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Unfused Heterobicycles as Amplifiers of Phleomycin. VII* Some Triazolyl-, Thiadiazolyl- and Oxadiazolyl-pyridines and Related Pyrimidines

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Abstract

Syntheses are described for several 4-(1′,2′,4′-triazol-3′-yl)pyridines, 3- and 4-(1′,3′,4′-thiadiazol-2′-yl)-pyridines, 3- and 4-(1′,3′,4′-oxadiazol-2′-yl)pyridines, 5-(1′,3′,4′-thiadiazol-2′-yl)pyrimidines and 5-(1′,3′,4′-oxadiazol-2′-yl)pyrimidines, all provided with a β-dimethylaminoethylthio side chain at the 5-position of the five-membered ring. The activities of these compounds as amplifiers of phleomycin-G against an *in vitro* culture of *Escherichia coli B* are tabulated and discussed.

Several unfused heterobicyclic systems with an attached basic side chain have shown appreciable activity as amplifiers of the antibiotic, phleomycin, in a bacterial system.[1–4] To date, systems composed of a five- and a six-membered ring[3,4] have proven generally superior to those consisting of two six-membered rings.[2] Thus thiazolylpyridines[3] and thienylpyrimidines[4] were outstanding although thiazolylpyrimidines[4] proved disappointing.

We now report preparations and activities for several triazolyl-, thiadiazolyl- and oxadiazolyl-pyridines, as well as some thiadiazolyl- and oxadiazolyl-pyrimidines, all bearing a sulfur-linked basic side chain.

Syntheses

Isonicotinohydrazide (1a) was converted by a known route[5] into the pyridinyltriazolethione (2a) which was treated with 2-chloro-*N*,*N*-dimethylethylamine to afford the potential amplifier (3a), isolated and tested for convenience as its dihydrobromide. To eliminate the undesirable[1] anionic centre in the latter, the same hydrazide

* Part VI, *Aust. J. Chem.*, 1982, **35**, 1209.

[1] Brown, D. J., and Grigg, G. W., *Med. Res. Rev.*, 1982, **2**, 193; Brown, D. J., Cowden, W. B., Grigg, G. W., and Kavulak, D., *Aust. J. Chem.*, 1980, **33**, 2291.

[2] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1981, **34**, 1353; Kowalewski, A., Strekowski, L., Szadja, M., Walenciak, K., and Brown, D. J., *Aust. J. Chem.*, 1981, **34**, 2629; Brown, D. J., and Cowden, W. B., *Aust. J. Chem.*, 1982, **35**, 1203.

[3] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423.

[4] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1982, **35**, 1209.

[5] Beyerman, H. C., Bontekoc, J. S., Burg, W. J. van der, and Veer, W. L. C., *Recl Trav. Chim. Pays-Bas*, 1954, **73**, 109.

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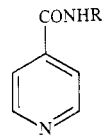
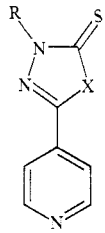
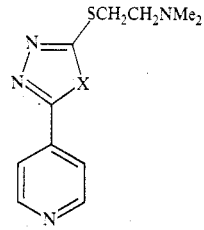
(1a) was first treated with methyl isothiocyanate to give the 4-methylated thiosemicarbazide (1b) which underwent alkaline cyclization to the *N*-methylated thione (2b) followed by *S*-alkylation to the amplifier (3b) devoid of anionic potential. In a second bid to achieve the same end, 2′-methylisonicotinohydrazide (1c) was allowed to react with thiocyanic acid to afford the 2-methylated thiosemicarbazide (1d) and thence the thione (2c) and the amplifier (4); the thione (2c) was made also by heating ethyl isonicotinimidate with 2-methyl(thiosemicarbazide).



