A Regioselective Synthesis of 3,5-Disubstituted Isoxazoles

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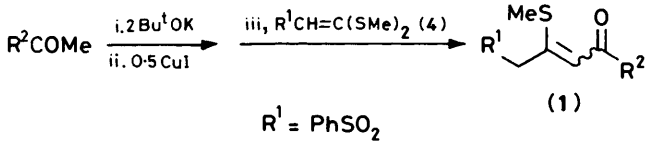
The 3-aryl-5- and 5-aryl-3-(phenylsulphonylmethyl)isoxazoles (**6**) and (**9**) respectively were regioselectively prepared from 1-aryl-3-methylthio-4-phenylsulphonylbut-2-en-1-one (**1**). As an application of the present method, 3-methyl-5-(4-pyridyl)isoxazole (**2**) was also synthesized from compound (**1**). The reaction of compound (**1**) with guanidine led to 2-amino-4-phenyl-6-(phenylsulphonylmethyl)-pyrimidine (**3**).

Isoxazoles, which have pharmacological interest[1,2] and are also found in Nature,[3] are prepared by a variety of methods including the reaction of 1,3-dicarbonyl compounds with hydroxylamine.[4] In such reactions, differences in reaction conditions may cause marked changes in the degree of regioselectivity.[5] β-Hetero substituted vinyl ketones may also be used in the reaction[4,6] and Kashima *et al.* have recently reported such work.[7] In spite of this there are few reports of the selective synthesis, by varying the conditions, of both possible isomers in such systems. We have recently reported a synthetic method for 5-substituted pyrazoles and pyrimethamine starting from 1-substituted 3-methylthio-4-phenylsulphonylbut-2-en-1-one (**1**) and 1-(4-chlorophenyl)-1-cyano-2-methylthio-3-phenylsulphonylpropene,[8] respectively.

We now present a good regioselective synthesis of isoxazoles from compound (**1**), *via* a new synthetic route to 3-methyl-5-(4-pyridyl)isoxazole (**2**), which is an agent for lowering blood sugar levels, and to 2-amino-4-phenyl-6-phenylsulphonylmethylpyrimidine (**3**).

Results and Discussion

Preparation of Compounds (**1**).—Compounds (**1**) were prepared by the reaction of 1,1-bis(methylthio)-2-phenylsulphonylethene (**4**)[8] and α-metallated ketones. The results are summarized in Table 1. In this reaction, copper(I) iodide acts as an inhibitor of 1,1,2-tris(methylthio)ethene formation.



Reaction of Compound (**4**) *with α-Metallated Esters.*—When treated with α-lithiated ester generated by lithium di-isopropylamide (LDA), compound (**4**) was converted into 1-substituted alkoxycarbonyl-2-methylthio-3-phenylsulphonylprop-1-ene (**5**). The results are shown in Table 2. In this reaction tetramethylethylenediamine (TMEDA) seems to reinforce the nucleophilicity of the ester carbanion.

The preparation of heterocycles using compounds (**5**) was unsuccessful.

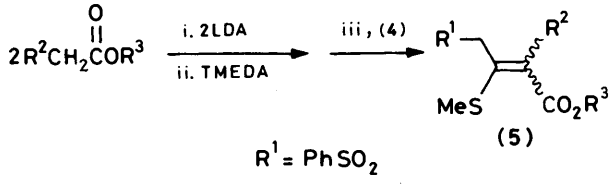
Regioselective Synthesis of Isoxazoles.—Taking p*K*a values for the first and the second dissociations of hydroxylamine into consideration,[9] we treated compound (**1**) with hydroxylamine hydrochloride by Methods A and B. Method A. Compound (**1**) (1.0 equiv.), hydroxylamine hydrochloride (2.5 equiv.), and 10% aqueous sodium hydroxide (5 ml). Method B. Compound (**1**)

Table 1. Preparation of compounds (**1**)

Product	R^2	Yield (%)
(**1a**)	Ph	72
(**1b**)	*p*-$MeOC_6H_4$	82
(**1c**)	*p*-ClC_6H_4	94
(**1d**)	2-Naphthyl	78
(**1e**)	2-Pyridyl	38
(**1f**)	4-Pyridyl	69
(**1g**)	2-Thienyl	64
(**1h**)	Me	57

Table 2. Preparation of compounds (**5**)

