Some 1*H*-4,1,2-Benzothiadiazines and 1*H*-4,1,2-Benzothiadiazine 4,4-Dioxides

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Intramolecular displacement of the *o*-nitro-group of 1-(2-nitrophenylthio)pyruvaldehyde 1-phenylhydrazone, under basic conditions, gives 3-acetyl-1-phenyl-1*H*-4,1,2-benzothiadiazine which was oxidised to the 4,4-dioxide. Ethyl 2-nitrophenylsulphonylglyoxylate phenylhydrazone gives only 2-nitrodiphenylamine under these conditions, but reduction to the 2-amino-compound and diazotisation yield 3-ethoxycarbonyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide. Hydrolysis and decarboxylation give the parent 1*H*-4,1,2-benzothiadiazine 4,4-dioxide.

SINCE the development of chlorothiazide and related compounds as diuretic and hypotensive agents, a very large number of substituted 3*H*-4,1,3-benzothiadiazine 4,4-dioxides (I) have been prepared. The related 1*H*-4,1,2-benzothiadiazines (II; X = S or SO_2) have been relatively little studied. Early claims of the synthesis of this ring system were later refuted.[1] Elegant syntheses of 3-aryl-1*H*-4,1,2-benzothiadiazines have been developed by Gibson and his co-workers [2] who also review other methods by which isolated 3-aryl and 3-phenylazo compounds have been prepared. One further compound, (IIa), has also been recently [3] prepared by cyclisation of the nitrile imine (III). This method may prove to be a general one and especially may lead to compounds without a 3-aryl substituent. Of the known 1*H*-4,1,2-benzothiadiazines, only one, (IIb), has been oxidised to the 4,4-dioxide (IIc).[2]

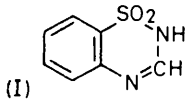
The objective of the present work was to prepare 1*H*-4,1,2-benzothiadiazine 4,4-dioxides, particularly compounds without a 3-aryl substituent, for pharmacological testing. Attempts to form a thiadiazine ring by diazotisation and cyclisation of *o*-aminophenyl sulphones (*cf.* synthesis of 1*H*-4-cinnolone [4]) gave only solvolysis products while 2-aminophenyl benzyl sulphone cyclised by a Pschorr reaction to form 6*H*-dibenzo[*b*,*d*]thiopyran 5,5-dioxide (IV). Attempts to cyclise nitrosoamide (V) to a thiadiazine were unsuccessful: reaction with sodium hydride gave triazene (VI).

1-Acetyl-6-bromo-3-phenyl-1*H*-4,1,2-benzothiadiazine (IId) [5] was debrominated by catalytic hydrogenation in the presence of a base to give 1-acetyl-3-phenyl-1*H*-4,1,2-benzothiadiazine (IIe) (72%). The bromo-compound (IId) was also oxidised by hydrogen peroxide in acetic acid to form 6-bromo-3-phenyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (IIc) [2] with concomitant deacetylation. Catalytic hydrogenation then gave 3-phenyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (IIf). Attempts to extend Gibson's synthesis by condensation of the 2,4-dibromophenylhydrazone of ethyl α-chloroglyoxylate with potassium thioacetate failed and the method appears to be limited to 3-aryl derivatives.

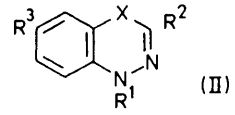
An interesting reaction reported by Sandison and Tennant [6] yielded 1-aryl-1*H*-4-cinnolones by displacement of an *o*-nitro-group from arylhydrazones, *e.g.* (VIIa), in sodium carbonate solution. Similar treatment of 1-(2-nitrophenylthio)pyruvaldehyde 1-phenylhydrazone (VIIb) gave a high yield of 3-acetyl-1-phenyl-1*H*-4,1,2-benzothiadiazine (IIg) which was oxidised with hydrogen peroxide in acetic acid to the 4,4-dioxide. Application of the same cyclisation procedure to sulphone (VIIc), however, gave *o*-nitrodiphenylamine (95%).

[1] A. Hugershoff, *Ber.*, 1903, **36**, 3134; G. Corsi, *Ann. Chim. (Italy)*, 1966, **56**, 1203.
[2] D. J. Vukov, M. S. Gibson, W. E. Lee, and M. F. Richardson, *J.C.S. Perkin I*, 1972, 192 and earlier papers.
[3] L. Garanti, A. Scandroglio, and G. Zecchi, *J. Heterocyclic Chem.*, 1976, **13**, 1339.
[4] K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 1948, 1170.
[5] I. T. Barnish and M. S. Gibson, *J. Chem. Soc.* (*C*), 1970, 854.
[6] A. A. Sandison and G. Tennant, *J.C.S. Chem. Comm.*, 1974, 752.

