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TETRAHEDRON

Synthesis of Pyrido-1,2,4-thiadiazines Related to Antihypertensive 1,2,4-Benzothiadiazine-1,1-dioxides

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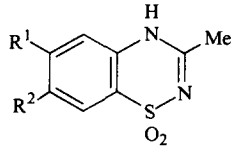
Abstract: Oxidation of 3-phenyl-2*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine with sodium hypochlorite and, separately, *m*-chloroperoxybenzoic acid afforded a 1,1-dioxide and a 5-oxide derivative, respectively. Further examples of such 1,1-dioxide derivatives were synthesised by treating 2-amino-5-methylpyridine with orthoesters and these were subsequently oxidised to novel 1,1,5-trioxides. A short route has been developed for the synthesis of 4-aminopyridine-3-sulfonamide which was used for the preparation of 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides; oxidation of the parent member of the series gave a 1,1,7-trioxide derivative. 3-Aminopyridine-4-sulfonamide has been prepared, and then condensed with triethyl orthoformate to afford 4*H*-pyrido[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide.

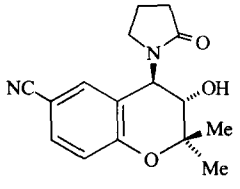
Keywords: Pyrido-1,2,4-thiadiazines; *N*-Oxides; Pyridines.

INTRODUCTION

It has been recognised that diuretic 1,2,4-benzothiadiazines† such as Chlorothiazide (**1a**) also possess antihypertensive properties [see *eg.* Diazoxide (**1b**)[1]]. It was subsequently discovered that the hyperglycaemic effects of such heterocycles relate to their properties as potassium channel openers [see *eg.* Chromakalim[2] (**2**) and Pinacidil[2] (**3**) as examples illustrating the structural diversity in this group].



1a $R^1 = Cl$, $R^2 = SO_2NH_2$
1b $R^1 = H$, $R^2 = Cl$



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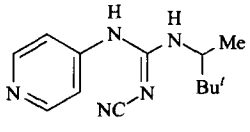

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A key feature from structure-activity relationships in the 1,2,4-benzothiadiazine series (**1**) is that antihypertensive action is enhanced by the presence of electron-withdrawing substituents (*eg.* Cl, Br, CF_3) at C-6 and/or C-7; in contrast, a sulfonamide group reduces antihypertensive action whilst increasing diuretic properties. The bioisosteric relationship of pyridine and benzene rings provides encouragement to attempt the synthesis of analogous pyrido[1,2,4]thiadiazine 1,1-dioxides for pharmacological studies; during the course of our work, Pirotte and coworkers prepared such compounds in the 4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine- (**4**, R = *eg.* H, Me)[3-5], 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine- (*eg.* **5a-c**)[3,4,6-9] and 4*H*-pyrido[3,2-*e*]-1,2,4-thiadiazine series (**6**, R = *eg.* H, Me).[3,4,10] Our programme has been directed towards the synthesis of novel condensed

† Benzothiadiazine dioxides (eg **1**) and analogous pyridothiadiazine dioxides (eg **4**) are represented arbitrarily in the 4*H*-tautomeric form. It should be noted that no attempt has been made in this work to establish the nature of such equilibria.

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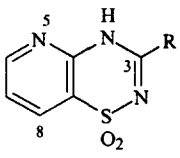
pyridine *N*-oxides in ring systems **4** and **5** described above; we also describe the synthesis of 4*H*-pyrido[3,4-*e*]-1,2,4-thiadiazine-1,1-dioxide (**7**), the first example of a compound in this class.



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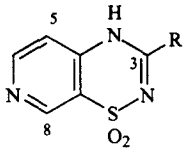
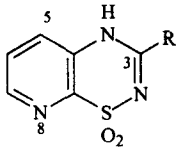


5a R = NHCH(Me)CMe$_3$
5b R = H
5c R = Me



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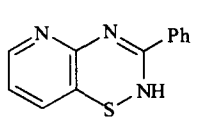
RESULTS AND DISCUSSION

4*H*-Pyrido[2,3-*e*][1,2,4]thiadiazines

The oxidation of 3-phenyl-2*H*-pyrido[3,2-*e*]thiadiazine[11] (**8**) was investigated in this work as a means of preparing both the 1,1-dioxide and -5-oxide derivatives. Aqueous sodium hypochlorite has been used successfully for the selective oxidation of sulfur in condensed thienopyridines whereas the use of organic peroxy acids gives products of *N*-oxidation.[12-15] In this work, oxidation of pyridothiadiazine **8** with hypochlorite and, separately, *m*-chloroperbenzoic acid afforded the 1,1-dioxide **9** and the 5-oxide **10** in 49 and 80% yields, respectively. The former (**9**) was characterised by ir absorption at 1335 and 1171 cm^{-1} (SO_2 asym and sym str) and observation of a negative Katritzky test for the *N*-oxide function.[16] Notable features in the ^{1}H-n.m.r. spectrum of **10** are downfield shifts (*ca* 1.5 ppm) observed in the resonances of H-6 and H-8 in passing from **8** to **10**, which would suggest that *N*-oxidation has occurred in the pyridine, and not the thiadiazine ring.



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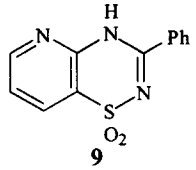

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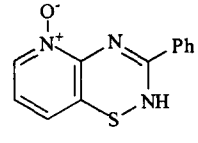

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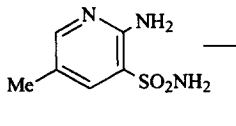
Further examples of 1,1-dioxides (**4a-c**) in this ring system were prepared, albeit in low yield (21-50%), by cyclisation reactions[3] of 2-amino-5-methylpyridine-3-sulfonamide (**11**)[17] with ortho esters. Oxidation of the 1,1-dioxides **4a-c** with *m*-chloroperbenzoic acid gave the 1,1,5-trioxides **12a-c** (41-68%). ^{1}H-n.m.r chemical shift differences for H-6 and H-8 of **4a-c** and **12 a-c** do not show a definitive trend, but it is notable that there is little difference in the position of the resonances for H-3 in the spectra of **4a** and **12a**; it can be assumed, therefore, that the condensed pyridine *N*-oxide structures depicted as **12** are akin to **10**.