Product	R^2	R^3	Yield (%)
(**5a**)	Ph	Me	38
(**5b**)	H	Bu^t^	77

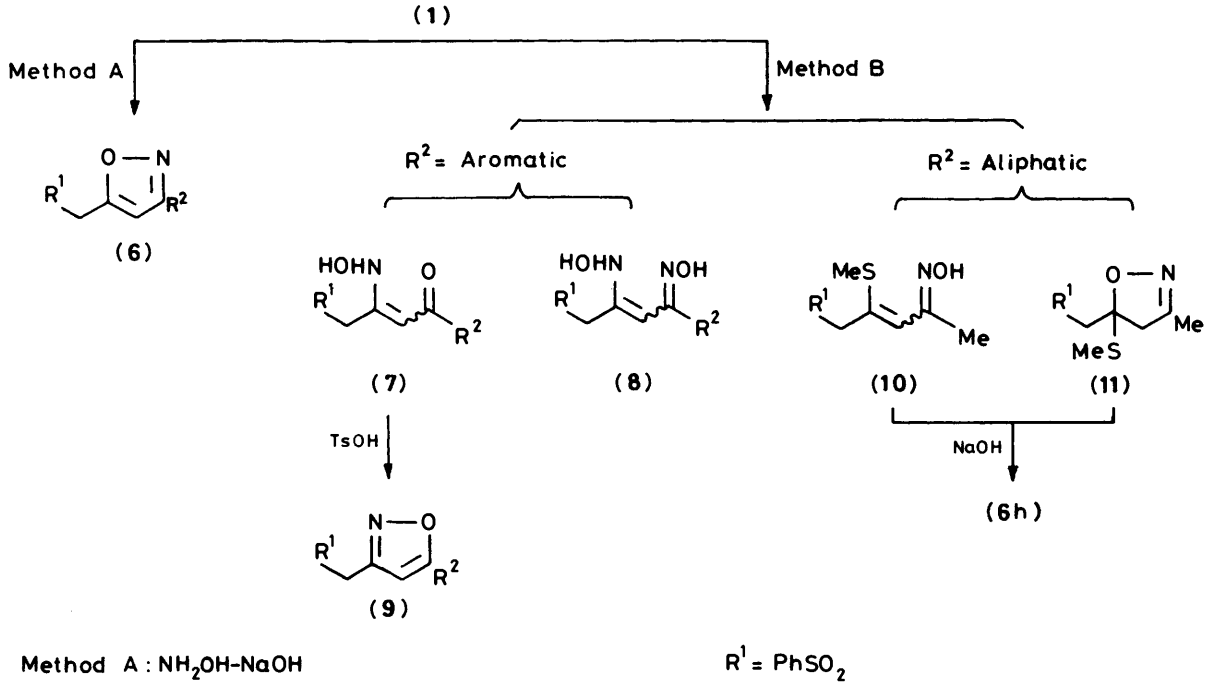


(1.0 equiv.), hydroxylamine hydrochloride (2.5 equiv.), and tributylamine (2.5 equiv.).

Method A gave 3-substituted 5-(phenylsulphonylmethyl)-isoxazoles (**6**) generated by introduction of oxygen exclusively into the position β to the carbonyl group. Method B afforded both the β-hydroxyaminovinyl ketones (**7**) (major product) and the corresponding oximes (**8**) generated by nucleophilic attack of nitrogen at the position β to the carbonyl group. Compound (**7**) could be converted into 5-substituted 3-(phenylsulphonylmethyl)isoxazoles (**9**) quantitatively on treatment with toluene-*p*-sulphonic acid.

However, in the case of compounds (**1h**), 2-hydroxyimino-4-methylthio-5-phenylsulphonylpent-3-ene (**10**) and 3-methyl-5-methylthio-5-phenylsulphonylmethyl-4,5-dihydroisoxazole (**11**) [precursors of 3-methyl-5-(phenylsulphonylmethyl)-isoxazole (**6h**)], were obtained in 24 and 33% yields, respectively. These conversions are outlined in Scheme 1; the yields of compounds (**6**), (**8**), and (**9**) are shown in Table 3. The structures of compounds (**6**) and (**9**) were determined by desulphonylation of 3-phenyl-5-(phenylsulphonylmethyl)isoxazole (**6a**) and 5-phenyl-3-(phenylsulphonylmethyl)isoxazole (**9a**) and comparison with authentic compounds.[10]

These results can be explained by the following mechanism (see Scheme 2). In method A, a Michael addition between the aminohydroxyl anion and compound (**1**) is followed by



Scheme 1.

Table 3. Yields of compounds (**6**), (**8**), and (**9**)

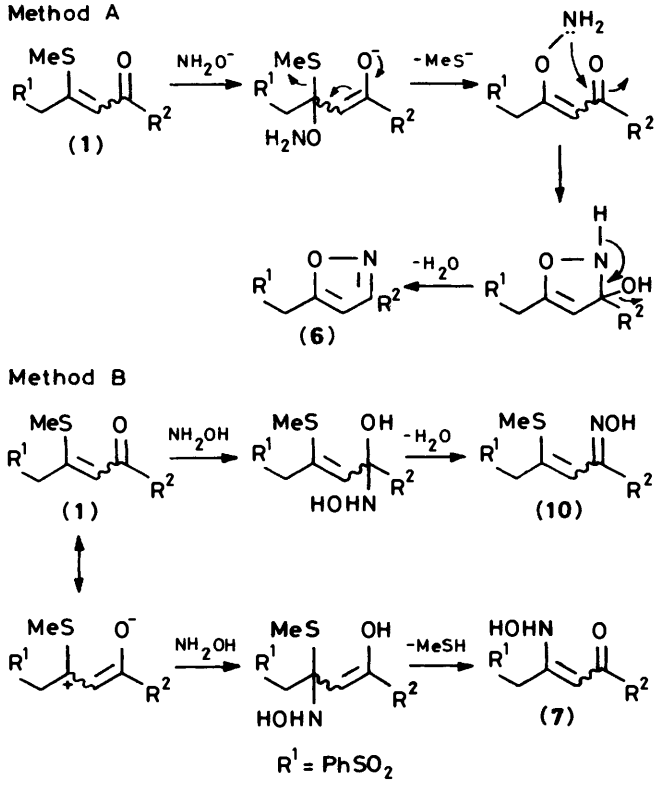
Method		A	B	
Starting ketone	(R^2)	(**6**) (%)	(**8**)	(**9**)*
Ph	(**1a**)	93	10	60
p-$MeOC_6H_4$	(**1b**)	96	14	52
p-ClC_6H_4	(**1c**)	84	2	79
2-Naphthyl	(**1d**)	98	11	75
2-Pyridyl	(**1e**)	64	0	74
2-Thienyl	(**1g**)	90	4	74
Me	(**1h**)	93	11	0

* These compounds were obtained by method B followed by acid treatment.

cyclization to give compound (**6**). In method B, the product is greatly dependent on whether R is aliphatic or aromatic. If R is aliphatic, free hydroxylamine attacks the 1-position of compound (**1**) leading to compound (**10**). If R is aromatic, the attack is at the 3-position of compound (**1**), leading to compound (**7**).

On account of the electron-withdrawing effect of the sulphonyl group, the present preparative procedure for isoxazoles is superior to Kashima's method (see Table 4) in terms of the regioselectivity and the yield.

Next, the introduction of electrophiles into the active methylene at the side chain of compound (**6a**) was investigated. After adding butyl-lithium dropwise to a THF solution of compound (**6a**), various alkyl halides were added to obtain 3-phenyl-5-(1-substituted phenylsulphonylmethyl)isoxazole (**14**). Furthermore, 3-phenyl-5-(1-phenylsulphonylethyl)-isoxazole (**14a**) was desulphonylated to give 5-ethyl-3-phenyl-isoxazole (**15**), which was identified with an authentic compound.[11] The results are summarized in Table 5.



Scheme 2.