Other bases, and even water–dimethyl sulphoxide, gave the same result which is attributed to an intramolecular

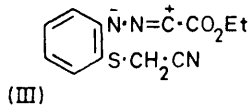


(I)

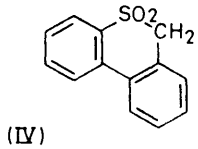


(II)

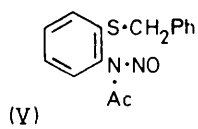
	X	R^1	R^2	R^3
(IIa)	S	H	CO_2Et	H
(IIb)	S	H	Ph	Br
(IIc)	SO_2	H	Ph	Br
(IId)	S	Ac	Ph	Br
(IIe)	S	Ac	Ph	H
(IIf)	SO_2	H	Ph	H
(IIg)	S	Ph	Ac	H
(IIh)	SO_2	Me	CO_2Me	H
(IIi)	SO_2	H	H	H



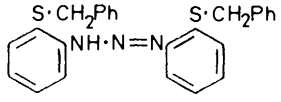
(III)



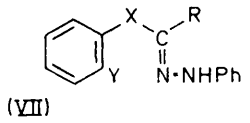
(IV)



(V)



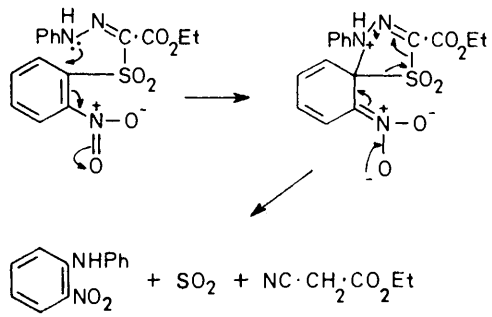
(VI)



(VII)

	X	Y	R
(VIIa)	CO	NO_2	CO_2Et
(VIIb)	S	NO_2	Ac
(VIIc)	SO_2	NO_2	CO_2Et

nucleophilic displacement (Scheme 1) of the sulphonyl group, activated by the *o*-nitro-substituent (compare Smiles rearrangement of *o*-nitrophenyl sulphones [7]).

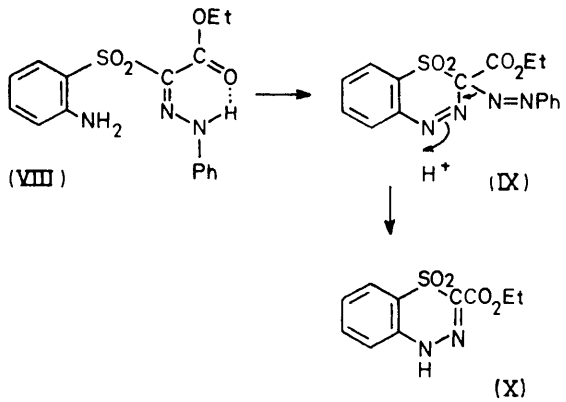


SCHEME 1

The nitro-intermediate (VIIc) was next reduced to examine possible formation of a benzothiadiazine by reductive coupling of the nitro and hydrazono groups. The corresponding amine was obtained in good yield.

[7] W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1935, 1234; T. S. Stevens and W. Watts, 'Selected Molecular Rearrangements,' Van Nostrand–Reinhold, London, 1973, p. 120.

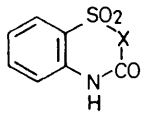
The stability of this ester, apparently without any tendency to form the lactam, is attributed to hydrogen bonding between the ester carbonyl and hydrazono groups (VIII); the ester carbonyl peak at 1 710 cm^{-1} was weak. Diazotisation of this amine unexpectedly gave 3-ethoxycarbonyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (X) in moderate yield (43%). Presumably the diazonium salt from (VIII) attacked the phenylhydrazono group to form the cyclic 'formazan' (IX) [8] which then eliminated benzenediazonium ion to furnish thiadiazine (X) (Scheme 2). The production of benzenediazonium



SCHEME 2

ion was detected by formation of the coupling product with β-naphthol.