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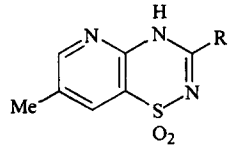
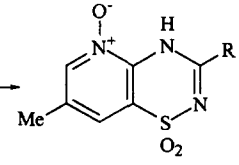
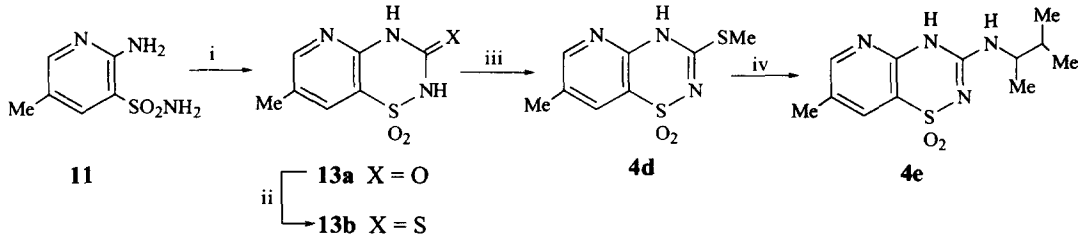


4a R = H
4b R = Me
4c R = Ph



12a R = H
12b R = Me
12c R = Ph

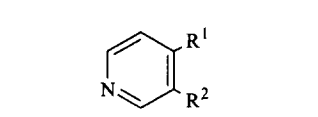
Pirotte *et al.* have noted[6] the structural analogy of Pinacidil (**3**) and Diazoxide (**1b**) in respect of the guanidino and *N*-sulfonylamidino frameworks, respectively. In order to achieve closer structural relationship between the two classes, they have prepared[6,7] 4*H*-pyrido [4,3-*e*]-1,2,4-thiadiazines (**5**) which incorporate an alkylamino substituent at C-3 (*eg.* **5a**). In our work, we have prepared a closely related compound (**4e**) in the 4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine series by employing a comparable sequence (**Scheme 1**).



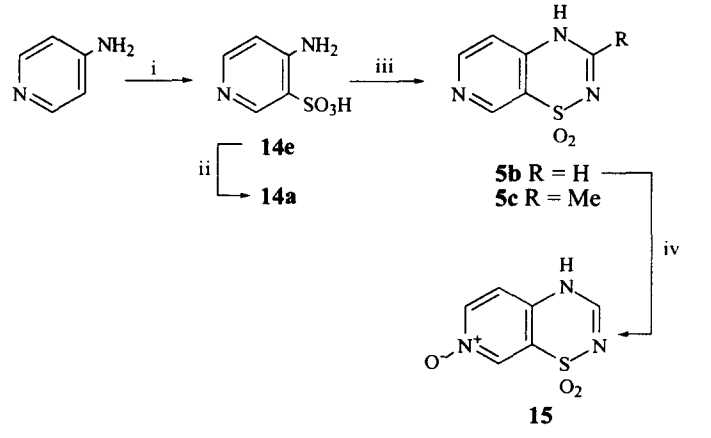
Scheme 1. i, urea, heat; ii, P_4S_{10}, pyridine; iii, MeI, $NaHCO_3$, MeOH-H_2O; iv, 2-amino-3-methylbutane, DMF.

4*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines

Compounds in this ring system (**5**) have been previously prepared[6,7] using 4-aminopyridine-3-sulfonamide (**14a**) as a key intermediate, but preparation of the latter is lengthy[6] (**14b** → **14c** → **14d** → **14a**) and we have devised a shorter route from readily available 4-aminopyridine. It is known that chlorosulfonylation ($ClSO_3H$, $SOCl_2$) of the latter can be achieved[18] under forcing conditions (170 °C/115 h) to give 4-aminopyridine-3,5-disulfonyl chloride. In the present work (**Scheme 2**) this type of reaction was carried out with modified conditions to afford 4-aminopyridine-3-sulfonic acid (**14e**) (49%). A notable feature in the ambient temperature ^1H n.m.r. spectrum of **14e** is the presence of separate resonances (δ = 7.45 and 8.58 ppm) for the NH_2 protons; a single resonance at δ = 7.93 ppm is observed when the spectrum is run at 90 °C so it can be inferred that intramolecular hydrogen bonding is disrupted at higher temperatures. The sulfonic acid derivative (**14e**) was then transformed ($POCl_3$, PCl_5) into the sulfonyl chloride and this was converted without rigorous purification



14a $R^1 = NH_2$, $R^2 = SO_2NH_2$
14b $R^1 = OH$, $R^2 = H$
14c $R^1 = OH$, $R^2 = SO_3H$
14d $R^1 = Cl$, $R^2 = SO_2NH_2$

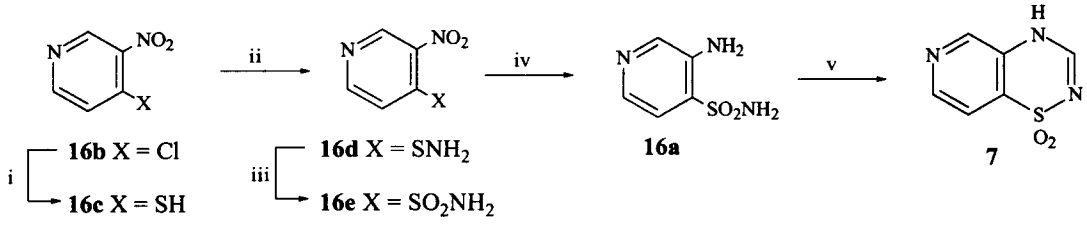


Scheme 2. i, $ClSO_3H$, 145 °C, 1 h, then $SOCl_2$, 120 °C, 0.5 h, then H_2O;
ii, PCl_5, $POCl_3$, then NH_3; iii, $RC(OEt)_3$, DMF; iv, MCPBA, DMF

into 4-aminopyridine-3-sulfonamide (**14a**) by treatment with aqueous ammonia. The aminosulfonamide **14a** was then heated with triethyl orthoformate and, separately, triethyl orthoacetate to give the condensed thiadiazines (**5b,c**), respectively in moderate yield; it should be noted that the latter (**5b,c**) were prepared during the course of this work using related condensations.[3] Oxidation of **5b** with *m*-chloroperbenzoic acid gave the *N*-oxide derivative (**15**) in moderate yield. The ^{1}H-n.m.r. chemical shifts of H-3 and H-5 in **15** are close to those of the precursor (**4b**) whereas comparative upfield shifts of 0.45 ppm are experienced by H-6 and H-8; it can be assumed, therefore, that *N*-oxidation has occurred in the pyridine, and not the thiadiazine ring.