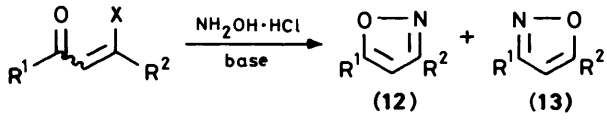


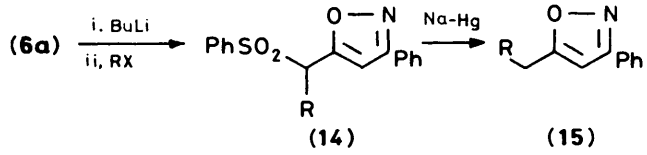
Table 4. The results of Kashima's method

Substrate			Et_3N (%)	NaOEt (%)
R^1	R^2	X	Treatment, yield	Treatment, yield
Ph	Me	SPh	43 (96:4)*	41 (21:79)
Ph	Me	SEt	52 (96:4)	22 (22:78)

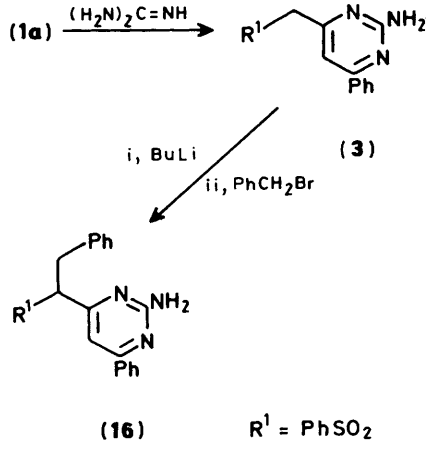
* The values in parentheses show the formation ratio of compounds (**12**) and (**13**)

Table 5. Preparation of compounds (**14**)

RX	Product	Yield (%)
MeI	(**14a**)	47
CH_2=$CHCH_2Br$	(**14b**)	51
$PhCH_2Br$	(**14c**)	57

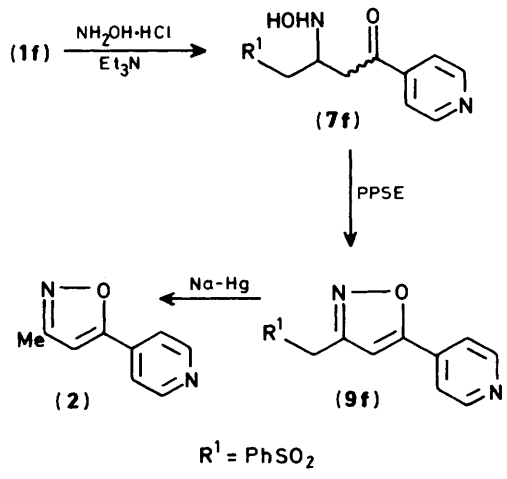


Synthesis of 2-*Amino*-4-*phenyl*-6-(1-*phenylsulphonyl*-2-*phenethyl*)*pyrimidine* (**16**).—When 3-methylthio-1-phenyl-4-phenylsulphonylbut-2-en-1-one (**1a**) was treated with guanidine instead of hydroxylamine, 2-amino-4-phenyl-6-(phenylsulphonylmethyl)pyrimidine (**3**) was obtained quantitatively.



Further, a benzyl group was introduced into the phenylsulphonylmethyl group in the usual way to give compound (**16**).

Synthesis of 3-*Methyl*-5-(4-*pyridyl*)*isoxazole* (**2**).—3-Methylthio-4-phenylsulphonyl-1-(4-pyridyl)but-2-en-1-one (**1f**) was converted into 3-hydroxyamino-4-phenylsulphonyl-1-(4-pyridyl)but-2-en-1-one (**7f**) in 72% yield on treatment with hydroxylamine in the presence of triethylamine. However, compound (**7f**) could not be cyclized to 3-phenylsulphonylmethyl-5-(4-pyridyl)isoxazole (**9f**) by the previous method (acid treatment). By using polyphosphoric acid trimethylsilyl ester (PPSE),[12] compound (**7f**) could be converted into compound (**9f**) in 61% yield. Next, compound (**9f**) was desulphonylated on treatment with 5% sodium amalgam to afford compound (**2**). In this way compound (**1**) is found to be a versatile starting material for pharmaceutically important heterocycles.



Experimental

Microanalyses were performed with a Perkin-Elmer 240 elemental analyser at the Chemical Analysis Center of Chiba University. I.r., mass, and ^1H n.m.r. spectra were measured with Hitachi 215, RMU 6MC instruments, Japan Electron Optics Lab. Co. C-60 HL, and FX-270 instruments, respectively. Silica gel used in column chromatography was Wako gel C-200 and silica gel used for t.l.c. was Wako gel B-5F.

Preparation of 1-*Substituted* 3-*Methylthio*-4-*phenylsulphonylbut*-2-*en*-1-*ones* (**1**): *General Procedure*.—To a suspension of ketone (1.0 mmol), potassium t-butoxide (274 mg, 2.2 mmol), and copper(I) iodide (100 mg, 0.5 mmol) in THF (5 ml) was added a solution of (**4**) (260 mg, 1.0 mmol) in THF (5 ml). After the mixture had been stirred for 15 h, it was diluted with water and chloroform and acidified with 2M HCl. It was then filtered through Celite and the organic layer dried (Na_2SO_4) and evaporated to give a brown oil. This was purified by t.l.c. on silica gel using ethyl acetate–hexane (2:3) as eluant to afford the following new *vinyl ketones*. [In the case of methyl 2-pyridyl ketone, copper(I) iodide was not used in the reaction.]

(**1a**) (239 mg, 72%), yellow *needles* (from EtOH), a 1:4 mixture of two stereoisomers (Found: C, 61.4; H, 4.85. $C_{17}H_{16}O_3S_2$ requires C, 61.42; H, 4.85%); $\nu_{max.}$(KBr) 3 050 (arom. CH), 2 960, 2 900 (CH), 1 640 (CO), 1 320, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.38, 2.43 (3 H, s, Me), 4.30, 5.00 (2 H, s, CH_2), 6.58, 6.70 (1 H, s, CH), and 7.10—8.08 (10 H, m, 2 Ph); *m/z* 332 (M^+).