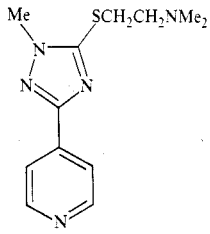
(1a) R = NH_2
(1b) R = NHCSNHMe
(1c) R = NHMe
(1d) R = $NMeCSNH_2$
(1e) R = $NHCS_2K$



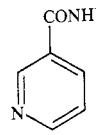
	R	X
(2a)	H	NH
(2b)	H	NMe
(2c)	Me	NH
(2d)	H	S
(2e)	H	O



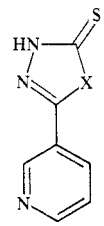
(3a) X = NH
(3b) X = NMe
(3c) X = S
(3d) X = O



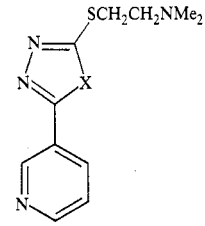
(4)



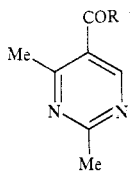
(5a) R = NH_2
(5b) R = $NHCS_2K$



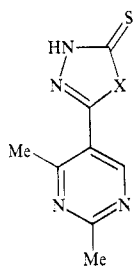
(6a) X = S
(6b) X = O



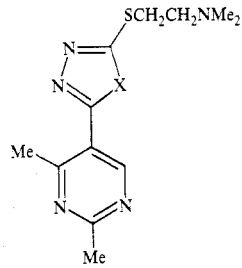
(7a) X = S
(7b) X = O



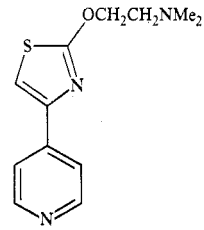
(8a) R = OEt
(8b) R = $NHNH_2$
(8c) R = $NHNHCS_2K$



(9a) X = S
(9b) X = O



(10a) X = S
(10b) X = O



(11)

Because imidazolylpyridines had proven much less active than thiazolylpyridines,[1] we then sought to replace one of the triazole-nitrogen atoms in the above amplifiers by a sulfur or oxygen atom. Thus isonicotinohydrazide (1a) was treated with carbon

disulfide in potassium hydroxide at room temperature to give potassium isonicotinyldithiocarbazate (1e) which was converted by concentrated sulfuric acid into the pyridin-4-ylthiadiazolethione (2d) and thence in the usual way into the amplifier (3c); a similar process converted nicotinohydrazide (5a) successively into the dithiocarbazate (5b), the pyridin-3-ylthiadiazolethione (6a) and the amplifier (7a) in which the pyridine nitrogen was displaced from *para* to *meta* position (cf.[1]). In contrast, treatment of isonicotinohydrazide (1a) or its isomer (5a) with carbon disulfide in ethanolic sodium hydroxide under reflux for several hours, followed by acidification, gave immediately the pyridin-4-yloxadiazolethione (2e) or its isomer (6b) which underwent *S*-alkylation normally to the amplifier (3d) or (7b), respectively.

In view of the essential balance of heteroatoms existing in the intercalating bithiazole portion of the phleomycin molecule and in many active amplifiers so based,[3,4] we thought to redress any imbalance in the above amplifiers (3c/d) and (7a/b) by replacing the pyridine with a pyrimidine ring. Accordingly, the pyrimidine ester (8a) was submitted to hydrazinolysis and the resulting hydrazide (8b) was transformed into the dithiocarbazate (8c) whence ring closure in sulfuric acid gave the thiadiazolethione (9a) and subsequent alkylation the amplifier (10a); rather similarly, treatment of the hydrazide (8b) with carbon disulfide in refluxing ethanolic sodium ethoxide gave on acidification the oxadiazolethione (9b) and thence the required amplifier (10b).

Activities as Amplifiers

The activities as amplifiers of phleomycin-G against *Escherichia coli* were measured *in vitro* by a procedure closely akin to that previously published:[3] as before, results are recorded for simplicity in Table 1 on a 1–5 star scale on which the standard control amplifier, caffeine, scored 1-star activity.