The analogous methyl ester gave the corresponding product; in each case, yields were *ca.* 50% but were rather variable. Ester (VIII) was first hydrolysed and then diazotised in an attempt to form the 3-phenylazobenzothiadiazine by decarboxylation rather than by loss of benzenediazonium ion. The product was apparently an impure sample of the lactam (XIa), presumably



(XI)

a; X = C=N·NH·Ph
b; X = CH_2

formed on acidification of the hydrolysate. Catalytic hydrogenation of ethyl 2-nitrophenylsulphonylacetate gave a small yield of the lactam (XIb).[9] Diazotisation of the remaining gum afforded the thiadiazine ester (X) (30%); this intramolecular diazo-coupling probably proceeds because the methylene group is enolisable in contrast to the unsuccessful examples above.

When ester (X) was hydrolysed with aqueous ethanolic potassium hydroxide, a dipotassium salt separated; with methyl iodide this gave 3-methoxycarbonyl-1-methyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (IIh). Prolonged heating of the salt with two moles of dilute hydrochloric acid effected decarboxylation to produce the parent 1*H*-4,1,2-benzothiadiazine 4,4-dioxide (IIi)

[8] *Cf.* S. M. Parmerter, *Org. Reactions*, 1959, **10**, 1.

[9] R. T. Coutts, H. W. Peel, and E. M. Smith, *Canad. J. Chem.*, 1965, **43**, 3227.

(73%). Treatment with hot sodium ethoxide or hydroxide solutions, followed by acidification, gave only water-soluble products, presumably owing to ring cleavage to a sulphonic acid derivative. The methyl and ethyl esters [*e.g.* (X)] were, however, more stable to sodium alkoxide solution and subsequent addition of methyl iodide gave the 1-methyl derivatives. Ethyl ester (X) reacted with ethanolic hydrazine to give the hydrazide; the anilide was prepared by action of anilinomagnesium bromide on the ester.

Further work is being carried out in order to extend these syntheses to other 3-substituted 4,1,2-benzothiadiazine derivatives.

EXPERIMENTAL

Evaporations were carried out (<40°) under reduced pressure using a rotary evaporator. I.r. spectra were determined on Nujol mulls on a Perkin-Elmer 257 spectrometer. U.v. spectra (in ethanol) were recorded on a Perkin-Elmer 137 spectrophotometer and ^{1}H n.m.r. spectra were measured on a Perkin-Elmer R32 spectrometer at 90 MHz (unless otherwise stated the solvent was deuteriochloroform with tetramethylsilane as internal standard).

Diazotisation of 2-Aminophenyl Methyl Sulphone.—The amine [10] (4 g) in 4M-sulphuric acid (200 ml) was diazotised at 0—2° by addition of sodium nitrite solution (8 ml; 20%), left overnight, and heated at 60° for 5 h. Isolation with ethyl acetate, and crystallisation (benzene–ethyl acetate) gave 2-hydroxyphenyl methyl sulphone (2.6 g, 60%), m.p. 65—67° (lit.,[11] 67°). A sample, sublimed at 120° and 0.5 mmHg, had m.p. 71—72°. Similarly diazotisation in 10M-hydrochloric acid gave 2-chlorophenyl methyl sulphone (57%), m.p. 88—89° (lit.,[12] 90°).

Diazotisation of 2-Aminophenyl Benzyl Sulphone.—The amino-sulphone [13] (1 g) was dissolved in concentrated hydrochloric acid (130 ml) and cooled. The suspension was stirred at 2—5° while sodium nitrite solution (3 ml, 20%) was added gradually. The mixture was kept at room temperature for 2 weeks and filtered; the solid was extracted with ethyl acetate. Evaporation gave 6*H*-dibenzo[*b*,*d*]thiopyran 5,5-dioxide (IV) (0.55 g, 60%), m.p. 140—142° (from ethanol) (lit.,[13] 140—141°), $\lambda_{max.}$ 270 (ε 1 300) and 292 (660) nm. When the diazotised mixture was heated at 100° for 1.5 h with copper (0.8 g), the yield of sulphone was 80%.