4*H*-Pyrido[3,4-*e*]-1,2,4-thiadiazines

Access to compounds in this ring system (**7**) has been hampered[3] by the unavailability of a key precursor, 3-aminopyridine-4-sulfonamide (**16a**). We have synthesised this intermediate from 4-chloro-3-nitropyridine (**16b**)[19] by the sequence shown below (**Scheme 3**). The thiol **16c** was generated (NaSH. xH_2O) from **16b** and used *in situ*, but its conversion ($ClNH_2$) into the sulfenamide **16d** and oxidation (*m*-$ClC_6H_4CO_3H$) of the latter into the sulfonamide **16e** could only be achieved in low yields (33 and 20%, respectively). Reduction of the nitrosulfonamide **16e** was effected routinely ($SnCl_2$, HCl) and the product (**16a**) was cyclised [$HC(OEt)_3$] to afford the 4H-pyrido[3,4-*e*]-1,2,4-thiadiazine (**7**), the first example of a compound in this ring system. We are presently preparing a wider variety of compounds in this class, including *N*-oxides.



Scheme 3. i, $NaSH.xH_2O$, MeOH, reflux; ii, NH_3aq, NaOCl; iii, MCPBA, CH_2Cl_2; iv, $SnCl_2$, HCl; v, $HC(OEt)_3$, DMSO

Conclusion

Condensed pyridine-*N*-oxide derivatives in the 4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine, and 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine series have been prepared and characterised. Short routes have been developed for the preparation of the previously reported 4-aminopyridine-3-sulfonamide and hitherto unknown 3-aminopyridine-4-sulfonamide; the latter has been used in a condensation with triethyl orthoacetate to afford 4*H*-pyrido[3,4-*e*]-1,2,4-thiadiazine-1,1-dioxide, the first example of a compound in this ring system.

EXPERIMENTAL

Reactions were monitored by TLC on pre-coated aluminium-backed plates, Kieselgel HF_{254} type 60 (Merck); detection was effected by u.v. light unless otherwise stated. Column chromatography was carried out using Kielsegel H type 60 (Merck); an external pressure was applied to the top of the column. Organic extracts were dried with anhydrous $MgSO_4$, and evaporations were carried out at reduced pressure using a rotary evaporator.

Melting points were determined on an electrothermal MkII apparatus in capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrometer. ^{1}H-N.m.r. spectra were recorded at 200 MHz on a Bruker WP200 instrument. Coupling constants (*J*) are given in Hz. ^{13}C-N.m.r. spectra were recorded on a Bruker WP200 spectrometer at 50 MHz unless otherwise stated. Mass spectrometry was performed using V.G. updated MS9 and V.G. ZABE high resolution EI/FAB instruments.

3-Phenyl-4*H* -pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (9). - To a suspension of 3-phenyl-2*H*-pyrido[2,3-*e*]1,2,4-thiadiazine (**8**) (90 mg, 0.4 mmol) in aqueous hydrochloric acid (0.5M, 8 cm^3) was added sodium hypochlorite solution (0.55M, 7.2 cm^3, 4 mmol) over a period of 15 min. The reaction mixture was stirred at room temperature for 6 h, after which time sodium sulfite was added to remove the excess oxidising agent (KI/starch test - negative). The aqueous mixture was extracted with chloroform (3 x 25 cm^3), and the combined organic layers were washed with H_2O (2 x 50 cm^3), dried and evaporated to give a yellow solid which was chromatographed on silica gel, with ethyl acetate-toluene [1:9] as eluant, to give 3-*phenyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**9**) (52 mg, 49%), as an off-white solid, m.p. 265-267 °C (dec); negative Katritzky test,[16] ν_{max} (KBr)/cm^{-1} 1599, 1536 (C=N str.) 1335 (SO_2 asym str.) and 1171 (SO_2 sym str.); δ_H ($CDCl_3$) 7.46 (1H, dd, $J_{7,6}$ = 4.9, $J_{7,8}$ = 7.8, H-7), 7.53-7.69 (3H, m, ArH), 8.04 - 8.10 (2H, m, ArH), 8.34 (1H, dd, $J_{8,6}$ = 1.7, $J_{8,7}$ = 7.8, H-8), 8.56 (1H, dd, $J_{6,7}$ = 4.9, $J_{6,8}$ = 1.5, H-6) and 9.82 (1H, br s, NH); *m/z* (EI) 259 (81%) $[M]^{\cdot+}$, 227 (6) $[M - O_2]^{\cdot+}$, 195 (14) $[M - SO_2]^{\cdot+}$, 156 (100) [M - PhCN]$^{\cdot+}$ and 92 (52); (Found: C, 55.6; H 3.5; N, 15.3%. $C_{12}H_9N_3O_2S$ requires C, 55.59; H 3.50; N, 16.21%. Found : $M^{\cdot+}$ 259.04062; $C_{12}H_9N_3O_2S$ requires 259.04155).