Table 1. Activities as amplifiers of phleomycin
Measured at 2 mM: for details see ref. 3

Compound	Activity	Compound	Activity
(3a)	*	(7a)	***
(3b)	**	(7b)	**
(3c)	****	(10a)	***
(3d)	***	(10b)	**
(4)	*	(11)	***

As might have been expected from results in a series of purine amplifiers,[6] the mildly acidic NH group in the triazolylpyridine (3a) was so little anionized at biological pH that its removal, by methylation in the derivatives (3b) and (4), caused only a minor improvement to 2-star activity in the former and none in the latter. Thus even the non-anionic triazolylpyridines showed far lower activities than the corresponding thiazolylpyridines.[3] However, replacement of one nitrogen atom in the triazole ring by a sulfur atom did cause a dramatic improvement in that the thiadiazolylpyridines (3c) and (7a) reached 4- and 3-star activity, respectively; similar replacement of

[6] Angyal, A. M., Grigg, G. W., Badger, R. J., Brown, D. J., and Lister, J. H., *J. Gen. Microbiol.*, 1974, **85**, 163.

nitrogen by oxygen was not as successful but the oxadiazolyl analogues (3d) and (7b) did reach 3- and 2-star activity, respectively. Increasing the nitrogen content of the six-member ring resulted in a mild 1-star decrease of activity in the thia- and oxa-diazolylpyrimidines (10a) and (10b) when compared with the corresponding thia- and oxa-diazolylpyridines (3c) and (3d); this last comparison was complicated by the presence of two *C*-methyl groups on the pyrimidine ring but experience has shown[1,6,7] that such groups usually increase rather than decrease activities.

We have included in Table 1 the result for a thiazolylpyridine (11) bearing an oxygen-linked basic side chain, omitted in error from an earlier paper[3] in which side-chain linkages were compared for efficiency in that system. With 3-star activity, the ether-linked amplifier (11) fell far short of its 5-star thioether- or NH-linked analogues although comparable with its 3-star amide- or directly carbon-linked analogues.

Experimental

Analyses were done by the Australian National University Analytical Services Unit. N.m.r. spectra were measured at 90 MHz and 30° in $CDCl_3$ with chemical shifts in δ from internal Me_4Si. Melting points were uncorrected.

N,N-*Dimethyl-2-[5'-(pyridin-4''-yl)-1',2',4'-triazol-3'-ylthio]ethylamine* (*3a*)

Isonicotinohydrazide (1a) was converted[5] into 5-(pyridin-4'-yl)-1,2,4-triazole-3(2*H*)-thione (2a). To a stirred suspension of this material (0·71 g) in ethanol (10 ml) was added solid sodium methoxide (0·45 g) followed by 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·63 g). The mixture was then heated under reflux for 4 h. After chilling, sodium chloride was filtered off. The residue, from evaporation of the filtrate under reduced pressure, was dissolved in ethanol (20 ml). The solution was mixed with ethanol containing hydrogen bromide (*c.* 0·65 g), boiled briefly and refrigerated to give the *dihydrobromide* (61%), m.p. 199–201° (from ethanol) (Found: C, 32·3; H, 4·4; N, 17·0; S, 7·6. $C_{11}H_{17}Br_2N_5S$ requires C, 32·1; H, 4·2; N, 17·0; S, 7·8%) (cf. the corresponding monohydrochloride made by a different procedure[8] in 18% yield).

N,N-*Dimethyl-2-[4'-methyl-5'-(pyridin-4''-yl)-1',2',4'-triazol-3'-ylthio]ethylamine* (*3b*)