(**1b**) (297 mg, 82%), pale yellow *prisms*, m.p. 106—107 °C (from EtOH) (Found: C, 59.35; H, 5.15. $C_{18}H_{18}O_4S_2$ requires C, 59.65; H, 5.01%); $\nu_{max.}$(KBr) 3 010 (arom. CH), 2 940, 2 850 (CH), 1 630 (CO), 1 320, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.35 (3 H, s, SMe), 3.88 (3 H, s, OMe), 4.35 (2 H, s, CH_2), 6.73 (1 H, s, CH), 6.88 and 7.70 (4 H, ABq, J_{AB} 9 Hz, 4-$MeOC_6H_4$), and 7.38—8.18 (5 H, m, Ph); *m/z* 362 (M^+).

(**1c**) (345 mg, 94%), brown *plates* (from EtOH), a 1:7 mixture of two stereoisomers (Found: C, 55.5; H, 4.15. $C_{17}H_{15}ClO_3S_2$ requires C, 55.65; H, 4.12%); $\nu_{max.}$(KBr) 3 050 (arom. CH), 3 000 (CH), 1 620 (CO), 1 300, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.43, 2.48 (3 H, s, Me), 4.33, 5.00 (2 H, s, CH_2), 6.70 (1 H, s, CH), and 7.20—8.15 (9 H, m, Ph, 4-ClC_6H_4); *m/z* 366 (M^+).

(**1d**) (298 mg, 78%), yellow *needles* (from EtOH), a 2:5 mixture of two stereoisomers (Found: C, 65.9; H, 4.8. $C_{21}H_{18}O_3S_2$ requires C, 65.94; H, 4.74%); $\nu_{max.}$(KBr) 3 050 (arom. CH), 2 990, 2 900 (CH), 1 640 (CO), 1 310, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.38, 2.45 (3 H, s, Me), 4.33, 5.05 (2

H, s, CH_2), 6.72, 6.78 (1 H, s, CH), and 7.20—8.30 (12 H, m, Ph, $C_{10}H_7$); *m/z* 382 (M^+).

(**1e**) (127 mg, 38%), greenish brown *needles* (from acetone), a 1:5 mixture of two stereoisomers (Found: C, 57.6; H, 4.5; N, 4.15. $C_{16}H_{15}NO_3S_2$ requires C, 57.64; H, 4.53; N, 4.20%); $\nu_{max.}$(KBr) 3 050 (arom. CH), 2 970, 2 890 (CH), 1 650 (CO), 1 310, and 1 140 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.48, 2.52 (3 H, s, Me), 4.38, 5.08 (2 H, s, CH_2), 7.63 (1 H, s, CH), 7.20—8.21 (8 H, m, C_5H_4N, Ph), and 8.43—8.75 (1 H, m, C_5H_4N); *m/z* 286 ($M^+ - 47$).

(**1f**) (230 mg, 69%), yellow *prisms* (from EtOH), a 1:6 mixture of two stereoisomers (Found: C, 57.65; H, 4.6; N, 4.2. $C_{16}H_{15}NO_3S_2$ requires C, 57.64; H, 4.53; N, 4.20%); $\nu_{max.}$(KBr) 3 000 (arom. CH), 2 900 (CH), 1 640 (CO), 1 320, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.50, 2.63 (3 H, s, Me), 4.40, 5.05 (2 H, s, CH_2), 6.58, 6.72 (1 H, s, CH), 7.18—8.16 (7 H, m, C_5H_4N, Ph), and 8.68—9.00 (2 H, m, C_5H_4N); *m/z* 333 (M^+).

(**1g**) (217 mg, 64%), white *prisms* (from $CHCl_3$), a 1:4 mixture of two stereoisomers (Found: C, 53.0; H, 4.15. $C_{15}H_{14}O_3S_3$ requires C, 53.23; H, 4.17%); $\nu_{max.}$(KBr) 3 080 (arom. CH), 2 950, 2 900 (CH), 1 620 (CO), 1 320, and 1 140 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.38, 2.48 (3 H, s, Me), 4.25, 5.01 (2 H, s, CH_2), 6.45 (1 H, s, CH), 6.86—7.20 (1 H, m, C_4H_3S), 7.20—7.68 (5 H, m, C_4H_3S, Ph), and 7.68—8.08 (2 H, m, Ph); *m/z* 338 (M^+).

(**1h**) (154 mg, 57%), white *plates* (from EtOH), a 3:5 mixture of two stereoisomers (Found: C, 53.35; H, 5.12. $C_{12}H_{14}O_3S_2$ requires C, 53.31; H, 5.22%); $\nu_{max.}$(KBr) 3 050 (arom. CH), 2 970, 2 900 (CH), 1 660 (CO), 1 300, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.00 (3 H, s, Me), 2.35 (3 H, s, SMe), 4.18, 4.85 (2 H, s, CH_2), 5.93 (1 H, s, CH), and 7.28—8.10 (5 H, m, Ph); *m/z* 270 (M^+).

Preparation of 1-*Substituted* 1-*Alkoxycarbonyl*-2-*methylthio*-3-*phenylsulphonylpropenes* (**5**)*: General Procedure.*—A 1.7M solution of butyl-lithium (BuLi) in hexane (0.65 ml, 1.1 mmol) was added to di-isopropylamine (0.15 ml, 1.1 mmol) in 2 ml of THF at −70 °C under nitrogen. After the mixture had been stirred for 1 h, the ester (1.0 mmol) in THF (3 ml) was added and the whole stirred for 1 h at −70 °C; *N,N,N',N'*-tetramethylethylene diamine (0.08 ml, 0.55 mmol) was then added followed by (**4**) (130.1 mg, 0.5 mmol) in THF (5 ml). After the mixture had been stirred for 1 h at room temperature it was diluted with water and ethyl acetate and acidified with 2M HCl. The organic layer was dried (Na_2SO_4) and evaporated and the residue purified by t.l.c. on silica gel. Elution with ethyl acetate–hexane (1:2) gave the following new *vinyl esters* (**5**).

(**5a**) (69 mg, 38%), white *needles*, m.p. 114.5—115.5 °C (from EtOH) (Found: C, 59.6; H, 5.0. $C_{18}H_{18}O_4S_2$ requires C, 59.65; H, 5.01%); $\nu_{max.}$(KBr) 1 690 (C=O), 1 315 (SO_2), 1 230 (C–O), and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.33 (3 H, s, SMe), 3.38 (3 H, s, OMe), 5.18 (2 H, s, CH_2), 6.90—7.75 (8 H, m, 2 Ph), and 7.90—8.18 (2 H, m, $PhSO_2$); *m/z* 362 (M^+).

