-4-sulphonic acid (10 mg) was heated to reflux for 10 h. The excess of the acetal was distilled off and the oily residue chromatographed, using 1:4 ether–dichloromethane as eluant, to yield the *title compound* (0.78 g, 67%), m.p. 128–130 °C (from ether); ν_{max} 3 340, 1 540, 1 506, 1 210, 1 177, 1 109, and 1 058 cm^{-1}; δ_H 1.72 (3 H, s, Me), 1.80 (3 H, s, Me), 5.07 (1 H, br s, exchanges with D_2O, NH), 5.65 (1 H, s, 6-H), 7.35–8.0 (10 H, m, aryl H); δ_C 27.99, 33.30, 69.93, 91.28, 126.79, 128.30, 128.76, 129.07, 131.04, 131.93, 135.69, 142.51, 152.82 (Found: C, 68.3; H, 5.8; N, 9.5; S, 10.5. $C_{17}H_{18}N_2OS$ requires C, 68.4; H, 6.1; N, 9.4; S, 10.7%).

6-*Bromo*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**45**).—To the thiadiazine (**13**) (290 mg, 1 mmol) in chloroform (50 ml) was added dropwise a solution of bromine (1 g) in chloroform (20 ml) until a persistent yellow colour formed. The organic solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated to give crystals of the *title bromide* (220 mg, 58%), m.p. 135–136 °C (from ether); ν_{max} 1 530, 1 492, 1 460, 1 385, 1 240, and 1 100 cm^{-1}; δ_H 7.1–8.1 (10 H, m, aryl H), 8.27 (1 H, s, 3-H) (Found: C, 51.6; H, 3.3; N, 8.1; S, 9.1; Br, 23.1. $C_{15}H_{11}BrN_2OS$ requires C, 51.9; H, 3.2; N, 8.1; S, 9.2; Br, 23.0%).

In a similar manner, using the oxo-derivative (**23**) as starting material, was prepared 6-*bromo*-3-*oxo*-1,5-*diphenyl*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**48**) (65%), m.p. 175–177 °C (from chloroform); ν_{max} 3 500, 3 160, 3 020, 2 880, 1 655, 1 590, 1 295, 1 240, and 1 102 cm^{-1}; δ_H[$(CD_3)_2SO$] 7.4–8.0 (10 H, m, aryl H), 11.5 (1 N, br s, exchanges with D_2O, NH) (Found: C, 49.6; H, 3.1; N, 7.8; S, 8.7; Br, 21.9. $C_{15}H_{11}BrN_2O_2S$ requires C, 49.6; H, 3.0; N, 7.7; S, 8.8; Br, 22.0%).

5-(3-*Nitrophenyl*)-1-*phenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**49**).—To a solution of the thiadiazine (**13**) (0.5 g, 1.9 mmol) in conc. H_2SO_4 (4 ml) at 10 °C was added conc. nitric acid (70%; 0.65 ml, 10 mmol), and the mixture stirred at 10 °C for 15 min before pouring it into ice-water 50 ml) and basifying with solid sodium carbonate. Extraction of the product with dichloromethane, drying, and evaporation of the solvent gave the colourless *product* (0.41 g, 70%), m.p. 138–139 °C (from chloroform–ether); ν_{max} 1 518, 1 398, 1 350, 1 240, 1 216, and 1 195 cm^{-1}; δ_H 6.37 (1 H, d, *J* 1 Hz, 6-H), 7.5–8.4 (9 H, m, aryl H and 3-H), 8.75 (1 H, m, aryl H) (Found: C, 57.8; H, 3.6; N, 13.3; S, 10.3. $C_{15}H_{11}N_3O_3S$ requires C, 57.5; H, 3.5; N, 13.4; S, 10.2%).