Isonicotinohydrazide (1a) (5·48 g), methyl isothiocyanate (2·92 g) and ethanol (50 ml) were boiled under reflux for 25 min. The mixture was refrigerated and then filtered to give 1-isonicotinoyl-4-methyl(thiosemicarbazide) (95%), m.p. > 215° (dec.) (cf.[8] 80%, 221–223°). This thiosemicarbazide (1b) (2·10 g) and 1 M sodium hydroxide (6·0 ml) were heated on the steam bath for 30 min. The cooled solution was diluted with water (10 ml) and then adjusted to pH 2–3 by the addition of 2 M hydrochloric acid. Recrystallization of the solid from methanol gave 4-methyl-5-(pyridin-4'-yl)-1,2,4-triazole-3(2*H*)-thione (2b) (78%), m.p. 284–285° (cf. lit.[8] 63%, m.p. 287°). The thione (0·79 g) was dissolved in water (10 ml) by the addition of 2 M sodium hydroxide. 2-Chloro-*N,N*-dimethylethylamine hydrochloride (0·86 g) was added to this solution which was then adjusted to pH 9·5 and stirred at 60° for 50 min. The cooled mixture was adjusted to pH 12 with 10 M sodium hydroxide and then extracted with chloroform (4 × 15 ml). The (weighed) residue from evaporation of the dehydrated extract was dissolved in ethanol (10 ml) and mixed with fresh ethanolic hydrogen bromide (2 equiv.). After boiling for a moment, the solution was chilled to give the product (3b) as *dihydrobromide* (46%), m.p. 226–227° (dec.) (Found: C, 34·1; H, 4·6; N, 16·3. $C_{12}H_{19}Br_2N_5S$ requires C, 33·9; H, 4·5; N, 16·5%). N.m.r. (base) 8·76, m, H2'',6''; 7·61, m, H3'',5''; 3·70, s, 4'-Me; 3·47, t, H2; 2·73, t, H1; 2·29, s, NMe_2.

[7] Brown, D. J., Grigg, G. W., Iwai, Y., McAndrew, K. N., Nagamatsu, T., and van Heeswyck, R., *Aust. J. Chem.*, 1979, **32**, 2713.
[8] Jones, D. H., Slack, R., Squires, S., and Wooldridge, K. R. H., *J. Med. Chem.*, 1965, **8**, 676.

N,N-*Dimethyl-2-[2'-methyl-5'-(pyridin-4''-yl)-1',2',4'-triazol-3'-ylthio]ethylamine (4)*

(A) 2'-Methylisonicotinohydrazide[9] (1c) (4·80 g), sodium thiocyanate (6·48 g) and 2·5 M hydrochloric acid (25 ml) were heated on the steam bath for 2 h. The cooled solution was adjusted to pH 4 with 2 M sodium hydroxide and refrigerated to give crude 1-isonicotinoyl-2-methyl(thiosemicarbazide) (1d), which was filtered off and dried prior to heating under reflux in 2 M sodium hydroxide (15 ml) for 2 h. The cooled mixture was adjusted to pH 4 with concentrated hydrochloric acid to give crude 2-methyl-5-(pyridin-4'-yl)-1,2,4-triazole-3(2*H*)-thione (2c) (13%), m.p. >290°.

(B) Alternatively, ethyl isonicotinimidate[10] (3·0 g) and finely powdered 2-methyl(thiosemicarbazide)[11] (2·1 g) were heated in xylene (25 ml) under reflux for 2 h. The residue from evaporation under reduced pressure crystallized from ethanol to give the same *thione* (31%), m.p. >290° (Found: C, 49·9; H, 4·1; N, 29·0. $C_8H_8N_4S$ requires C, 50·0; H, 4·2; N, 29·1%).

The above thione (0·79 g) was converted, as in the preparation of (3b) above, into the product (4) which was isolated as a *dihydrobromide* (52%), m.p. 252–254° (Found: C, 33·9; H, 4·5; N, 16·5. $C_{12}H_{19}Br_2N_5S$ requires C, 33·9; H, 4·5; N, 16·5%). N.m.r. (base) 8·66, m, H2'',6''; 7·90, m, H3'',5''; 3·78, s, 2'-Me; 3·42, t, H2; 2·68, t, H1; 2·28, s, NMe_2.