3-Phenyl-2*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 5-oxide (10). - (a): *m* -Chloroperoxybenzoic acid (50% dispersion in H_2O, 134 mg, 0.4 mmol) was added with stirring to a solution of 3-phenyl-2*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine (**8**) (90 mg, 0.4 mmol) in chloroform (5 cm^3). After 1 h at room temperature, the resulting bright yellow precipitate was collected by filtration and further purified by chromatography on silica gel, with EtOAc as eluant, to give 3-*phenyl*-2H-*pyrido*[2,3-e]-1,2,4-*thiadiazine*-5-*oxide* (**10**) (75 mg, 80%), m.p. 249-251 °C; positive Katritzky test;[16] ν_{max} (KBr)/cm^{-1} 1596, 1540 (C=N str.), 1315 (*N*-oxide) and 1018; δ_H (d_6-DMSO) 7.53 (1H, dd, $J_{7,6}$ = 4.9, $J_{7,8}$ = 7.7, H-7), 7.55 - 7.70 (3H, m, ArH), 8.03 - 8.11 (2H, m, ArH), 8.35 (1H, dd, $J_{8,6}$ = 1.8, $J_{8,7}$ = 7.7, H-8), 8.72 (1H, dd, $J_{6,7}$ = 4.9, $J_{6,8}$ = 1.8, H-6) and 12.80 (1H, br s, NH); *m/z* (EI) 243 (22%) $[M]^{\cdot+}$, 227 (15) $[M - O]^{\cdot+}$, 196 (72) and 124 (10) (Found: $[MH]^+$ 244.05507; $C_{12}H_{10}N_3OS$ requires 244.05446).
(b): To a stirred solution of 3-phenyl-2*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine (**8**) (0.1 g, 0.4 mmol) in acetic acid (4 cm^3) was added a warm (40 °C) solution of magnesium monoperoxyphthalate hexahydrate (80%, 137 mg, 0.2 mmol) in acetic acid (1 cm^3). The reaction mixture was heated to 120 °C for 3 h, when TLC showed total disappearance of starting material. The mixture was cooled, diluted with water (10 cm^3), neutralised with $NaHCO_3$ (aq.) and extracted with chloroform (3 x 50 cm^3) The combined organic layers were dried and evaporated to give a yellow solid. Chromatography on silica gel, with EtOAc as eluant) gave 3-*phenyl*-2H-*pyrido*[2,3-*e*]-1,2,4-*thiadiazine* 5-*oxide* (**10**) (55 mg, 51%) as a yellow solid, m.p. 248-250 °C with spectroscopic properties identical with those for material prepared by method (a). A positive Katritzky test[16] was also obtained.

7-Methyl-4*H*-pyrido[2, 3-e]-1,2,4-thiadiazine 1,1-dioxide (4a) - Triethyl orthoformate (25 cm^3) was added to a solution of 2-amino-5-methylpyridine-3-sulfonamide[17] (0.59 g, 3.2 mmol) in dimethylformamide (4 cm^3) and the reaction mixture was heated to 120°C for 3 h, after which time TLC showed total disappearance of starting material. Evaporation gave a yellow solid which was chromatographed on silica gel, with ethyl acetate-toluene [7:3] as eluant, to give 7-*methyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**4a**) (0.31 g, 50%), m.p. >300 °C (dec); υ_{max} (KBr)/cm^{-1} 1630, 1590, 1523 (C=N str.), 1302 (SO_2 asym. str.) and 1160 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.40 (3H, s, Me), 8.04 (1H, s, H-3), 8.20 (1H, d, $J_{8,6} \approx 1.0$, H-8), 8.56 (1H, d, $J_{6,8}$~1.0, H-6) and 12.75 (1H, br s, NH); δ_C (d_6-DMSO) 17.4, 118.1, 133.0, 133.1, 143.8, 147.6 and 153.6; *m/z* (FAB) 198 (21%) $[MH]^{\cdot+}$, 165 (8) $[M - O_2]^{\cdot+}$ and 149 (51) (Found : C, 42.3; H, 3.6; N, 21.0; S, 16.0%; $C_7H_7N_3O_2S$ requires C, 42.63; H, 3.58; N, 21.31; S, 16.26%).

3,7-Dimethyl-4*H* pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (4b). - Triethyl orthoacetate (30cm^3) was added to a solution of 2-amino-5-methyl-pyridine-3-sulfonamide (0.50 g, 2.7 mmol) in dimethylformamide (9 cm^3) and the reaction mixture was maintained at 125°C for 2 h in an open vessel. The residue after evaporation was

chromatographed on silica gel, with ethyl acetate-toluene [1:1] as eluant, to give 3, 7-*dimethyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**4b**) (0.18 g, 32%), m.p. 318 °C (dec); υ_{max} (KBr)/cm^{-1} 1602, 1515(C = N str.), 1289 (SO_2 asym. str.) and 1148 (SO_2 sym. str.); δ_H (d_6-DMSO) 1.83 and 2.18 (each 3H, s, Me), 8.32 (1H, d, $J_{8,6} \approx 1.0$, H-8), 8.70 (1H, d, $J_{6,8} \approx 1.0$, H-6) and 12.50 (1H, br s, NH); *m/z* (FAB) 212 (48%) $[MH]^{\cdot+}$, 165 (20), 149 (100) $[M - SO_2]^{\cdot+}$ and 136 (79); (Found : $M^{\cdot+}$ 211.04219; $C_8H_9N_3O_2S$ requires 211.04155).

7-Methyl-3-phenyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (4c) - A solution of 2-amino-5-methylpyridine-3-sulfonamide (0.69 g, 3.7 mmol) in triethyl orthobenzoate (13 cm^3) was maintained at 120 °C for 3 h. After cooling, the precipitate was collected and purified by chromatography on silica gel, with ethyl acetate-toluene [1:1] as eluant, to give 7-*methyl*-3-*phenyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**4c**) (0.21 g, 21%) as an off-white solid, m.p. 288-290 °C (dec); υ_{max} (KBr)/cm^{-1} 1597, 1559 (C=N str.), 1294 (SO_2 asym. str.) and 1167 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.40 (3H, s, Me), 7.50-7.70 (3H, m, ArH), 8.03-8.10 (2H, m, ArH), 8.22 (1H, d, $J_{8,6} \approx 1.0$, H-8), 8.62 (1H, d, $J_{6,8} \approx 1.0$, H-6) and 13.0 (1H, br, NH); *m/z* (FAB) 274 (12%) $[MH]^{\cdot+}$, 253 (31), 210 (3) $[MH - SO_2]^{\cdot+}$ and 150 (100); Found : C, 57.0; H, 4.3; N, 15.2; S, 11.5%; $C_{13}H_{11}N_3O_2S$ requires C, 57.13; H, 4.06; N, 15.37; S, 11.73%. Found: M^+ 273.05666; $C_{13}H_{11}N_3O_2S$ requires 273.05720).