1,5-*Diphenyl*-6-*phenylthio*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**46**).—Thiophenol (0.59 ml, 5.8 mmol) was added to a suspension of sodium hydride (80%; 174 mg, 5.8 mmol) in DMF (50 ml) at room temperature. The bromide (**45**) (2 g, 5.8 mmol) was then added and the mixture stirred at 50 °C for 4 h. The mixture was diluted with ethyl acetate and washed with water, then the organic extract was dried and the solvent removed to afford, after crystallisation from ethyl acetate, the *title sulphide* (1.54 g, 71%), m.p. 160–161 °C; ν_{max} 1 512, 1 442, 1 417, 1 390, 1 245, and 1 192 cm^{-1}; δ_H 6.8–7.7 (15 H, m, aryl H), 8.31 (1 H, s, 3-H) (Found: C, 66.7; H, 4.5; N, 7.4; S, 16.8. $C_{21}H_{16}N_2OS_2$ requires C, 67.0; H, 4.3; N, 7.4; S, 17.0%).

6-*Ethoxycarbonyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**47**).—To a solution of the bromide (**45**) (0.5 g, 1.4 mmol) in dry THF (20 ml) at −70 °C was added, dropwise, butyllithium (2.14M solution in hexane; 0.68 mmol) and the mixture stirred at −70 °C for 30 min before adding tetramethylethylenediamine (TMEDA) (0.23 ml, 1.5 mmol) and, after a further 30 min, ethyl chloroformate (0.15 ml, 1.5 mmol). The reaction mixture was stirred and allowed to warm to room temperature overnight, then it was quenched with aqueous

ammonium chloride and then extracted with ethyl acetate. After drying, the extract was concentrated and the residue chromatographed (1:3 ether–light petroleum) to give crystals of the *title ester* (0.15 g, 31%), m.p. 91–93 °C (from ether–dichloromethane); ν_{max} 1 718, 1 510, 1 400, 1 235, 1 210, and 1 055 cm^{-1}; δ_H 0.75 (3 H, t, *J* 5 Hz, Me), 3.8 (2 H, q, *J* 5 Hz, OCH_2), 7.4–7.9 (10 H, m, aryl H), 8.3 (1 H, s, 3-H) (Found: C, 63.5; H, 4.7; N, 8.2; S, 9.3. $C_{18}H_{16}N_2O_3S$ requires C, 63.5; H, 4.7; N, 8.2; S, 9.4%).

Alkylation of 3-*Oxo*-1,5-*diphenyl*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**23**).—*General procedure.* To a solution of the thiadiazine (10 mmol) in DMF (20 ml) containing potassium carbonate (15 mmol) was added the alkyl halide (11 mmol) and the mixture stirred at 50 °C until all the starting material had been consumed. The mixture was then diluted with ethyl acetate, washed with water, the organic extract dried, concentrated and examined by NMR spectroscopy, to establish the *O*:*N* alkylation ratios, followed, in some instances, by separation of the products by silica gel chromatography.

With methyl iodide. The crude product (94%) showed 96:4 *N*:*O* alkylation. The *N*-alkylated product was isolated by chromatography; 4-*methyl*-3-*oxo*-1,5-*diphenyl*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**50**) showed m.p. 192–193 °C (from ethyl acetate; ν_{max} 1 648, 1 580, 1 560, 1 270, 1 183, and 1 065 cm^{-1}; δ_H 3.22 (3 H, s, NMe), 5.65 (1 H, s, 6-H), 7.2–8.0 (10 H, m, aryl H) (Found: C, 64.1; H, 4.8; N, 9.4; S, 10.5. $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4; S, 10.7%).

With ethyl iodide. The crude product (89%) showed 38:62 *N*:*O* alkylation. The *N*-ethyl derivative (**51**) was assigned ^1H NMR signals at 1.1 (t, CH_3CH_2N), 3.7–3.83 (m, CH_3CH_2N), 5.57 (s, 6-H); the *O*-ethyl derivative was assigned signals at 1.42 (t, CH_3CH_2O), 4.95 (t, CH_3CH_2O), 6.1 (s, 6-H).

With isopropyl iodide. The crude product (92%) showed complete *O*-alkylation; crystallisation from ethyl acetate–ether afforded 3-*isopropyloxy*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**55**), m.p. 66–67 °C; ν_{max} 1 530, 1 440, 1 425, 1 305, 1 230, and 1 195 cm^{-1}; δ_H 1.4 (6 H, dd, Me_2), 5.4 (1 H, heptet, $OCHMe_2$), 6.05 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 66.2; H, 5.6; N, 8.6; S, 9.9. $C_{18}H_{18}N_2O_2S$ requires C, 66.2; H, 5.6; N, 8.6; S, 9.8%).