Attempted Cyclisation of Benzyl 2-Nitrosoacetamidophenyl Sulphide (V).—2-Acetamidophenyl benzyl sulphide [14] (10 g) in dimethylacetamide (40 ml) was stirred and cooled at 5—10° while nitrosyl chloride (5.2 g) in acetic anhydride (18 ml) was added dropwise. The mixture was stirred for 15 min and poured onto ice. The bright yellow, crude nitroso-compound was filtered off, washed with water, and dried at 0.5 mmHg (over P_2O_5). The crude nitroso-compound (2.8 g) in dimethylacetamide (30 ml) was added slowly to a suspension of sodium hydride (1 g, 50%) in *NN*-dimethylacetamide (30 ml) at 0—5°. After a further 30 min, the mixture was poured into ice–M-sulphuric acid (100 ml). Isolation with benzene and chromatography on alumina in benzene–ethyl acetate (4 : 1) gave 1,3-*bis*-(2-*benzylthiophenyl*)*triazene* (VI) (0.15 g), m.p. 152—153° (from methanol) (Found: C, 70.4; H, 5.2; N, 9.2; S, 14.3. $C_{26}H_{23}N_3S_2$ requires C, 70.7; H, 5.2; N, 9.5; S, 14.5%), $\nu_{max.}$ 3 275 cm^{-1}, δ 1.48 (1 H, s, NH, exchanges with D_2O), 4.00 (4 H, s, 2SCH_2Ph), and 7.16 (18 H, m, ArH).

1-*Acetyl*-3-*phenyl*-1H-4,1,2-*benzothiadiazine* (IIe).—A solution of 1-acetyl-6-bromo-3-phenyl-1*H*-4,1,2-benzothiadiazine [5] (IId) (0.5 g) in ethyl acetate (75 ml) containing triethylamine (0.5 ml) was hydrogenated at 40° with palladium–charcoal catalyst (0.5 g, 5% Pd). Absorption ceased when *ca.* 1 mol. equiv. had been absorbed (5 h), the mixture was filtered at the b.p., and the catalyst was washed with hot ethyl acetate. The cooled filtrates were washed with sodium carbonate solution and water and evaporated. Chromatography on alumina in ethyl acetate–light petroleum (1 : 20) gave 1-acetyl-3-phenyl-1*H*-4,1,2-benzothiadiazine (0.28 g, 72%), m.p. 126—128° [from light petroleum (b.p. 80—100°)] (Found: C, 67.3; H, 4.5; N, 10.3; S, 12.0. Calc. for $C_{15}H_{12}N_2OS$: C, 67.2; H, 4.5; N, 10.3; S, 11.9%) (lit.,[15] 123—126°).

3-*Phenyl*-1H-4,1,2-*benzothiadiazine* 4,4-*Dioxide* (IIf).—A solution of 1-acetyl-6-bromo-3-phenyl-1*H*-4,1,2-benzothiadiazine (IId) (2 g) in acetic acid (90 ml) was heated at 80° while hydrogen peroxide (15 ml, 30%) was added over 10 min. The solution was heated at 90° for 5.5 h, more hydrogen peroxide (10 ml) being added after 1.5 h. The cooled solution was poured onto ice and the precipitate was collected and crystallised from ethyl acetate to give 6-bromo-3-phenyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (IIc) (1.2 g), m.p. 244—246° (Found: C, 46.5; H, 2.7; N, 8.6; S, 9.9. Calc. for $C_{13}H_9BrN_2O_2S$: C, 46.3; H, 2.7; N, 8.3; S, 9.5%) (lit.,[2] 249—250°). This compound (0.2 g) was catalytically hydrogenated as described to give the *dioxide* (IIf) (0.12 g), m.p. 186—188° (from ethyl acetate–light petroleum) (Found: C, 60.6; H, 3.9; N, 10.9. $C_{13}H_{10}N_2O_2S$ requires C, 60.5; H, 3.9; N, 10.9%), $\nu_{max.}$ 3 290 cm^{-1} (NH).

Reaction of Ethyl α-Chloroglyoxylate 2,4-Dibromophenylhydrazone with Potassium Thioacetate.—The hydrazone (1.92 g) [16] was added to a suspension of potassium thioacetate (0.57 g) in acetonitrile (50 ml) (*cf.* ref. 5). The mixture was heated under reflux for 4 h and filtered hot, the solid being washed with hot acetonitrile (25 ml). The filtrate deposited yellow crystals on cooling; these were combined with the solid and crystallised from ethyl acetate–light petroleum (b.p. 80—100°) to give *bis*-(2,4-*dibromophenylhydrazonoethoxycarbonylmethyl*) *sulphide* (1 g), m.p. 162—164° (Found: C, 33.0; H, 2.4; Br, 44.2; N, 7.7; S, 4.7. $C_{20}H_{18}Br_4N_4O_4S$ requires C, 32.9; H, 2.5; Br, 43.8; N, 7.7; S, 4.4%), $\lambda_{max.}$ 243 (ε 16 800), 305 (12 000), and 373 (26 200) nm; δ 1.27 (6 H, t, *J* 7 Hz, 2 CH_2CH_3), 4.27 (4 H, q, *J* 7 Hz, 2CH_2CH_3), 7.2—7.8 (6 H, m, ArH), and 10.24 (2 H, s, NH).