7-Methyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1,5-trioxide (12a). - *m*-Chloroperoxybenzoic acid (50% dispersion in H_2O, 0.7 g, 2 mmol) was added to a solution of 7-methyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**4a**) (0.10 g, 0.5 mmol) in dimethylformamide (8 cm^3) and the mixture was stirred at room temperature for 48 h. Evaporation gave an off-white solid that was purified by chromatography on silica gel, with ethyl acetate-methanol [4 : 1] as eluant, to give 7-*methyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1,5-*trioxide* **12a** (73 mg, 68%) as a white solid, m.p. 274 °C (dec); positive Katritzky test;[16] υ_{max} (KBr)/cm^{-1} 1636, 1577, 1516 (C=N str.), 1318 (N-O) and 1159 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.32 (3H, s, Me), 7.75 (1H, s, H-8), 7.96 (1H, s, H-3) and 8.58 (1H, s, H-6); *m/z* (EI) 213 (4%) $[M]^{\cdot+}$, 197 (33) $[M - O]^{\cdot+}$, 170 (8) $[197 - HCN]^{\cdot+}$, 156 (26) $[197 - NHCN]^{\cdot+}$ and 139 (23); (Found: $[MH]^{\cdot+}$ 214.02894; $C_7H_8N_3O_3S$ requires 214.02864. Found: C, 38.6; H, 3.2; N, 19.2; S, 14.8%; $C_7H_7N_3O_3S$. $0.25H_2O$ requires C, 38.62, H, 3.47; N, 19.30; S, 14.73%).

3,7-Dimethyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1,5-trioxide (12b). - *m*-Chloroperoxybenzoic acid (50% dispersion in H_2O, 0.59 g, 1.7 mmol) was added to a solution of 3,7-dimethyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**4a**) (90 mg, 0.43 mmol) in chloroform (5 cm^3) and the mixture was stirred at room temperature for 3 h. Evaporation, and chromatography of the residue on silica gel, with ethyl acetate-methanol [4:1] as eluant, gave 3, 7-*dimethyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1,5-*trioxide* (**12b**) (40 mg, 41%) as a white solid, m.p. 286-288 °C; positive Katritzky test;[16] υ_{max} (KBr)/cm^{-1} 1632, 1631, 1589, 1573 (C=N str.), 1319 (N-O) and 1171 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.30 and 2.40 (each 3H, s, Me), 7.68 (1H, s, H-8), 8.59 (1H, s, H-6) and 12.7 (1H, br, NH); *m/z* (EI) 227 (7%) $[M]^{\cdot+}$, 211 (55) $[M - O]^{\cdot+}$, 170 (56) $[211 - NHCN]^{\cdot+}$, 153 (51) and 136 (44); (Found: $[MH]^{\cdot+}$ 228.04438; $C_8H_{10}N_3O_3S$ requires 228.04429).

7-Methyl-3-phenyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1,5-trioxide (12c). - *m*-Chloroperoxybenzoic acid (50% dispersion in H_2O, 0.76 g, 2.2 mmol) was added to a solution of 7-methyl-3-phenyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**4c**) (0.1 g, 0.4 mmol) in chloroform (10 cm^3) and the mixture was stirred at room temperature for 12 h. The residue after evaporation was chromatographed on silica, with ethyl acetate -methanol [4:1] as eluant, to give 7-*methyl*-3-*phenyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1,5-*trioxide* (**12c**) (73 mg, 68%) as a white solid, m.p. 298 °C (dec); positive Katritzky test;[16] υ_{max} (KBr) cm^{-1} 1624, 1552, 1511 (C=N str.), 1314 (N-O) and 1165 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.38 (3H, s, Me), 7.50-7.70 (3H, m, ArH), 8.03 (1H, d, $J_{8,6} \approx 1.0$, H-8), 8.07-8.15 (2H, m, ArH) and 8.74 (1H, d, $J_{6,8} \approx 1.0$, H-6); *m.z* (FAB) 290 (62%) $[MH]^{\cdot+}$, 274 (12) $[MH - O]^{\cdot+}$ and 165 (36); (Found: $[MH]^{\cdot+}$ 290.05922; $C_{13}H_{12}N_3O_3S$ requires 290.05994).

3-Oxo-2,3-dihydro-7-methyl-4*H*-pyrido [2,3-*e*]-1, 2, 4-thiadiazine 1,1-dioxide (13a). - A mixture of 2-amino-5-methylpyridine-3-sulfonamide (4.40 g, 24 mmol) and urea (1.55 g 26 mmol) was heated at 210 °C (fusion) until the evolution of ammonia ceased. After cooling, the solid mass was dissolved in aqueous NaOH solution (2M), and the solution was treated with activated charcoal. Aqueous HCl (1M) was added to bring the solution to pH2, and the crystalline product was collected by filtration, washed with water and dried to give 3-*oxo*-2,3-*dihydro*-7-*methyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**13a**) (1.5 g, 29%) , m.p. 300°C (dec); υ_{max} (KBr)/cm^{-1} 1717 (C=O str.), 1608, 1591, 1518 (C=N str.), 1338 (SO_2 asym. str.) and 1169 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.33 (3H, s, Me), 8.12 (1H, d, $J_{8,6} \approx 1.0$, H-8), 8.47 (1H, d, $J_{6,8} \approx 1.0$, H-6) and 11.8 (1H, br s, NH); *m/z* (FAB) 214 (6%) $[MH]^{\cdot+}$, 149 (17) $[M - SO_2]^{\cdot+}$ 137 (69) and 136 (100); (Found : C, 39.1; H, 3.1; N, 19.8; S, 15.4%; $C_7H_7N_3O_3S$ requires C, 39.43; H, 3.31; N, 19.71; S, 15.04%).

3-Thioxo-2, 3-dihydro-7-methyl-4*H*-pyrido[2,3-*e*]-1,2, 4-thiadiazine 1,1-dioxide (13b). - A mixture of 3-oxo-2,3-dihydro-7-methyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**13a**) (0.25 g, 1.2 mmol) and phosphorus pentasulfide (0.39 g, 0.9 mmol) in anhydrous pyridine (4 cm^3) was heated under reflux for 24 h. The suspension was concentrated under reduced pressure and the residue was dissolved in the minimum volume of aqueous NaOH solution (2M). The alkaline solution was treated with decolourizing charcoal and then adjusted to pH2 with aqueous HCl (1M). The solution was evaporated to dryness and the crude product was chromatographed on silica with ethyl acetate-methanol [9:1] as eluant, to give colourless 3-*thioxo*-2,3-*dihydro*-7-*methyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**13b**) (0.17 g, 63%), m.p. 181-183 °C; υ_{max} (KBr)/cm^{-1} 1601, 1539, (C=N str.) 1334 (SO_2 asym. str.) and 1171 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.34 (3H, s, Me), 8.22 (1H, s, H-8) and 8.54 (1H, s, H-6); *m/z* (EI) 229 (100%) $[M]^{\cdot+}$, 171 (30) $[M - NCS]^{\cdot+}$, and 107 (66) $[171 - SO_2]^{\cdot+}$; (Found: $[MH]^{\cdot+}$ 230.00611; $C_7H_8N_3O_2S_2$ requires 230.00580).