(**5b**) (126 mg, 77%), white *needles*, m.p. 82—83 °C (from EtOH) (Found: C, 54.95; H, 6.15. $C_{15}H_{20}O_4S_2$ requires C, 54.85; H, 6.14%); $\nu_{max.}$(KBr) 2 950, 2 900 (CH), 1 696 (C=O), 1 600 (C=C), 1 340 (SO_2), 1 240 (C–O), and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 1.38 (9 H, s, Me_3C), 2.30 (3 H, s, SMe), 4.93 (2 H, s, CH_2), 5.50 (1 H, s, CH), 7.45—7.70 (3 H, m, Ph), and 7.80—8.10 (2 H, m, Ph); *m/z* 328 (M^+).

Reaction of (**1**) *with Hydroxylamine Hydrochloride: Method A.*—A mixture of (**1**) (0.3 mmol), hydroxylamine hydrochloride (52 mg, 0.75 mmol), 10% aqueous sodium hydroxide (5 ml), and EtOH (5 ml) was refluxed for 20 min. After removal of EtOH under reduced pressure, the residue was extracted with ethyl acetate. Standard work-up yielded the following new 3-substituted 5-(phenylsulphonylmethyl)isoxazoles (**6**).

(**6a**) (83 mg, 93%), white *needles*, m.p. 130—131 °C (from EtOH) (Found: C, 64.25; H, 4.4; N, 4.7. $C_{16}H_{13}NO_3S$ requires C, 64.20; H, 4.38; N, 4.68%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 310, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.61 (2 H, s, CH_2), 6.71 (1 H, s, CH), and 7.25—7.88 (10 H, m, 2 Ph); *m/z* 299 (M^+).

(**6b**) (95 mg, 96%), brown *plates*, m.p. 144 °C (from EtOH) (Found: C, 61.85; H, 4.7; N, 4.3. $C_{17}H_{15}NO_4S$ requires C, 61.99; H, 4.59; N, 4.25%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 300, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.90 (3 H, s, Me), 4.68 (2 H, s, CH_2), 6.75 (1 H, s, CH), 7.05 and 7.85 (4 H, ABq, J_{AB} 9 Hz, 4-$MeOC_6H_4$), and 7.35—8.10 (5 H, m, Ph); *m/z* 329 (M^+).

(**6c**) (84 mg, 84%), white *needles*, m.p. 161—162 °C (from EtOH) (Found: C, 57.4; H, 3.65; N, 4.2. $C_{16}H_{12}ClNO_3S$ requires C, 57.57; H, 3.62; N, 4.20%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 320, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.60 (2 H, s, CH_2), 6.70 (1 H, s, CH), and 7.48—8.10 (9 H, m, 4-ClC_6H_4, Ph); *m/z* 333 (M^+).

(**6d**) (103 mg, 98%), white *plates*, m.p. 164—166 °C (from EtOH) (Found: C, 68.6; H, 4.5; N, 3.95. $C_{20}H_{15}NO_3S$ requires C, 68.75; H, 4.33; N, 4.01%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 330, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.58 (2 H, s, CH_2), 6.80 (1 H, s, CH), 7.08—8.00 (11 H, m, Ph, $C_{10}H_7$), and 8.15 (1 H, s, $C_{10}H_7$); *m/z* 349 (M^+).

(**6e**) (58 mg, 64%), white *needles*, m.p. 140—141 °C (from EtOH) (Found: C, 60.0; H, 4.05; N, 9.3. $C_{15}H_{12}N_2O_3S$ requires C, 59.99; H, 4.03; N, 9.33%); $\nu_{max.}$(KBr) 1 596 (C=N), 1 305, and 1 155 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.67 (2 H, s, CH_2), 7.03 (1 H, s, CH), 7.15—8.18 (8 H, m, C_5H_4N, Ph), and 8.68 (1 H, s, C_5H_4N); *m/z* 300 (M^+).

(**6g**) (82 mg, 90%), white *prisms*, m.p. 123—124 °C (from EtOH) (Found: C, 55.0; H, 3.7; N, 4.45. $C_{14}H_{11}NO_3S_2$ requires 55.07; H, 3.63; N, 4.59%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 310, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.58 (2 H, s, CH_2), 6.60 (1 H, s, CH), 6.93—7.13 (1 H, m, C_4H_3S), and 7.33—8.03 (7 H, m, C_4H_3S, Ph); *m/z* 305 (M^+).

(**6h**) (66 mg, 93%), white *needles*, m.p. 71—72 °C (from EtOH) (Found: C, 55.65; H, 4.65; N, 5.85. $C_{11}H_{11}NO_3S$ requires C, 55.68; H, 4.67; N, 5.90%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 316, and 1 156 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.25 (3 H, s, Me), 4.48 (2 H, s, CH_2), 6.23 (1 H, s, CH), and 7.40—7.93 (5 H, m, Ph); *m/z* 237 (M^+).

Reaction of (**1**) *with Hydroxylamine Hydrochloride: Method B.*— A mixture of (**1**) (0.3 mmol), hydroxylamine hydrochloride (52 mg, 0.75 mmol), tributylamine (0.18 ml, 0.75 mmol), and ethanol (5 ml) was refluxed for 5—24 h. EtOH was removed under reduced pressure and then tributylamine by short column chromatography on silica gel using ethyl acetate as eluant. The resulting oil was purified by t.l.c. on silica gel, eluting with ethyl acetate–benzene (1:5), to give the 1-substituted 3-hydroxyamino-4-phenylsulphonylbut-2-en-1-ones (**7**) and the 1-substituted 3-hydroxyamino-1-hydroxyimino-4-phenylsulphonylbut-2-enes (**8**). In the case of (**1h**), 2-hydroxyimino-4-methylthio-5-phenylsulphonylpent-3-ene (**10**) and 3-methyl-5-methylthio-5-phenylsulphonylmethyl-4,5-dihydroisoxazole (**11**) were obtained instead of (**7**).

(**7a**) (57 mg, 60%), colourless oil; $\nu_{max.}$(neat) 3 400 (NHOH), 1 674 (CO), 1 317, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.19 (2 H, s, CH_2), 3.33, 3.41, 4.36, and 4.43 (2 H, s, NHOH), and 7.20—8.08 (11 H, m, 2 Ph, CH); *m/z* 317 (M^+).