With allyl bromide. The crude product (84%) showed 64:36 *N*:*O* alkylation. Treatment of this mixture with palladium acetylacetonate (25 mg per g), heating at 200 °C for 2 h, gave complete conversion to the *N*-alkylated product (**52**). After crystallisation from dichloromethane–ether, 4-*allyl*-3-*oxo*-1,5-*diphenyl*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* showed m.p. 104–106 °C; ν_{max} 3 060, 1 636, 1 560, 1 395, 1 255, 1 230, and 1 200 cm^{-1}; δ_H 4.32 (2 H, m, CH_2), 4.9 (1 H, m, vinylic H), 5.15 (1 H, m, vinylic H), 5.67 (1 H, s, 6-H), 5.82 (1 H, m, vinylic H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 66.8; H, 4.7; N, 8.7; S, 9.7. $C_{18}H_{16}N_2O_2S$ requires C, 66.6; H, 5.0; N, 8.6; S, 9.9%).

3-*Chloro*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**57**).—The thiadiazine (**23**) (13.9 g, 50 mmol) was added to freshly distilled phosphorus oxychloride (50 ml) and then heated at reflux for 30 min. The excess of reagent was removed by distillation under reduced pressure and the residue dissolved in chloroform, washed with water, dried, and evaporated. After trituration with a little ethanol the residue crystallised to give the *title chloride* (10.8 g, 73%), m.p. 117–118 °C (from ether); ν_{max} 1 535, 1 450, 1 360, 1 225, and 1 200 cm^{-1}; δ_H 6.35 (1 H, s, 6-H), 7.1–8.0 (10 H, m, aryl H) (Found: C, 59.2; H, 3.7; N, 9.1; S, 10.7; Cl, 11.9. $C_{15}H_{11}ClN_2OS$ requires C, 59.5; H, 3.7; N, 9.2; S, 10.6; Cl, 11.7%).

The chloride (**57**) was used as starting material to make a variety of 3-substituted thiadiazines as follows:

(i) 3-*Methoxy*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**53**) (72%), by treatment with methanol containing 4 equiv. sodium carbonate at room temperature for 18 h; m.p. 99–101 °C (from ether); ν_{max} 1 530, 1 470, 1 383, 1 323, and 1 238 cm^{-1}; δ_H 4.05 (3 H, s, Me), 6.08 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 64.3; H, 4.8; N, 9.3; S, 10.6. $C_{16}H_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4; S, 10.7%).

(ii) 3-*Ethoxy*-1,5-*diphenyl*-1H-1,2,4-*thiadiazine* 1-*oxide* (**54**) (84%), by treatment with ethanol as described above; m.p. 105–107 °C (from ether); ν_{max} 3 040, 1 582, 1 537, 1 473, and 1 450 cm^{-1}; δ_H 1.40 (3 H, t, *J* 7 Hz, CH_3CH_2), 4.95 (2 H, q, *J* 7 Hz, CH_3CH_2), 6.02 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 65.1; H, 5.1; N, 9.0; S, 10.1. $C_{17}H_{16}N_2O_2S$ requires C, 63.4; H, 5.2; N, 9.0; S, 10.3%).

(iii) 1,5-*Diphenyl*-3-*piperidino*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**58**) (70%), by heating with neat piperidine at 100 °C for 1 h, m.p. 164–165 °C (from ether–dichloromethane); ν_{max} 1 520, 1 500, 1 450, 1 430, 1 365, and 1 280 cm^{-1}; δ_H 1.5–1.7 (6 H, m, methylenes), 3.85 (4 H, m, 2 × CH_2N), 5.65 (1 H, s, 6-H), 7.2–8.0 (10 H, m, aryl H) (Found: C, 68.0; H, 6.1; N, 12.0; S, 9.0. $C_{20}H_{21}N_3OS$ requires C, 68.3; H, 6.0; N, 12.0; S, 9.1%).

(iv) 3-*Amino*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**41**) (93%), by heating with ammoniacal ethanol in an autoclave at 100 °C for 1 h, m.p. and mixed m.p. with material described above, 169–170 °C.