7-Methyl-3-methylthio-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (4d) - To a solution of 3-thioxo-2,3-dihydro-7-methyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**13b**) (1.14 g, 4.6 mmol) and $NaHCO_3$ (0.78 g, 9.3 mmol) in water (33 cm^3) was added methanol (22 cm^3) and then methyl iodide (1.6 cm^3, 25 mmol). After 1 h at room temperature, the resulting suspension was concentrated to a final volume of 8 cm^3, and then adjusted to pH3 by addition of HCl (2M). The precipitated crystalline compound was collected by filtration, washed with water and dried at 120 °C. Recrystallisation from water gave colourless 3-*methylthio*-7-*methyl*-4H-*pyrido*[2,3-*e*]-1,2,4-*thiadiazine* 1,1-*dioxide* (**4d**) (1.0 g, 84%), m.p. >300 °C; υ_{max} (KBr)/cm^{-1} 1622, 1485 (C=N str.), 1385 (SO_2 asym. str.) and 1159 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.37 (3H, s, ArMe), 2.47 (3H, s, SMe), 8.11 (1H, s, H-8), 8.50 (1H, s, H-6) and 13.10 (1H, br, NH); *m/z* (EI) 2243 (91%) $[M]^{\cdot+}$, 179 (64) $[M - SO_2]^{\cdot+}$, 132 (24) $[179 - SMe]^{\cdot+}$ and 105 (100) $[132 - HCN]^{\cdot+}$; (Found: $[MH]^{\cdot+}$ 244.02189; $C_8H_{10}N_3O_2S_2$ requires 244.02145).

3-(1',2'-Dimethylpropyl)amino-7-methyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (4e). - A solution of the methylthio compound **4 d** (0.10 g, 0.4 mmol) and 1,2-dimethylpropylamine (3 cm^3) in dimethylformamide (2 cm^3) was heated under reflux for 55 h. The residue after evaporation was dissolved in water (3 cm^3) and the aqueous suspension was extracted with chloroform (3 x 10 cm^3). The combined organic layers were dried and evaporated to give a brown syrup which was purified by chromatography on silica, with ethyl acetate-hexane [2:3] as eluant, to give 3-(1',2'-*dimethylpropyl)amino*-7-*methyl*-4H-*pyrido*[2,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**4e**) (55 mg, 51%) as an off-white solid, m.p. 210-212 °C; υ_{max} (KBr)/cm^{-1} 3355 (N-H str.), 2963 (CH_{alkyl} str.), 2874 (CH_{alkyl} str.), 1617, 1584 (C=N str.), 1281 (SO_2 asym. str.) and 1167 (SO_2 sym. str.); δ_H ($CDCl_3$) 1.15 (3H, d, J = 2.0, NHCH*Me*), 1.20 (6H, d, J = 2.0, CH*Me*$_2$), 1.68-1.77 (1H, m, C*H*Me$_2$), 2.35 (3H, s, Ar*Me*), 3.28-3.35 (1H, m, C*H*-NH), 5.90 (1H, br, N*H*-CH), 7.99 (1H, d, $J_{8,6}$ = 1.5, H-8), 8.15 (1H, d, $J_{6,8}$ = 1.5, H-6) and 12.25 (1H, br, NH); *m/z* (EI) 282 (10%) $[M]^{\cdot+}$, 267 (4) $[M - CH_3]^{\cdot+}$, 239 (100) $[M - CHMe_2]^{\cdot+}$, 213 (72) (Found : C, 50.4; H, 6.4; N, 19.5%; $C_{12}H_{18}N_4O_2S$ requires C, 50.05; H, 6.43; N, 19.84%).

4-Aminopyridine-3-sulfonic acid (14e) - 4-Aminopyridine (5.0 g, 53 mmol) was added to chlorosulfonic acid (35.3cm^3, 531mmol) and the reaction mixture heated to 145 °C for 1 h. Thionyl chloride (15.5 cm^3, 212 mmol) was added to the cooled mixture and heating continued at 120 °C for 30 min. The dark coloured liquid was cooled to room temperature then cautiously added to ice (150 g). The precipitate that formed was collected by filtration and washed with cold water. Recrystallisation from water gave 4-aminopyridine-3-sulfonic acid (**14e**) (4.5 g, 49%) as colourless crystals, m.p. 315-318 °C; υ_{max} (KBr)/cm^{-1} 3408 (N-H str.), 3230 (N-H str.), 1660, 1584 (C=N str.), 1234 (SO_2asym str.) and 1165 (SO_2sym str.); δ_H (d_6-DMSO, +18°C) 6.90 (1H, d, $J_{5,6} \approx$ 6, H-5), 7.45 (1H, br s, N*H*) 8.07 (1H, d, $J_{6,5} \approx$ 6, H-6), 8.35 (1H, s, H-2), 8.58 (1H, br s, N*H*) and 13.05 (1H, br, O*H*); δ_H (d_6-DMSO, +90°C) 6.90 (1H, d, $J_{5,6} \approx$ 6, H-5), 7.93 (2H, br s, NH_2), 8.00 (1H, d, $J_{6,5} \approx$ 6, H-6) 8.30 (1H, s, H-2) and 12.85 (1H, br, O*H*); *m/z* (FAB) 175 (100%) $[MH]^{\cdot+}$ (Found: C, 34.4; H, 3.3; N, 16.3; S, 18.4. $C_5H_6N_2O_3S$ requires C, 34.48; H, 3.47; N, 16.08; S, 18.41%).