1-(2-*Nitrophenylthio*)*pyruvaldehyde* 1-*Phenylhydrazone* (VIIb).—Aniline (4.8 g, 52 mmol) in 2M-hydrochloric acid (40 ml) was diazotised at 0—5° with sodium nitrite (4 g) in water (20 ml). The solution was added gradually to (*o*-nitrophenylthio)acetone [17] (5 g, 24 mmol) in pyridine (40

[10] M. Claasz, *Ber.*, 1912, **45**, 1015.
[11] M. E. Heppenstall and S. Smiles, *J. Chem. Soc.*, 1938, 899.
[12] H. R. Todd and R. L. Shriner, *J. Amer. Chem. Soc.*, 1934, **56**, 1382.
[13] S. Bradamante, S. Maiorana, A. Mangia, and G. Pagani, *J. Chem. Soc.* (*B*), 1971, 74.
[14] A. Sieglitz and H. Koch, *Ber.*, 1925, **58**, 78.
[15] I. T. Barnish, P. D. Callaghan, and M. S. Gibson, *J.C.S. Perkin I*, 1974, 215.
[16] F. D. Chattaway and R. J. Lye, *Proc. Roy. Soc.*, 1932, **A137**, 489.
[17] M. Claasz, *Ber.*, 1911, **44**, 769.

ml) at 0—5°. The mixture was stirred at 0—5° for 3 h and filtered; recrystallisations from ethyl acetate gave the *phenylhydrazone* (6.6 g, 88%), m.p. 173—174° (Found: C, 57.4; H, 4.2; N, 13.0. $C_{15}H_{13}N_3O_3S$ requires C, 57.1; H, 4.2; N, 13.3%), $\nu_{max.}$ 3 220br (NH) and 1 710 cm^{-1} (C=O); δ 2.65 (3 H, s, $COCH_3$), 6.9—7.5 (8 H, m) and 8.1—8.3 (1 H, m) (both ArH), and 9.5br (1 H, s, NH exchanges with D_2O). Similarly 2-nitrophenylsulphonylacetone [18] gave 1-(2-*nitrophenylsulphonyl*)*pyruvaldehyde* 1-*phenylhydrazone* (57%), m.p. 192—193° (from ethyl acetate) (Found: C, 51.8; H, 3.8; N, 12.1. $C_{15}H_{13}N_3O_5S$ requires C, 51.8; H, 3.7; N, 11.5%), $\nu_{max.}$ 3 270br (NH) and 1 680 cm^{-1} (C=O); δ 2.38 (3 H, s, $COCH_3$), 7.0—8.5 (9 H, m, ArH), 11.97br (1 H, s, NH, exchanges with D_2O). *Ethyl* 2-*nitrophenylsulphonylglyoxylate phenylhydrazone* (VIIa) (83%), prepared similarly, had m.p. 164—167° (from ethyl acetate) (Found: C, 51.1; H, 4.1; N, 10.8. $C_{16}H_{15}N_3O_6S$ requires C, 50.9; H, 4.0; N, 11.1%), $\nu_{max.}$ 1 670vwk cm^{-1} (CO_2Et); δ 1.28 (3 H, t *J* 7 Hz, CH_3), 4.35 (2 H, q, *J* 7 Hz, CH_2), and 7.1—8.4 (9 H, m, ArH). The corresponding *methyl ester* (58%) had m.p. 187—190° (from methanol) (Found: C, 49.4; H, 3.0; N, 11.4; S, 8.9. $C_{15}H_{13}N_3O_6S$ requires C, 49.5; H, 3.6; N, 11.6; S, 8.8%), $\nu_{max.}$ 1 680vwk cm^{-1} (CO_2Me); δ 3.85 (3 H, s, Me), 7.0—7.9 (9 H, m, ArH), and 12.46 (1 H, s, NH, exchanges with D_2O).

3-*Acetyl*-1-*phenyl*-1H-4,1,2-*benzothiadiazine* (IIg).—1-(2-Nitrophenylthio)pyruvaldehyde 1-phenylhydrazone (0.7 g) in warm ethanol (100 ml) and M-sodium carbonate (50 ml) were boiled under reflux for 4 h. Removal of ethanol by distillation under reduced pressure and then filtration gave the red *product* (0.5 g, 85%), m.p. 116—118° (from ethanol) (Found: C, 67.2; H, 4.7; N, 10.6; S, 12.2. $C_{15}H_{12}N_2OS$ requires C, 67.2; H, 4.5; N, 10.4; S, 11.9%), $\nu_{max.}$ 1 685 cm^{-1} (C=O); $\lambda_{max.}$ (MeOH) 225 (ε 17 000) and 283 (16 000) nm; δ 2.48 (3 H, s, $COCH_3$) and 6.5—7.6 (9 H, m, ArH).