(v) 3-*Hydrazino*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**59**) (55%), by heating with 4 equiv. of hydrazine hydrate in ethanol at reflux for 1 h, m.p. 186–187 °C (from ethyl acetate); ν_{max} 3 360, 1 535, 1 497, 1 465, 1 400, and 1 235 cm^{-1}; δ_H 3.65 (2 H, br s, exchanges with D_2O, NH_2), 5.8 (1 H, s, 6-H), 6.9 (1 H, br s, exchanges with D_2O, NH), 7.2–8.1 (10 H, m, aryl H) (Found: C, 60.2; H, 4.8; N, 18.5; S, 10.7. $C_{15}H_{14}N_4OS$ requires C, 60.4; H, 4.7; N, 18.8; S, 10.7%).

(vi) 3-*Methylthio*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**60**) (74%), by treatment with a solution of sodium methanethiolate in DMF at room temperature for 1 h, m.p. 148–150 °C (from dichloromethane–ether); ν_{max} 1 440, 1 388, 1 370, 1 225, and 1 190 cm^{-1}; δ_H 1.6 (3 H, s, Me), 6.05 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 61.4; H, 4.5; N, 8.8; S, 19.9. $C_{16}H_{14}N_2OS_2$ requires C, 61.1; H, 4.5; N, 8.9; S, 20.4%).

(vii) 3-*Ethylthio*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**61**) (66%), by treatment with sodium ethanethiolate in THF at room temperature for 2 h, m.p. 78–79 °C (from ethyl acetate); ν_{max} 1 445, 1 418, 1 360, 1 220, and 1 195 cm^{-1}; δ_H 1.4 (3 H, t, *J* 7 Hz, Me), 3.18 (2 H, q, *J* 7 Hz, CH_2), 6.05 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 62.3; H, 4.9; N, 8.5; S, 19.5. $C_{17}H_{16}N_2OS_2$ requires C, 62.2; H, 4.9; N, 8.5; 19.5%).

(viii) 1,5-*Diphenyl*-3-*thioxo*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**62**) (79%), by treatment with 2 equiv. sodium hydrosulphide in ethanol at room temperature for 2 h, m.p. 232–234 °C (from ethyl acetate); ν_{max} 1 605, 1 515, 1 440, 1 335, 1 245, and 1 180 cm^{-1}; δ_H 6.25 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H), 11.87 (1 H, s, exchanges with D_2O, NH) (Found: C, 59.8; H, 4.1; N, 9.2; S, 21.1. $C_{15}H_{12}N_2OS_2$ requires C, 60.0; H, 4.0; N, 9.3; S, 21.3%).

5,7-*Diphenyl*-1H-[1,2,4]*triazolo*[3,4-c][1λ⁴,2,4]*thiadiazine* 1-*oxide* (**63**).—To a solution of the hydrazine derivative (**59**) (200 mg, 0.67 mmol) in DMF (3 ml) was added dimethylformamide dimethyl acetal (**11**) (100 mg, 0.8 mmol) and the mixture heated for 15 min at 60 °C before diluting with ethyl acetate, washing with water, drying and removal of the solvent to give the intermediate (**64**) (170 mg, 72%), m.p. 207–208 °C (from ethyl acetate); ν_{max} 3 260, 1 570, 1 540, 1 512, 1 492, 1 430, 1 365, and 1 217 cm^{-1}; δ_H 2.77 (6 H, s, NMe_2), 5.71 (1 H, s, 6-H), 7.25–8.00 (12 H, m, aryl H and NH) (Found: C, 61.1; H, 5.5; N, 19.7; S, 9.1. $C_{18}H_{19}N_5OS$ requires C, 61.2; H, 5.4; N, 19.8; S, 9.1%). This intermediate (150 mg, 0.42 mmol) was heated at 150 °C in xylene (5 ml) containing toluene-*p*-sulphonic acid (10 mg) for 1

h, then evaporation of the solvent and direct crystallisation of the product from dichloromethane–light petroleum gave the *title compound* (115 mg, 88%), m.p. 193–195 °C; ν_{max} 1 612, 1 535, 1 400, 1 245, 1 207, and 1 050 cm^{-1}; δ_H 6.21 (1 H, s, 6-H), 7.5–8.05 (10 H, m, aryl H), 8.12 (1 H, s, 1-H) (Found: C, 62.2; H, 4.1; N, 18.2; S, 10.2. $C_{16}H_{12}N_4OS$ requires C, 62.3; H, 3.9; N, 18.2; S, 10.4%).