N,N-*Dimethyl-2-[5'-(pyridin-4''-yl)-1',3',4'-thiadiazol-2'-ylthio]ethylamine (3c)*

Isonicotinohydrazide (10·96 g) was dissolved at room temperature in ethanol (80 ml) containing potassium hydroxide (5·3 g). Carbon disulfide (6·25 g) was then added with stirring, which was continued for 1 h. Filtration gave crude potassium 3-isonicotinoyldithiocarbazate (1e) (80%), m.p. 315–318° (cf.[12] >300°) which was washed with ethanol and then ether, followed by drying in a vacuum: it was reasonably stable to storage under nitrogen. This salt (5·0 g) was added slowly with stirring to concentrated sulfuric acid (25 ml) maintained at −5°. Stirring was continued for an additional 5 min and then the reaction mixture was poured slowly into hand-stirred crushed ice (*c.* 250 g). After 10 min, the solid was filtered off. It was washed with water and recrystallized from methanol to give 5-(pyridin-4'-yl)-1,3,4-thiadiazole-2(3*H*)-thione (2d) (51%), m.p. 288–291° (cf. 278–280° for material made in lower yield by a longer route[13]). This thione (0·78 g) was *S*-alkylated, as in the preparation of (3b), to give the product (3c) as its *dihydrobromide* (50%), m.p. 244–246° (dec.) (Found: C, 30·8; H, 3·9; N, 13·1. $C_{11}H_{16}Br_2N_4S_2$ requires C, 30·9; H, 3·8; N, 13·1%). N.m.r. (base) 8·75, m, H2'',6''; 7·74, m, H3'',5''; 3·58, t, H2; 2·76, t, H1; 2·32, s, NMe_2.

N,N-*Dimethyl-2-[5'-(pyridin-3''-yl)-1',3',4'-thiadiazol-2'-ylthio]ethylamine (7a)*

By procedures similar to those used to prepare the isomer (3c), nicotinohydrazide (5a) was converted successively into crude potassium 3-nicotinoyldithiocarbazate (5b) (94%); 5-(pyridin-3'-yl)-1,3,4-thiadiazole-2(3*H*)-thione (6a) (33%), m.p. 275–280° (cf.[14] 30%, 219–221°) (Found: C, 42·9; H, 2·5; N, 21·4. Calc. for $C_7H_5N_3S_2$: C, 43·1; H, 2·6; N, 21·4%); and the product (7a) as its *dihydrobromide* (47%), m.p. 190–192° (Found: C, 30·8; H, 3·7; N, 12·8. $C_{11}H_{16}Br_2N_4S_2$ requires C, 30·9; H, 3·8; N, 13·1%). N.m.r. (base) 8·21, m, H2'',4''–6''; 3·56, t, H2; 2·76, t, H1; 2·31, s, NMe_2.

N,N-*Dimethyl-2-[5'-(pyridin-4''-yl)-1',3',4'-oxadiazol-2'-ylthio]ethylamine (3d)*

Isonicotinohydrazide (1a) (3·43 g) was dissolved in ethanolic sodium hydroxide (1%; 100 ml) at 20°. Carbon disulfide (2·0 g) was added and the mixture was heated under reflux for 3·5 h. The residue from evaporation was dissolved in water (50 ml) and then adjusted to pH *c.* 3 with concentrated hydrochloric acid. The solid was filtered off and washed with water followed by acetone to give 5-(pyridin-4'-yl)-1,3,4-oxadiazole-2(3*H*)-thione (2e) (78%), m.p. 270° (cf.[13,15] 49–57%, 269–273°).

[9] Cymerman-Craig, J., and Willis, D., *J. Chem. Soc.*, 1955, 4315.
[10] Schaefer, F. L., and Peters, G. A., *J. Org. Chem.*, 1961, **26**, 412.
[11] Greer, A. H., and Smith, G. B. L., *J. Am. Chem. Soc.*, 1950, **72**, 874.
[12] Ainsworth, C., *J. Am. Chem. Soc.*, 1956, **78**, 4475.
[13] König, H. B., Siefken, W., and Offe, H. A., *Chem. Ber.*, 1954, **87**, 825.
[14] Baron, M., and Wilson, C. V., *J. Org. Chem.*, 1958, **23**, 1021.
[15] Young, R. W., and Wood, K. H., *J. Am. Chem. Soc.*, 1955, **77**, 400.