4-Aminopyridine-3-sulfonamide (14a) - A mixture of 4-aminopyridine-3-sulfonic acid (**14e**) (2.0 g, 11 mmol), phosphorus pentachloride (8 g, 39 mmol) and phosphorus oxychloride (12 cm^3, 129 mmol) was heated at 130°C for 9 h. The solid that formed on cooling was collected by filtration and added to ammonium hydroxide solution (20 cm^3, d = 0.88), at 0 °C (ice bath). The resultant yellow solution was stirred at room temperature for 24 h. The volume was reduced by evaporation to cause precipitation of a yellow solid; purification by chromatography on silica, with ethyl acetate-methanol [7:3] as eluant, gave off-white 4-aminopyridine-3-sulfonamide (**14a**) (0.93 g, 47%), m.p. 202-204 °C (Lit.[6] 212-215 °C); υ_{max} (KBr)/cm^{-1} 3485 (N-H str.), 3461 (N-H str.), 3382 (N-H str.), 1636, 1600 (C=N str.), 1314 (SO_2 asym. str.) and 1150 (SO_2 sym. str.); δ_H (d_6-DMSO) 6.75 (1H, d, $J_{5,6} \approx$ 6, H-5), 6.85 (2H, br s, NH_2), 7.35 (2H, s, SO_2NH_2), 8.05 (1H, d, $J_{6,5} \approx$ 6, H-6) and 8.45 (1H, s, H-2); *m/z* (FAB) 174 (100%) $[MH]^{\cdot+}$, 149 (29) and 146 (18); (Found: C, 34.9; H, 3.8; N, 23.9; S, 18.4%; $C_5H_7N_3O_2S$ requires C, 34.68; H, 4.07; N, 24.26; S, 18.51%).

4*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (5b). - To a solution of 4-aminopyridine-3-sulfonamide (**14a**) (0.18 g, 1.0 mmol) in dimethylformamide (4 cm^3) was added triethyl orthoformate (15 cm^3) and the mixture was heated to 140 °C for 2 h. Evaporation gave a dark coloured solid which was chromatographed on silica, with ethyl acetate-methanol [9:1] as eluant to give off-white 4H-*pyrido*[4,3-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**5b**) (85 mg, 45%), m.p. 280 °C (dec); υ_{max} (KBr)/cm^{-1} 1629, 1577, 1507 (C=N str.), 1314 (SO_2 asym. str.) and 1167 (SO_2 sym. str.); δ_H (d_6-DMSO) 7.26 (1H, d, $J_{5,6} \approx$ 6, H-5), 8.10 (1H, s, H-3), 8.68 (1H, d, $J_{6,5} \approx$ 6, H-6), 9.00 (1H, s, H-8) and 12.5 (1H, br, NH); *m/z* (FAB) 184 (36%) $[MH]^{\cdot+}$, 147 (23) and 128 (23); (Found: C, 39.0; H, 2.6; N, 22.7; S, 17.1%; $C_6H_5N_3O_2S$ requires C, 39.34; H, 2.75; N, 22.94; S, 17.50%).

3-Methyl-4*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (5c). - Triethyl orthoacetate (10 cm^3, freshly distilled) was added to a solution of 4-aminopyridine-3-sulfonamide (**14a**) (0.21 g, 1.2 mmol) in dimethylformamide (2 cm^3). The mixture was heated to 120 °C for 1 h and then evaporated to give a brown oil which was purified by chromatography on silica, with ethyl acetate-methanol [9:1] as eluant, to give an off-white solid. Recrystalisation from methanol gave 3-methyl-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**5c**) (106 mg, 43%), m.p. 280-282 °C (lit.[3] 264-268 °C for the monohydrate); υ_{max} (KBr)/cm^{-1} 3430 (N-H str.), 1637, 1614, 1575 (C=N str.), 1335 (SO_2 asym str.) and 1167 (SO_2 sym. str.); δ_H (d_6-DMSO) 2.21 (3H, s, Me) 7.17 (1H, d, $J_{5,6} \approx$ 6, H-5), 8.67 (1H, d, $J_{6,5} \approx$ 6, H-6), 8.94 (1H, s, H-8) and 12.30 (1H, br, NH); *m/z* (EI) 197 (2%) $[M]^{\cdot+}$, 105 (3) and 78 (100); (Found: $[MH]^{\cdot+}$ 198.03390; $C_7H_8N_3O_2S$ requires 198.03372).

4H-Pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1,7-trioxide (15).- To a solution of 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**5b**) (74 mg, 0.4 mmol) in dimethylformamide (4 cm^3) was added *m*-chloroperoxybenzoic acid (50% dispersion in H_2O, 0.56 g, 1.6 mmol) and the mixture was stirred at room temperature for 60 h. Evaporation gave a white solid that was washed with methanol and chromatographed on silica, with ethyl acetate as eluant, to give 4H-*pyrido*[4,3-e]-1,2,4-*thiadiazine* 1,1,7-*trioxide* (**15**) (41 mg, 51%), as a white solid, m.p. 295-298 °C; positive Katritzky test;[16] υ_{max} (KBr)/cm^{-1} 3500-3400 (O-H str.), 1634, 1597 (C=N

str.),1307 (N-O) and 1159 (SO_2 sym. str.); δ_H (d_6-DMSO) 7.30 (1H, d, $J_{5,6} \approx 6$, H-5), 8.05 (1H, s, H-3), 8.23 (1H, dd, $J_{6,5} \approx 1$, H-6) and 8.65 (1H, d, $J_{8,6} \approx 1$, H-8); *m/z* (FAB) 200 (10%) $[MH]^{\cdot+}$, 184 (3) $[MH - O]^{\cdot+}$, 169 (29) and 149 (30); (Found: C, 34.7; H, 2.4; N, 20.3; S, 15.5. $C_6H_5N_3O_3S$. $0.5H_2O$ requires C, 34.62; H, 2.90; N, 20.18; S, 15.40%; Found: $[MH]^{\cdot+}$ 200.01323; $C_6H_6N_3O_3S$ requires 200.01299).