1,5-*Diphenyl*-3-*piperidinomethyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**66**).—A mixture of 3-chloromethyl-1,5-diphenyl-1*H*-1λ⁴,2,4-thiadiazine 1-oxide (**19**) (2.6 g, 8.3 mmol) and piperidine (10 ml) was heated at 100 °C for 1 h before pouring into water and extraction with dichloromethane. The organic extract was dried and evaporated to give an oil that crystallised on trituration with chloroform–ether. The *amine* (2.1 g, 69%) had m.p. 136–137 °C; ν_{max} 1 530, 1 450, 1 395, 1 335, 1 250, and 1 210 cm^{-1}; δ_H 1.4 and 1.6 (6 H, m, piperidine H), 2.6 (4 H, m, piperidine H), 3.6 (2 H, m, CH_2N), 6.15 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 69.0; H, 6.3; N, 11.5; S, 8.7. $C_{21}H_{23}N_3OS$ requires C, 69.0; H, 6.3; N, 11.5; S, 8.8%).

1,5-*Diphenyl*-3-*phenylthiomethyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**67**).—To a solution of sodium thiophenoxide (from 0.66 g thiophenol, 6 mmol) in DMF (60 ml) was added the chloride (**19**) (1.8 g, 5.7 mmol) and the mixture stirred at 50 °C for 2 h before dilution with ethyl acetate and washing with water. The organic extract was dried, and evaporated to give the *title compound* (1.9 g, 85%), m.p. 139–140 °C from ethyl acetate–ether); ν_{max} 1 580, 1 530, 1 453, 1 445, 1 384, 1 244, 1 200, and 1 102 cm^{-1}; δ_H 4.09 (2 H, s, CH_2S), 6.07 (1 H, s, 6-H), 7.0–8.0 (15 H, m, aryl H) (Found: C, 67.6; H, 4.8; N, 7.1; S, 16.4. $C_{22}H_{18}N_2OS_2$ requires C, 67.7; H, 4.7; N, 7.2; S, 16.4%).

3-*Ethylthiomethyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**68**).—This was prepared by the same method as described for the phenyl sulphide (**67**), but using instead sodium ethanethiolate. The *ethyl sulphide* (56%) showed m.p. 79–81 °C (from ethyl acetate–light petroleum), ν_{max} 1 522, 1 445, 1 427, 1 380, 1 232, and 1 191 cm^{-1}; δ_H 1.30 (3 H, t, *J* 6 Hz, Me), 1.80 (2 H, q, *J* 6 Hz, CH_3C_2S), 2.70 (2 H, ABq, *J* 14 Hz, CH_2S), 6.17 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 63.2; H, 5.3; N; 8.2; S, 18.7. $C_{18}H_{18}N_2OS_2$ requires C, 63.1; H, 5.3; N, 8.2; S, 18.7%).

3-*Methylaminomethyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*Oxide* (**69**).—To a solution of methylamine in methanol (40% w/v; 40 ml) was added the bromomethyl compound (**20**) (0.5 g, 1.4 mmol) and the solution stirred at room temperature for 6 h before evaporation of the solvent and excess of amine. The residue was recrystallised from ethyl acetate to give the *title amine* (0.38 g, 87%), m.p. 105–107 °C; ν_{max} 3 300, 1 520, 1 435, 1 378, 1 239, 1 200, and 1 097 cm^{-1}; δ_H 2.07 (1 H, br s, exchanges with D_2O, NH), 2.52 (3 H, s, Me), 3.77 (2 H, s, CH_2N), 6.13 (1 H, s, 6-H), 7.3–8.0 (10 H, m, aryl H) (Found: C, 65.5; H, 5.3; N, 13.4; S, 10.3. $C_{17}H_{17}N_3OS$ requires C, 65.6; H, 5.5; N, 13.5; S, 10.3%).