3-*Acetyl*-1-*phenyl*-1H-4,1,2-*benzothiadiazine* 4,4-*Dioxide*.—The thiadiazine (0.9 g) in acetic acid (20 ml) and hydrogen peroxide (10 ml; 30%) were heated at 50° for 1 h. The solution was cooled, poured onto ice and filtered; recrystallisations from benzene gave the *dioxide* (0.4 g; 34%), m.p. 220—222° (Found: C, 60.1; H, 4.0; N, 9.3. $C_{15}H_{12}N_2O_3S$ requires C, 60.0; H, 4.0; N, 9.3%); $\nu_{max.}$ 1 680 cm^{-1} (C=O); δ 2.38 (3 H, s, $COCH_3$) and 6.8—8.2 (9 H, m, ArH).

Conversion of Ethyl 2-*Nitrophenylsulphonylglyoxylate Phenylhydrazone into* 2-*Nitrodiphenylamine*.—The phenylhydrazone (0.5 g) in hot ethanol (40 ml) was treated with M-sodium carbonate (40 ml) and the solution was boiled under reflux for 1 h. Removal of ethanol by distillation and dilution with water gave 2-nitrodiphenylamine (0.27 g, 95%), m.p. and mixed m.p. 76—77°, after crystallisation from light petroleum (b.p. 60—80°). Treatment of the hydrazone with triethylamine, sodium hydride–1,2-dimethoxyethane, dimethylaniline, or water–dimethyl sulphoxide each gave the same result.

Ethyl 2-*Aminophenylsulphonylglyoxylate Phenylhydrazone* (VIII).—Ethyl 2-nitrophenylsulphonylglyoxylate phenylhydrazone (5 g) was dissolved in warm, freshly distilled tetrahydrofuran (100 ml) and hydrogenated with palladium–charcoal catalyst (2 g, 5% Pd). Absorption ceased when 3 mol. equiv. had been taken up; filtration, evaporation, and recrystallisations from ethanol gave the *amine* (4.1 g), m.p. 126—128° (decomp.) (Found: C, 55.6; H, 4.9; N, 12.5; S, 8.8. $C_{16}H_{17}N_3O_4S$ requires C, 55.3; H, 4.9; N, 12.1; S, 9.2%), $\nu_{max.}$ 3 420, 3 340 (NH_2), and 1 685 cm^{-1} (CO_2Et); δ 1.27 (3 H, t, *J* 8 Hz, CH_3), 4.27 (2 H, q, *J* 8 Hz, CH_2), 6.6—8.0 (11 H, m, ArH and NH_2), and 12.54 (1 H, s, NH, exchanges with D_2O). The corresponding *methyl ester* had m.p. 136—138° (from methanol) (Found: C, 53.9; H, 4.5; N, 12.8; S, 9.5. $C_{15}H_{15}N_3O_4S$ requires C, 54.1; H, 4.5; N, 12.6; S 9.6%), $\nu_{max.}$ 3 500, 3 400 (NH_2), and 1 695 cm^{-1} (CO_2Me); δ 3.84 (3 H, s, CH_3), 6.7—7.9 (11 H, m, ArH and NH_2), and 12.43 (1 H, s, NH).

3-*Ethoxycarbonyl*-1H-4,1,2-*benzothiadiazine* 4,4-*Dioxide* (X).—Finely powdered ethyl amino-ester (5 g) was dissolved in acetic acid (300 ml) at 30—35° and the solution was stirred while 2M-hydrochloric acid (150 ml) was added dropwise. The mixture was immediately cooled to 0—5° and the stirred suspension of amine hydrochloride was treated with sodium nitrite (1.5 g) in water (20 ml) over 15 min. The resulting solution was kept at 0—5° for 3 h and then stirred at 5—10° while 10M-sodium hydroxide (250 ml) was added dropwise. Isolation with chloroform, washing with sodium carbonate solution, yielded the *thiadiazine-ester* (1.54 g, 43%), m.p. 180—182° (from ethyl acetate) (Found: C, 47.1; H, 4.1; N, 11.0; S, 12.4%; M^+, 254. $C_{10}H_{10}N_2O_4S$ requires C, 47.3; H, 4.0; N, 11.0; S, 12.6%; *M*, 254), $\nu_{max.}$ 3 220 (NH) and 1 710 cm^{-1} (CO_2Et); $\lambda_{max.}$ 328 nm (ε 13 000); δ 1.41 (3 H, t, *J* 8 Hz, CH_3), 4.44 (2 H, q, *J* 8 Hz, CH_2), 7.3—8.1 (4 H, m, ArH), and 12.75br (1 H, s, NH). When a small portion of the acidic reaction mixture was added to a cold solution of β-naphthol in 2M-sodium hydroxide, a red precipitate was formed. Extraction with chloroform and comparison with the coupling product from diazotised aniline gave identical spots in t.l.c.