(**7b**) (54 mg, 52%), white powder; $\nu_{max.}$(KBr) 3 300 (NHOH), 1 670 (CO), 1 310, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.88 (3 H, s, CH_3), 4.05—4.40 (2 H, m, NHOH), 4.50 (2 H, s, CH_2), 6.63 (1 H, s, CH), 6.95 and 7.83 (4 H, ABq, J_{AB} 9 Hz, 4-$MeOC_6H_4$), and 7.25—8.18 (5 H, m, Ph); *m/z* 347 (M^+).

(**7c**) (83 mg, 79%), white powder; $\nu_{max.}$(KBr) 3 400 (NHOH), 1 310, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.33, 3.45, 4.28, and 4.38 (2 H, s, NHOH), 4.23 (2 H, s, CH_2), 7.23 (1 H, s, CH), 7.35—8.08 (5 H, m, Ph), and 7.40 (4 H, s, 4-ClC_6H_4); *m/z* 351 (M^+).

(**7d**) (83 mg, 75%), white powder; $\nu_{max.}$(KBr) 3 410 (NHOH), 1 670 (CO), 1 310, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.15 (2 H, s, CH_2), 3.20—3.53, 4.27—4.62 (2 H, br, NHOH), and 7.18—8.20 (13 H, m, Ph, $C_{10}H_7$, CH); *m/z* 367 (M^+).

(**7e**) (71 mg, 74%), white powder; $\nu_{max.}$(KBr) 3 040 (NHOH), 1 600 (CO), 1 300, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.40—3.65, 3.86—4.13 (2 H, br, NHOH), 4.27, 4.40 (2 H, s, CH_2), 6.98—8.11 (9 H, m, Ph, C_5H_4N, CH), and 8.40—8.63 (1 H, m, C_5H_4N); *m/z* 318 (M^+).

(**7g**) (72 mg, 74%), white powder; $\nu_{max.}$(KBr) 3 400 (NHOH), 1 660 (CO), 1 310, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.10 (2 H, s, CH_2), 4.27, 4.40 (2 H, s, NHOH), 6.97—7.25 (2 H, m, C_4H_3S, CH), and 7.25—8.00 (7 H, m, Ph, C_4H_3S); *m/z* 323 (M^+).

(**8a**) (10 mg, 10%), white *powder*, m.p. 144—145 °C (from EtOH) (Found: C, 57.8; H, 4.85; N, 8.4. $C_{16}H_{16}N_2O_4S$ requires C, 57.82; H, 4.85; N, 8.43%); $\nu_{max.}$(KBr) 3 200 (NH, OH), 1 320, and 1 160 cm^{-1} (SO_2); *m/z* 299 ($M^+ - 33$).

(**8b**) (15 mg, 14%), colourless oil; $\nu_{max.}$(neat) 3 350 (NH, OH), 1 310, and 1 160 cm^{-1} (SO_2); *m/z* 329 ($M^+ - 33$).

(**8c**) (2 mg, 2%), colourless oil; $\nu_{max.}$ (neat) 3 300 (NH, OH), 1 310, and 1 150 cm^{-1} (SO_2).

(**8d**) (13 mg, 11%), white powder; $\nu_{max.}$(KBr) 3 250 (NH, OH), 1 310, and 1 160 cm^{-1} (SO_2); *m/z* 349 ($M^+ - 33$).

(**8g**) (4 mg, 4%), white powder; $\nu_{max.}$(KBr) 3 250 (NH, OH), 1 320, and 1 170 cm^{-1} (SO_2); *m/z* 305 ($M^+ - 33$).

(**8h**) (9 mg, 11%), colourless oil; $\nu_{max.}$ (neat) 3 250 (NH, OH), 1 300, and 1 160 cm^{-1} (SO_2); *m/z* 270 (M^+).

(**10**) (21 mg, 24%), colourless oil; $\nu_{max.}$(neat) 3 400 (OH), 1 580 (C=N), 1 305, and 1 146 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 1.71, 1.90 (3 H, s, Me), 2.28 (3 H, s, SMe), 4.12, 4.26 (1 H, s, OH), 4.68 (2 H, s, CH_2), 5.46, 5.72 (1 H, s, CH), 7.41—7.70 (3 H, m, Ph), and 7.77—8.02 (2 H, m, Ph).

(**11**) (28 mg, 33%), white *prisms*, m.p. 79—81 °C (from EtOH) (Found: 50.6; H, 5.3; N, 4.9. $C_{12}H_{15}NO_3S_2$ requires C, 50.51; H, 5.30; N, 4.91%); $\nu_{max.}$(KBr) 3 050 (arom. CH), 2 960, 2 910 (CH), 1 318, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 1.98 (3 H, s, Me), 2.03 (3 H, s, Me), 2.93 (1 H, d, *J* 19 Hz, CH_2), 3.90 (2 H, s, $PhSO_2CH_2$), 4.06 (1 H, d, *J* 19 Hz, CH_2), 7.35—7.75 (3 H, m, Ph), and 7.75—8.00 (2 H, m, Ph); *m/z* 238 ($M^+ - 47$).

Preparation of 5-Substituted 3-(Phenylsulphonylmethyl)-isoxazoles (**9**): *General Procedure*.—To a solution of (**7**) (0.1 mmol) in EtOH (5 ml) was added toluene-*p*-sulphonic acid monohydrate (38.0 mg, 0.2 mmol) and the resulting mixture was refluxed for 3 h. The EtOH was removed, the residue extracted with ethyl acetate, and the extract washed with saturated aqueous sodium hydrogen carbonate; standard work-up yielded the following new isoxazoles (**9**) almost quantitatively.

(**9a**) (54 mg, 60%), white plates, m.p. 160 °C (from EtOH); $\nu_{max.}$(KBr) 1 600 (C=N), 1 300, and 1 170 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.61 (2 H, s, CH_2), 6.76 (1 H, s, CH), and 7.23—7.94 (10 H, m, 2 Ph); *m/z* 299 (M^+).