Rearrangement of the Bromomethyl Derivative (**20**).—To a solution of the halide (0.2 g, 0.6 mmol) in ethanol (10 ml) was added 1M NaOH (2 ml) and the mixture stirred for 35 min at room temperature. The solution was diluted with water (100 ml), acidified with dilute HCl, and extracted with dichloromethane. The organic extract was dried and the solvents removed to give an oil which was chromatographed through silica gel, eluting with dichloromethane and dichloromethane–ether mixtures to give, in order of increasing polarity, the following;

3-*Ethoxymethyl*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* (**70**) (90 mg, 51%), m.p. 92–93 °C; ν_{max} 1 523, 1 438, 1 242, 1 200, 1 131, and 1 098 cm^{-1}; δ_H 1.3 (3 H, t, *J* 7 Hz, Me), 3.75 (2 H, q, *J* 7 Hz, CH_2), 4.5 (2 H, s, CH_2), 6.17 (1 H, s, 6-H), 7.3–8.1 (10 H, m, aryl H) (Found: C, 66.3; H, 5.6; N, 8.5; S, 9.7. $C_{18}H_{18}N_2O_2S$ requires C, 66.2; H, 5.6; N, 8.6; S, 98%);

S-Benzoylmethyl-*S*-phenylsulphoximide (**10**) (11 mg, 8%), identified by spectral and chromatographic comparison with the material described above;

1,6-*Diphenyl*-3,5-*dihydro*-1λ⁴,2,5-*thiadiazepin*-4-*one* 1-*oxide* (**71**) (40 mg, 24%), m.p. 91–92 °C (from chloroform–ether); ν_{max} 1 700, 1 592, 1 335, 1 235, and 1 125 cm^{-1}; δ_H 4.0 (1 H, dd, *J* 1, 15 Hz, 3-H), 4.4 (1 H, d, *J* 15 Hz, 3-H), 6.22 (1 H, d, *J* 1 Hz, 7-H), 7.3–8.2 (11 H, m, aryl H and NH) (Found: C, 64.4; H, 4.8; N, 9.4; S, 10.7. $C_{16}N_{14}N_2O_2S$ requires C, 64.4; H, 4.7; N, 9.4; S, 10.7%).

Hydrolysis of the Thiadiazepinone (**71**).—The compound (**71**) (200 mg, 0.7 mmol) in ethanol (20 ml) was treated with 2M NaOH (4 ml) at reflux for 2 h, before cooling, addition of water (100 ml), and extraction with dichloromethane. The aqueous solution was acidified with 2M HCl and extracted with chloroform and the chloroform extract dried and evaporated to leave a solid. Treatment of a suspension of the solid in ether with an excess of ethereal diazomethane afforded a solution which was evaporated, and the residue chromatographed through silica gel to give methyl *N*-(*S*-benzoylmethyl-*S*-phenylsulphoximidoyl)acetate (**73**) (95 mg, 41%) as an oil, ν_{max}(film) 1 742, 1 670, 1 445, 1 276, and 1 200 cm^{-1}; δ_H 3.65 (3 H, s, Me), 3.77 and 3.95 (2 H, AB q, *J* 17.5 Hz, CH_2N), 4.75 and 5.0 (2 H, AB q, *J* 12.5 Hz, CH_2CO), 7.25–8.0 (10 H, m, aryl H); δ_C 44.9, 51.8, 63.3, 128.5, 129.1, 133.4, 133.9, 136.0, 137.6, 172.0, 188.3.

Acylation and Cyclisation of the Enamine (**5**).—*General method.* The enamine (1.8 g, 7 mmol) in dichloromethane (40 ml) containing triethylamine (2 g, 20 mmol) was treated with the acid chloride or anhydride (1.1 equiv.) and the mixture stirred overnight at room temperature. The organic mixture was washed with water, dried and evaporated and the crude product suspended in xylene (60 ml) and heated with DBN (0.5 ml, 4 mmol) at reflux for 6 h. After cooling, the reaction mixture was washed with water, dried, and evaporated. The residue was either directly crystallised and recrystallised or chromatographed through silica gel as necessary. Yields and analyses of the product thiadiazines are listed in the Table.