The corresponding *methyl ester* (50%), prepared similarly, had m.p. 228—230° (from methanol) (Found: C, 45.1; H, 3.7; N, 11.8. $C_9H_8N_2O_4S$ requires C, 45.0; H, 3.4; N, 11.7%); $\nu_{max.}$ 3 180 (NH) and 1 710 cm^{-1} (CO_2Me); $\lambda_{max.}$ 326 nm (ε 11 000); δ 3.95 (3 H, s, CH_3), 7.3—8.1 (4 H, m, ArH), and 12.98br (1 H, s, NH, exchanges with D_2O).

Hydrolysis and Diazotisation of Ethyl 2-*Aminophenylsulphonylglyoxylate Phenylhydrazone*.—The base (0.5 g) in ethanol (60 ml) was treated with potassium hydroxide (0.2 g) in water (0.5 ml) and the solution was kept at room temperature for 18 h. It was added dropwise to a stirred mixture of acetic acid (30 ml) and 2M-hydrochloric acid (15 ml) at 0—5° and then sodium nitrite (150 mg) in water (2 ml) was added. After 3 h, 10M-sodium hydroxide (25 ml) was added gradually and the mixture was diluted with water. Isolation with chloroform gave crude 2,3-dihydro-1*H*-4,1-benzothiazine-2,3-dione 4,4-dioxide 3-phenylhydrazone (XIa) (Found: C, 52.5; H, 3.4; N, 14.0. Calc. for $C_{14}H_{11}N_3O_3S$: C, 55.9; H, 3.7; N, 14.0%); $\nu_{max.}$ 3 315 (NH) and 1 650 cm^{-1} (C=N); δ 7.2—8.1 (m, ArH) and 13.3br (s, NH).

Reduction and Diazotisation of Ethyl 2-*Nitrophenylsulphonylacetate*.—The nitro-ester (1 g) in ethanol (50 ml) was hydrogenated with palladium–charcoal catalyst (1 g, 5% Pd) until absorption ceased (*ca.* 3.5 mol. equiv. of hydrogen were taken up). The mixture was filtered and the catalyst washed with ethanol; concentration of the filtrates gave 2,3-dihydro-1*H*-4,1-benzothiazin-2-one 4,4-dioxide (100 mg, 14%), m.p. 207—210°, $\nu_{max.}$ 3 300 (NH) and 1 700 cm^{-1} (C=O); δ 4.20 (2 H, s, 3-CH_2) and 7.1—8.0 (4 H, m, ArH) (lit.,[9] 208.5—209.8°).

Evaporation of the filtrate gave an oil which was dissolved in ethanol (10 ml) and 2M-hydrochloric acid (10 ml). The solution was cooled at 0—5° while sodium nitrite (0.2 g) in water (15 ml) was added gradually. The precipitate

[18] I. L. Finar and A. J. Montgomery, *J. Chem. Soc.*, 1967, 367.

was collected and crystallised from ethyl acetate to give 3-ethoxycarbonyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (0.3 g), m.p. 184—185°, identical with that described above.

3-*Methoxycarbonyl*-1-*methyl*-1H-4,1,2-*benzothiadiazine* 4,4-*Dioxide* (IIh).—(a) The foregoing ethyl ester (1.35 g) in hot ethanol (50 ml) was treated with potassium hydroxide (1 g) in water (1 ml) and the mixture was boiled for 10 min, cooled, and filtered to give crude dipotassium salt (1.8 g). This (400 mg) in *NN*-dimethylacetamide (50 ml) was heated with methyl iodide (5 ml) for 10 h, more methyl iodide (5 ml) being added after 5 h. Addition of water and isolation with chloroform yielded 3-*methoxycarbonyl*-1-*methyl*-1H-4,1,2-*benzothiadiazine* 4,4-*dioxide* (100 mg), m.p. 177—178° (from methanol) (Found: C, 47.3; H, 4.1; N, 11.3; S, 12.4. $C_{10}H_{10}N_2O_4S$ requires C, 47.3; H, 4.0; N, 11.0; S, 12.6%), $\nu_{max.}$ 1 710 cm^{-1} (CO_2Me); δ 4.00 (6 H, s, NMe and OMe coincident) and 7.2—8.2 (4 H, m, ArH).