(**9b**) (51 mg, 52%), white plates, m.p. 145.5—146 °C (from EtOH); $\nu_{max.}$(KBr) 1 620 (C=N), 1 310, and 1 170 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.88 (3 H, s, Me), 4.50 (2 H, s, CH_2), 6.60 (1 H, s, CH), 6.98 and 7.65 (4 H, ABq, J_{AB} 9 Hz, 4-$MeOC_6H_4$), and 7.23—8.00 (5 H, m, Ph); *m/z* 329 (M^+).

(**9c**) (79 mg, 79%), white prisms, m.p. 175 °C (from EtOH; $\nu_{max.}$(KBr) 1 600 (C=N), 1 320, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.58 (2 H, s, CH_2), 6.85 (1 H, s, CH), and 7.23—8.02 (9 H, m, 4-ClC_6H_4, Ph); *m/z* 333 (M^+).

(**9d**) (79 mg, 75%), white prisms, m.p. 193.5—194 °C (from EtOH); $\nu_{max.}$(KBr) 1 580 (C=N), 1 300, and 1 165 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.51 (2 H, s, CH_2), 6.88 (1 H, s, CH), 7.16—8.05 (11 H, m, Ph, $C_{10}H_7$), and 8.25 (1 H, s, $C_{10}H_7$); *m/z* 349 (M^+).

(**9e**) (67 mg, 74%), white prisms, m.p. 156—157 °C (from EtOH); $\nu_{max.}$(KBr) 1 317 and 1 170 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.53 (2 H, s, CH_2), 7.13 (1 H, s, CH), 7.23—7.95 (8 H, m, C_5H_4N, Ph), and 8.85 (1 H, s, C_5H_4N); *m/z* 300 (M^+).

(**9g**) (68 mg, 74%), colourless plates, m.p. 160—161 °C (from EtOH); $\nu_{max.}$(KBr) 1 600 (C=N), 1 300, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 4.45 (2 H, s, CH_2), 6.58 (1 H, s, CH), 6.98—7.23 (1 H, m, C_4H_2S), and 7.35—7.90 (7 H, m, C_4H_3S, Ph); *m/z* 305 (M^+).

Desulphonylation of Compounds (**6a**) *and* (**9a**).—To a solution of (**6a**) (100 mg, 0.33 mmol) and anhydrous disodium hydrogenphosphate (170 mg, 1.2 mmol) in dry methanol (10 ml) was added 5% sodium amalgam (1 g). The reaction mixture was stirred for 2 h, after which it was diluted with water and $CHCl_3$ and the whole filtered through Celite. Work-up afforded a white powder, which was purified by t.l.c. on silica gel, eluting with ethyl acetate–hexane (1:2), to give 5-methyl-3-phenylisoxazole (**17**) (50 mg, 96%), m.p. 39—41 °C (from EtOH) (lit.,[10] 42—43 °C). The same treatment as described above converted (**9a**) (100 mg, 0.33 mmol) into 3-methyl-5-phenylisoxazole (**18**) (51 mg, 98%), m.p. 62—63 °C (from EtOH) (lit.,[10] 67—68 °C).

Preparation of 3-Phenyl-5-(1-substituted phenylsulphonylmethyl)isoxazoles (**14**): *General Procedure*.—To a solution of (**6a**) (100 mg, 0.33 mmol) in THF (5 ml) was added a 1.25M solution of BuLi in hexane (0.29 ml, 0.36 mmol) at −70 °C under nitrogen. The mixture was stirred for 40 min after which alkyl halide (0.36 mmol) was added and the whole stirred for 10 min at −70 °C and then for 1 h at room temperature. After being quenched with water, the mixture was extracted with ethyl acetate and the extract dried (Na_2SO_4) and evaporated. The residue was purified by t.l.c. on silica gel using ethyl acetate–benzene (1:4) as eluant to afford (**14**). The following new isoxazoles were thus prepared.

(**14a**) (49 mg, 47%), white *needles*, m.p. 105—106 °C (from EtOH) (Found: C, 65.15; H, 4.9; N, 4.4. $C_{17}H_{15}NO_3S$ requires C, 65.16; H, 4.82; N, 4.47%); $\nu_{max.}$(KBr) 1 596 (C=N), 1 320, and 1 155 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 1.81 (3 H, d, *J* 7 Hz, Me), 4.58 [1 H, q, *J* 7 Hz, $PhSO_2$ (Me)C*H*], 6.69 (1 H, s, CH), and 7.18—7.93 (10 H, m, 2 Ph); *m/z* 313 (M^+).

(**14b**) (57 mg, 51%), white *plates*, m.p. 75—77 °C (from EtOH) (Found: C, 67.2; H, 5.1; N, 4.1. $C_{19}H_{17}NO_3S$ requires C, 67.24; H, 5.05; N, 4.13%); $\nu_{max.}$(KBr) 1 600 (C=N), 1 324, and 1 160 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 2.90—3.28 (2 H, m, CH_2=CHCH_2), 4.50 (1 H, dd, J_{trans} 18 Hz, J_{cis} 10 Hz, $PhSO_2CH$), 5.03 (1 H, dd, J_{cis} 10 Hz, J_{gem} 1 Hz, CH_2=CH), 5.05 (1 H, dd, J_{trans} 18 Hz, J_{gem} 1 Hz, CH_2=CH), 5.30—6.00 (1 H, m, CH_2C*H*), 6.68 (1 H, s, CH), and 7.20—7.90 (10 H, m, 2 Ph); *m/z* 339 (M^+).

(**14c**) (73 mg, 57%), white *needles*, m.p. 130.5—131 °C (from EtOH) (Found: C, 70.9; H, 4.95; N, 3.6. $C_{23}H_{19}NO_3S$ requires C, 70.93; H, 4.92; N, 3.60%); $\nu_{max.}$(KBr) 1 594 (C=N), 1 308, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.50 (1 H, dd, CH_2), 3.85 (1 H, dd, CH_2), 4.73 (1 H, dd, $PhSO_2CH$), 6.63 (1 H, s, CH), 7.15 (5 H, s, *Ph*CH_2), and 7.30—7.93 (10 H, m, 2 Ph); *m/z* 389 (M^+).

Preparation of 5-Ethyl-3-phenylisoxazole (**15**).—The same treatment as described in the preparation of (**17**) or (**18**) converted (**14a**) (62.7 mg, 0.2 mmol) into (**15**) (27 mg, 78%), m.p. 89—90 °C (from EtOH) (lit.,[11] 92 °C).