3-Nitropyridine-4-sulfenamide (16d). - To a solution of sodium hydrogen sulfide hydrate (17.75 g, 240 mmol) in methanol (100 cm^3) was added 4-chloro-3-nitropyridine (**16b**)[19] (20 g, 126 mmol) in methanol (100 cm^3) and the dark red mixture was heated on an oil bath (60 °C) for 5 min. The solvent was evaporated, water was added, and the solution was acidified with acetic acid. The resultant precipitate was filtered, washed with water and dried at 60 °C. The product, 4-mercapto-3-nitropyridine (**16c**), m.p. 150-154 °C (Lit.[19] m.p.153 °C) was used without further purification. Chloramine was prepared by adding ammonium hydroxide (d = 0.880, 40 cm^3) to sodium hypochlorite (0.55M, 200 cm^3) at -10 °C. A solution of the crude thiol in aqueous NaOH (2M) was added to the chloramine and the resulting precipitate was filtered, washed with water and dried to give *3-nitropyridine-4-sulfenamide* (**16d**) (7.0g, 33%), m.p. 137-138 °C; υ_{max} (KBr)/cm^{-1} 3251 (NH str.), 1637, 1618, 1580 (C=N str.), 1496 (NO_2 asym. str.) and 1352 (NO_2 sym. str.); δ_H (d_6-DMSO) 4.50 (2H, s, SNH_2), 7.96 (1H, d, $J_{5,6}$ = 5.6, H-5), 8.72 (1H, d, $J_{6,5}$ = 5.6, H-6) and 9.23 (1H, s, H-2); *m/z* (FAB) 172 (100%) $[MH]^{\cdot+}$ and 123 (21) $[M - SNH_2]^{\cdot+}$; (Found: $[M]^{\cdot+}$ 171.01086; $C_5H_5N_3O_2S$ requires 171.01025).

3-Nitropyridine-4-sulfonamide (16e). - 3-Nitropyridine-4-sulfenamide (**16d**) (0.50 g, 2.9 mmol) and *m*-chloro-peroxybenzoic acid (50% dispersion in H_2O, 2.0 g, 5.9 mmol) were stirred in dichloromethane (25 cm^3) for 14h Filtration and evaporation gave a cream coloured solid. Chromatography on silica, with ethyl acetate-toluene [4:1] as eluant, gave *3-nitropyridine-4-sulfonamide* (**16e**) (0.12 g, 20%), as an off-white solid, m.p. 159-160 °C; negative Katritzky test;[16] υ_{max} (KBr)/cm^{-1} 1637, 1586 (C=N str.) 1528 (NO_2 asym. str.) 1362, 1351 (NO_2 sym. str.; SO_2 asym. str.) and 1172 (SO_2 sym. str.); δ_H (d_6-DMSO) 8.02 (1H, d, $J_{5,6}$ = 5.4, H-5), 8.17 (2H, s, SO_2NH_2), 9.10 (1H, d, $J_{6,5}$ = 5.4, H-6) and 9.28 (1H, s, H-2); *m/z* (EI) 203 (73%) $[M]^{\cdot+}$, 187 (61) $[M - NH_2]^{\cdot+}$, 139 (9) $[M - SO_2]^{\cdot+}$ and 124 (3) $[MH - SO_2NH_2]^{\cdot+}$; (Found: C, 29.7; H, 2.2; N, 20.4; S, 15.3%; $C_5H_5N_3O_4S$ requires C, 29.56; H, 2.48; N, 20.68; S, 15.78%. Found: $[M]^{\cdot+}$ 202.99825; $C_5H_5N_3O_4S$ requires 203.00008. Found $[M - NH_2]^{\cdot+}$ 186.98127 $C_5H_3N_2O_4S$ requires 186.98135).

3-Aminopyridine-4-sulfonamide (16a). - 3-Nitropyridine-4-sulfonamide (**16e**) (0.09 g, 0.44 mmol) was added to a solution of tin (II) chloride dihydrate (1.0 g., 4.4 mmol) in conc. hydrochloric acid (2 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and then stirred for 4h. after which time it was cooled to 0 °C (ice bath) and the resulting precipitate was filtered. The precipitate was stirred in water (5 cm^3) and then made basic by addition of aqueous NaOH (2M, 5 cm^3). The aqueous mixture was evaporated under reduced pressure to give a dark solid that was purified by chromatography on silica, with ethyl acetate as eluant, to give *3-aminopyridine-4-sulfonamide* (**16a**) (0.055 g, 72%) as a grey solid, m.p. 197-199 °C; υ_{max} (KBr)/cm^{-1} 3479 (N-H str.), 3371 (N-H str.), 1618, 1470 (C=N str.), 1343 (SO_2 asym. str.) and 1143 (SO_2 sym. str.); δ_H (d_6-DMSO) 6.02 (2H, s, NH_2) 7.37 (1H, d, $J_{5,6}$ = 5.0, H-5) 7.6 (2H, br s, SO_2NH_2), 7.83 (1H, d, $J_{6,5}$ = 5.0, H-6) and 8.21 (1H, s, H-2); *m/z* (EI) 173 (80%) $[M]^{\cdot+}$, 156 (32), 109 (3) $[M\text{-}SO_2]^{\cdot+}$ and 93 (32) $[M\text{-}SO_2NH_2]^{\cdot+}$ (Found: C, 35.1; H, 3.9; N, 24.2; S, 18.4%; $C_5H_7N_3O_2S$ requires C, 34.68; H, 4.07; N, 24.26; S, 18.51%).

***4H*-Pyrido[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (7).** - Triethyl orthoformate (4 cm^3) was added to a solution of 3-aminopyridine-4-sulfonamide (**16a**) (40 mg, 0.23 mmol) in dimethyl sulfoxide (1 cm^3) and the mixture was heated to 130 °C for 3 h. The crude product after evaporation was chromatographed on silica, with ethyl acetate as eluant, to give *4H-pyrido*[3,4-e]-1,2,4-*thiadiazine* 1,1-*dioxide* (**7**) (30 mg, 71%) as an off-white solid, m.p. 270-274 °C (dec); υ_{max} (KBr)/cm^{-1} 3475 (N-H str.), 1618, 1568, 1533 (C=N str.), 1305 (SO_2 asym. str.) and 1165 (SO_2 sym. str.); δ_H (d_6-DMSO) 7.78 (1H, d, $J_{8,7}$ = 5.1, H-8) 8.03 (1H, s, H-3), 8.60 (1H, d, $J_{7,8}$ = 5.1, H-7) and 8.70 (1H, s, H-5); *m/z* (FAB) 184 (25%) $[MH]^{\cdot+}$, 169 (21), 153 (20) and 119 (7) $[M - SO_2]^{\cdot+}$; (Found: C, 39.4; H, 2.5; N, 23.0; S, 17.9%; $C_6H_5N_3O_2S$ requires C, 39.34; H, 2.75; N, 22.94; S, 17.50%).

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