(b) 3-Methoxycarbonyl-1*H*-4,1,2-benzothiazine 4,4-dioxide (200 mg) was dissolved in boiling, dry methanol and sodium methoxide solution [from sodium (100 mg) and methanol (2.5 ml)] and methyl iodide (2 ml) were added successively. The mixture was boiled under reflux for 3 h, evaporated, and treated with acetic acid (2 ml) and water (8 ml). The 1-methyl derivative (70 mg), which was filtered off and crystallised, was identical with the previous sample. Methylation of the ethyl ester in ethanol similarly gave 3-*ethoxycarbonyl*-1-*methyl*-1H-4,1,2-*benzothiadiazine* 4,4-*dioxide* (40%), m.p. 135—137° (from benzene) (Found: C, 49.3; H, 4.5; N, 10.1; S, 11.6. $C_{11}H_{12}N_2O_4S$ requires C, 49.3; H, 4.5; N, 10.5; S, 11.9%), $\nu_{max.}$ 1 710 cm^{-1} (CO_2Et); $\lambda_{max.}$ 331 nm (ε 14 000); δ 1.40 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.97 (3 H, s, NCH_3), 4.47 (2 H, q, *J* 7 Hz, CH_2-CH_3), and 7.1—8.2 (4 H, m, ArH).

1H-4,1,2-*Benzothiadiazine* 4,4-*Dioxide* (IIi).—3-Ethoxycarbonyl-1*H*-4,1,2-benzothiadiazine 4,4-dioxide (1.35 g) was hydrolysed as above and the resulting potassium salt (1.8 g) was dissolved in hot water (200 ml) and 2M-hydrochloric acid (5.4 ml, 2 equiv.) was added to the boiling solution. The mixture was boiled under reflux for 24 h and filtered hot. The filtrate was kept at 0° for 5 days and then the *thiadiazine* (0.71 g, 73%), m.p. 198—200° (from water), was collected (Found: C, 46.0; H, 3.4; N, 15.2; S, 17.5. $C_7H_6N_2O_2S$ requires C, 46.2; H, 3.3; N, 15.4; S, 17.6%), $\nu_{max.}$ 3 300 cm^{-1} (NH), $\lambda_{max.}$ 302 nm (ε 9 000); δ[$CDCl_3$–$(CD_3)_2SO$] 7.0—8.0 (5 H, m, ArH) and 11.98 (1 H, s, NH).

Derivatives of 3-*Carboxy*-1H-4,1,2-*benzothiadiazine* 4,4-*Dioxide*.—(a) The ethyl ester (0.3 g) in ethanol (20 ml) and hydrazine hydrate (99%, 0.5 g) was left at room temperature for 4 days. The *hydrazide* was collected and washed with ethanol; it had m.p. 294—295° (Found: C, 40.3; H, 3.5; N, 22.9. $C_8H_8N_4O_3S$ requires C, 40.0; H, 3.4; N, 23.3%), $\nu_{max.}$ 3 320 and 3 260 (NH) and 1 700 cm^{-1} (C=O).

(b) Aniline (1.5 g) in ether (20 ml) was added to butylmagnesium bromide [from butyl bromide (1.5 g) and magnesium (0.24 g)] in ether (40 ml) and the solution was heated under reflux for 15 min. A solution of the ethyl ester (0.25 g) in boiling benzene (30 ml) was added and the mixture was left at room temperature with occasional shaking for 2 h. Addition of saturated ammonium chloride solution (50 ml), thorough shaking, and filtration yielded the *anilide* (0.16 g, 50%), m.p. 300—305° (decomp.) (from ethyl acetate and then ethanol) (Found: C, 55.9; H, 3.8; N, 13.7. $C_{14}H_{11}N_3O_3S$ requires C, 55.8; H, 3.7; N, 14.0%), $\nu_{max.}$ 3 240, 3 320 (NH), 1 660, and 1 675 cm^{-1}; δ 7.0—8.0 (9 H, m, ArH) and 9.65br (2 H, s 2NH, exchange with D_2O).

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