Optically Active Thiadiazines.—Optically pure (+)-(*R*)-*S*-methyl-*S*-phenylsulphoximide [(+)(*R*)-(**4**)], $[\alpha]_D^{20}$ +36.7° (*c* 4, acetone) and (−)-(*S*)-*S*-phenylsulphoximide [(−)-(*S*)-(**4**)], $[\alpha]_D^{20}$ −36.1° (*c* 4.2, acetone) were prepared by crystallisation with D-10-camphorsulphonic acid and L-10-camphorsulphonic acid, respectively, as described by Johnson and Schroek.[11]

Using the procedures described above for the preparation of racemic products the following optically active 1λ⁴,2,4-thiadiazines were prepared.

(−)-(**R**)-1,5-*Diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* [(−)-(R)-(**13**)] (37%), m.p. 102–103 °C (from ether); $[\alpha]_D^{21}$ −120.7° (*c* 4, acetone);

(+)-(*S*)-1,5-*Diphenyl*-1H-1λ⁴,2,4-*thiadiacine* 1-*oxide* [(+)-(*S*)-(**13**)] (52%), m.p. 102–103 °C (from ether); $[\alpha]_D^{21}$ +119.4° (*c* 4.1, acetone);

(+)-(*R*)-3-*Oxo*-1,5-*diphenyl*-3,4-*dihydro*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* [(+)-(*R*)(**23**)] (43%), m.p. 218–221 °C (from chloroform); $[\alpha]_D^{20}$ +360.1° (*c* 0.2, chloroform);

(+)-(*R*)-3-*Methoxy*-1,5-*diphenyl*-1H-1λ⁴,2,4-*thiadiazine* 1-*oxide* [(+)-(*R*)-(**53**) (78%), m.p. 134–135 °C (from ether); $[\alpha]_D^{20}$ +123.9 °C (*c* 2, acetone).

References

1 For reviews on cyclic sulphoximides see P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, 1975, **4**, 189; *ibid.*, 1980, **9**, 477; W. E. Truce,

T. C. Klinger, and W. W. Brand, 'Organic Chemistry of Sulfur,' ed. S. Oae, Plenum Press, New York, 1977, 588.
2 Ger. Offen. 2451 566 (1975) (*Chem. Abstr.*, 1975, **83**, 97399m).
3 Swiss Patent 599 226 (1978) (*Chem. Abstr.*, 1978, **89**, 109608t).
4 Ger. Offen. 2530 792 (1977) (*Chem. Abstr.*, 1977, **86**, 155606i).
5 K. Schaffner-Sabba, H. Tomaselli, B. Henrici, and H. B. Renfroe, *J. Org. Chem.*, 1977, **42**, 952.
6 C. R. Johnson, R. A. Kirchoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, 1973, **95**, 4287.
7 S. M. McElvain and B. F. Pinzon, *J. Am. Chem. Soc.*, 1945, **67**, 690.
8 F. Beyerstadt and S. M. McElvain, *J. Am. Chem. Soc.*, 1937, **59**, 1273.
9 M. Ikeda, H. Tsuboudi, M. Tsunekawa, H. Kondo, and Y. Tamura, *Heterocycles*, 1983, **20**, 2185.
10 Unpublished work.
11 C. R. Johnson and C. W. Schroek, *J. Am. Chem. Soc.*, 1973, **95**, 7418.
12 E. Cohen and J. Mahnke, *Chem. Ber.*, 1972, **105**, 757.
13 L. Sternbach, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 34.
14 D. D. Perrin, W. L. F. Amarego, and D. Perrin, 'Purification of Laboratory Chemicals,' Pergamon Press, Oxford, 1980.
15 E. Juaristi, A. Martinez-Richa, A. Garcia-Rivera, and J. Cruz-Sanchez, *J. Org. Chem.*, 1983, **48**, 2603.
16 (*a*) A. Kucsman, I. Kapovits, and B. Tanacs, *Tetrahedron*, 1962, **18**, 75; (*b*) H. S. Veale, J. Levin, and D. Swern, *Tetrahedron Lett.*, 1978, 503; (*c*) N. Furukawa, T. Omata, T. Yoshimura, T. Aida, and S. Oae, *ibid.*, 1972, 1619.

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