Conversion of (**10**) *or* (**11**) *into* (**6h**).—To a solution of (**10**) or (**11**) (0.15 mmol) in EtOH (4 ml) was added 10% aqueous sodium hydroxide (4 ml). The resulting mixture was refluxed for 30 min, evaporated, and the residue extracted with ethyl acetate. Work-up afforded a white powder which was identified as (**6h**) by spectroscopic methods.

Preparation of 2-*Amino*-4-*phenyl*-6-(*phenylsulphonylmethyl*)-*pyrimidine* (**3**).—To sodium (7.6 mg, 0.33 mmol) dissolved in absolute EtOH (5 ml) under nitrogen was added (**1a**) (100 mg, 0.3 mmol) and guanidine hydrochloride (39.0 mg, 0.66 mmol) in absolute EtOH (5 ml). The resulting mixture was refluxed for 2 h, evaporated, and water and $CHCl_3$ added to the residue; the organic layer was separated, dried (Na_2SO_4), and evaporated to give a brown powder (97.6 mg, 100%) which was recrystallized from EtOH to give (**3**) as white prisms, m.p. 213—215 °C (from EtOH) (Found: C, 62.55; H, 4.7; N, 12.9. $C_{17}H_{15}N_3O_2S$ requires C, 62.75; H, 4.65; N, 12.91%); $\nu_{max.}$(KBr) 3 420, 3 290, 3 150 (NH), 1 320, and 1 150 cm^{-1} (SO_2); δ_H (270 MHz, $CDCl_3$) 4.36 (2 H, s, CH_2), 4.98 (2 H, br, NH_2), 7.10 (1 H, s, CH), 7.44—7.97 (10 H, m, 2 Ph); *m/z* 325 (M^+).

Preparation of 2-*Amino*-4-*phenyl*-6-(1-*phenylsulphonyl*-2-*phenyl*)*ethylpyrimidine* (**16**).—A solution of (**3**) (97.6 mg, 0.3 mmol) in THF (5 ml) was added to a 1.25 M solution of BuLi in hexane (0.26 ml, 0.33 mmol) at −70 °C under nitrogen. The mixture was stirred for 40 min after which benzyl bromide (56.4 mg, 0.33 mmol) was added and the stirring continued for 10 min at −70 °C and then for 3 h at room temperature. The mixture was quenched with water, extracted with ethyl acetate, and the extract dried (Na_2SO_4) and evaporated. The residue was purified by t.l.c. on silica gel. Elution with ethyl acetate–hexane (2:3) gave (**16**) (66 mg, 53%) as yellow prisms, m.p. 79—80 °C (from EtOH) (Found: C, 69.1; H, 5.15; N, 10.2. $C_{24}H_{21}N_3O_2S$ requires C, 69.38; H, 5.09; N, 10.11%); $\nu_{max.}$(KBr) 3 450, 3 350, 3 150 (NH), 1 305, and 1 150 cm^{-1} (SO_2); δ_H (60 MHz, $CDCl_3$) 3.63 (1 H, d, *J* 9 Hz, CH_2), 3.64 (1 H, d, *J* 6 Hz, CH_2), 4.03—4.69 (1 H, m, $PhSO_2CH$), 5.35 (2 H, br, NH_2), 6.88 (1 H, s, CH), 7.13 (5 H, s, *Ph*CH_2), and 7.13—8.03 (10 H, m, 2 Ph); *m/z* 415 (M^+).

Preparation of 3-*Hydroxyamino*-4-*phenylsulphonyl*-1-(4-*pyridyl*)*but*-2-*en*-1-*one* (**7f**).—A mixture of (**1f**) (1.0 g, 3 mmol), hydroxylamine hydrochloride (520 mg, 7.5 mmol), triethylamine (1.0 ml, 7.5 mmol), and EtOH (30 ml) was refluxed for 2 h after which EtOH was removed under reduced pressure. The resulting white powder was washed with water. Recrystallization from EtOH yielded (**7f**) (690 mg, 72%) as white crystals; $\nu_{max.}$(KBr) 3 350 (NHOH), 1 600 (CO), 1 320, and 1 170 cm^{-1} (SO_2); *m/z* 318 (M^+).

Preparation of 3-*Phenylsulphonylmethyl*-5-(4-*pyridyl*)-*isoxazole* (**9f**).—Phosphorus pentaoxide (3 g, 0.02 mol) and hexamethyldisiloxane (6 ml, 0.03 mol) were dissolved in dry $CHCl_3$ (10 ml) and the resulting mixture was refluxed until the white suspension had completely disappeared. Compound (**7f**) (300 mg, 0.94 mmol) in dry $CHCl_3$ (10 ml) was added to the clear solution, and the resulting mixture was refluxed for 5 h. After this, saturated aqueous sodium hydrogen carbonate was carefully added to the mixture at 0 °C and the whole extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give a white powder (172 mg, 61%), which recrystallized from EtOH to give (**9f**) as white prisms, m.p. 169—170 °C (from EtOH) (Found: C, 59.95; H, 4.05; N, 9.3. $C_{15}H_{12}N_2O_3S$ requires C, 59.99; H, 4.03; N, 9.33%); $\nu_{max.}$(KBr) 1 580 (C=N), 1 320, and 1 170 cm^{-1} (SO_2); δ_H (270 MHz, $CDCl_3$) 4.53 (2 H, s, CH_2), 6.99 (1 H, s, CH), 7.54—7.79 (7 H, m, C_5H_4N, Ph), and 8.78 (2 H, s, C_5H_4N); *m/z* 300 (M^+).

Preparation of 3-*Methyl*-5-(4-*pyridyl*)*isoxazole* (**2**).—5% Sodium amalgam (3 g) was added to a solution of (**9f**) (120 mg, 0.4 mmol) and anhydrous disodium hydrogenphosphate (227 mg, 1.6 mmol) in dry methanol (10 ml). After being stirred for 2 h the reaction mixture was quenched with water and filtered through Celite. It was then acidified with 2M HCl and washed thrice with ether. After neutralization, the solvent was evaporated and the residue was washed thrice with hot acetone. Removal of acetone from the washings gave (**2**) (51 mg, 80%), m.p. 58—60 °C (from cyclohexane) (lit.,[1] 62—65 °C).

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Received 9th April 1985; *Paper* 5/583