This thione was treated with 2-chloro-*N,N*-dimethylethylamine, as in the preparation of (3b) above to give the product (3d) as *dihydrobromide* (32%), m.p. 210–211° (from methanol) (Found: C, 32·2; H, 4·0; N, 13·7. $C_{11}H_{16}Br_2N_4OS$ requires C, 32·1; H, 3·9; N, 13·6%). N.m.r. (base) 8·80, m, H2″,6″; 7·85, m, H3″,5″; 3·49, t, H2; 2·76, t, H1; 2·32, s, NMe_2.

N,N-*Dimethyl-2-*[*5′-(pyridin-3″-yl)-1′,3′,4′-oxadiazol-2′-ylthio*]*ethylamine* (*7b*)

As in the preceding preparation, nicotinohydrazide (5a) was converted into 5-(pyridin-3″-yl)-1,3,4-oxadiazole-2(3*H*)-thione (6b) (85%), m.p. 233–235° (cf.[12] 72%, 235–237°), and thence into the product (7b) as its hygroscopic *dihydrobromide* (30%), m.p. 174–176° (from methanol) (Found: C, 32·1; H, 4·0; N, 13·7. $C_{11}H_{16}Br_2N_4OS$ requires C, 32·1; H, 3·9; N, 13·6%). N.m.r. (base) 8·30, m, H2″,4″–6″; 3·49, t, H2; 2·76, t, H1; 2·31, s, NMe_2.

5-(2′,4′-Dimethylpyrimidin-5′-yl)-1,3,4-thiadiazole-2(3H)-*thione* (*9a*)

Ethyl 2,4-dimethylpyrimidine-5-carboxylate[16] (8a) (3·60 g) was added with stirring to hydrazine hydrate (15·0 ml) in methanol (10 ml) maintained at 20°. Stirring was continued at 20° for 20 min and then at 40–45° for 10 min. After chilling, filtration gave *2,4-dimethylpyrimidine-5-carbohydrazide* (8b) (83%), m.p. 175–176° (from methanol) (Found: C, 50·7; H, 6·0; N, 33·9. $C_7H_{10}N_4O$ requires C, 50·6; H, 6·1; N, 33·7%). N.m.r. [$(CD_3)_2SO$] 9·63, s, br, NH; 8·54, s, H6; 4·51, s, br, NH_2; 2·59, s, 2-Me; 2·50, s, 4-Me.

The hydrazide (1·66 g) was dissolved in ethanol (15 ml) containing potassium hydroxide (85%: 0·67 g) and to the stirred solution was added carbon disulfide (0·84 g). After stirring this mixture for 1 h at 20–25°, potassium 3-(2′,4′-dimethylpyrimidin-5′-ylcarbonyl)dithiocarbazate (8c) (*c.* 96%) was filtered off. This crude salt (2·0 g) was added in small portions to concentrated sulfuric acid (8·0 ml) at <2°. After stirring for an additional 5 min, the mixture was poured into crushed ice (*c.* 25 g) and the solution, maintained at 0°, was adjusted to pH 2 by the slow addition of 10 M sodium hydroxide. The solid was removed, washed with water, and recrystallized from methanol to give the *thiadiazolethione* (9a) (50%), m.p. 228–230° (Found: C, 42·9; H, 3·7; N, 24·9. $C_8H_8N_4S_2$ requires C, 42·9; H, 3·6; N, 25·0%). N.m.r. 8·67, s, H6′; 2·76, s, 2′-Me; 2·72, s, 4′-Me.

2-[*5′-(2″,4″-Dimethylpyrimidin-5″-yl)-1′,3′,4′-thiadiazol-2′-ylthio*]-N,N-*dimethylethylamine* (*10a*)

To a suspension of the thione (9a) (0·56 g) in water (10 ml) was added 2 M sodium hydroxide until solution was complete. 2-Chloro-*N,N*-dimethylethylamine hydrochloride (0·39 g) was added with stirring and the solution adjusted subsequently to pH 8–9 with 2 M sodium hydroxide. The mixture was stirred at 20° for 10 min and then at 50° for 20 min. It was then cooled to 0°, adjusted to pH 12 with 10 M sodium hydroxide, and extracted with ether (3 × 20 ml). The dehydrated extracts were evaporated to give the *base* (10a) (47%), m.p. 75–76° (from light petroleum) (Found: C, 48·7; H, 5·7; N, 23·8. $C_{12}H_{17}N_5S_2$ requires C, 48·8; H, 5·8; N, 23·7%). N.m.r. 8·80, s, H6″; 3·57, t, H2; *c.* 2·8, t (partly obscured), H1; 2·77, s, 2″-Me; 2·72, s, 4″-Me; 2·32, s, NMe_2.

5-(2′,4′-Dimethylpyrimidin-5′-yl)-1,3,4-oxadiazole-2(3H)-*thione* (*9b*)

The hydrazide (8b) (1·10 g) was dissolved in ethanol containing sodium methoxide (0·36 g). Carbon disulfide (0·51 g) was added to the solution which was then heated under reflux for 3·5 h. The residue from evaporation was dissolved in water (10 ml) and adjusted to pH 3 with concentrated hydrochloric acid. Refrigeration gave the *oxadiazolethione* (9b) (64%), m.p. 198–199° (from isopropyl alcohol) (Found: C, 46·3; H, 3·8; N, 26·7. $C_8H_8N_4OS$ requires C, 46·2; H, 3·9; N, 26·9%). N.m.r. [$(CD_3)_2SO$] 8·96, s, H6′; 2·70, s, 2′-Me; 2·67, s, 4′-Me.

2-[*5′-(2″,4″-Dimethylpyrimidin-5″-yl)-1′,3′,4′-oxadiazol-2′-ylthio*]-N,N-*dimethylethylamine* (*10b*)

The *S*-alkylation of this oxadiazolethione was done as for its thiadiazolethione analogue (9a), to give the *base* (10b) (42%), m.p. 78–79° (from light petroleum) (Found: C, 51·4; H, 6·1; N, 25·2. $C_{12}H_{17}N_5OS$ requires C, 51·6; H, 6·1; N, 25·1%). N.m.r. 9·01, s, H6″; 3·49, t, H2; *c.* 2·8, t (partly obscured), H1; 2·87, s, 2″-Me; 2·76, s, 4″-Me; 2·33, s, NMe_2.

[16] Urban, R., and Schnider, O., *Helv. Chim. Acta*, 1958, **41**, 1806.

N,N-*Dimethyl-2-[4′-(pyridin-4″-yl)thiazol-2′-yloxy]ethylamine* (*11*)

4-(2′-Methylsulfonylthiazol-4′-yl)pyridine[3] (0·38 g) was added to a solution of potassium t-butoxide (0·18 g) in 2-dimethylaminoethanol (5·0 ml) with stirring at 20°. After stirring this mixture for a further 3 h, the residue from removal of solvent under reduced pressure was broken up and extracted with chloroform (3 × 10 ml). The residue from evaporating the extracts was weighed, dissolved in ethanol (5 ml) and treated with fresh 10% hydrogen bromide in ethanol (2 equiv.). The mixture was warmed and then chilled to give the product as *dihydrobromide* (69%), m.p. 181–185° (from ethanol) (Found: C, 35·2; H, 4·3; N, 10·3. $C_{12}H_{17}Br_2N_3OS$ requires C, 35·1; H, 4·2; N, 10·2%). N.m.r. (base) 8·50, m, H2″,6″; 7·58, m, H3″,5″; 7·05, s, H5′; 4·45, t, H2; 2·66, t, H1; 2·25, s, NMe_2.

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