Aust. J. Chem., 1985, **38**, 1257–61

Unfused Heterobicycles as Amplifiers of Phleomycin. VIII* Some Bithiazoles; Thienyl-, Furanyl- and Thiazolyl-thiadiazoles and Related Oxadiazoles

William B. Cowden,[A,B] *Sean J. Sullivan*[A] *and Desmond J. Brown*[A]

[A] John Curtin School of Medical Research, Australian National University, P.O. Box 334, Canberra, A.C.T. 2601.
[B] Author to whom correspondence should be addressed.

Abstract

Syntheses are described for several unfused heterobicycles including 4,5′- and 2,4′-bithiazoles, 5-(thiazol-4′ and 5′-yl)-1,3,4-thiadiazoles, 5-(thien-2′-yl)-, 5-(furan-2′ and 3′-yl)-, thiadiazoles and related oxadiazoles, all with side chains containing dialkylamine terminal groups. The activities of these compounds as amplifiers of phleomycin-G are reported.

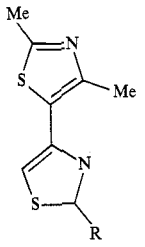
Within the general framework of compounds which amplify the activity of phleomycin as an antibacterial[1] or antitumour agent,[2] we have recently synthesized several promising derivatives of unfused heterobicycles.[3–5] This work is now extended by the preparation of appropriate derivatives of systems composed of two five-membered heterocyclic rings.

Thus, 2′,4′-dimethyl-4,5′-bithiazole-2(3*H*)-thione and 2-chloro-*N*,*N*-dimethylethylamine or 3-chloro-*N*,*N*-dimethylpropylamine gave the corresponding amplifiers, (1a) and (1b), respectively; rather similarly, 5-bromoacetyl-2,4-dimethylthiazole was converted into the bithiazolylethylamine (1c) by reaction with 3-dimethylamino-(thiopropanamide) and 2-bromoacetyl-4-methylthiazole likewise into the analogue (2). Treatment of 2,4-dimethyl-5-thiazolecarbohydrazide with carbon disulfide and potassium hydroxide gave the corresponding dithiocarbazate which underwent cyclization in sulfuric acid to the thiazolylthiadiazolethione (3a) and thence alkylation

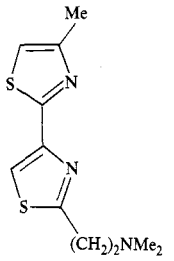
* Part VII, *Aust. J. Chem.*, 1983, **36**, 1469.

[1] Brown, D. J., and Grigg, G. W., *Med. Res. Rev.*, 1982, **2**, 193.
[2] Allen, T. E., Brown, D. J., Cowden, W. B., Grigg, G. W., Hart, N. K., Lamberton, J. A., and Lane, A., *J. Antibiot.*, 1984, **37**, 376; Aliano, A. N., Allen, T. E., Brown, D. J., Cowden, W. B., Grigg, G. W., Kavulak, D., and Lan, S.-B., *Aust. J. Chem.*, 1984, **37**, 2385.
[3] Brown, D. J., Cowden, W. B., Grigg, G. W., and Kavulak, D., *Aust. J. Chem.*, 1980, **33**, 2291; Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1982, **35**, 1209; Brown, D. J., and Cowden, W. B., *Aust. J. Chem.*, 1983, **36**, 1469.
[4] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423.
[5] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1981, **34**, 1353; Kowalewski, A., Strekowski, L., Szajda, 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.

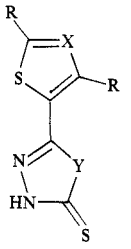
0004-9425/85/081257$02.00



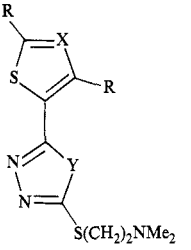
(1a) R = $S(CH_2)_2NMe_2$
(1b) R = $S(CH_2)_3NMe_2$
(1c) R = $CH_2CH_2NMe_2$



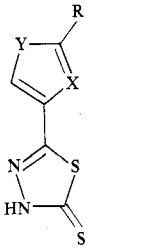
(2)



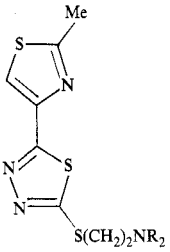
	R	X	Y
(3a)	Me	N	S
(3b)	H	CH	S
(3c)	H	CH	O



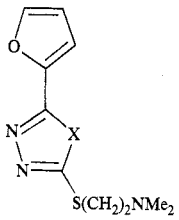
	R	X	Y
(4a)	Me	N	S
(4b)	H	CH	S
(4c)	H	CH	O



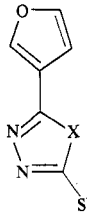
	R	X	Y
(5a)	Me	N	S
(5b)	H	CH	O



(6a) R = Me
(6b) R = Et



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



	X	R
(8a)	S	$CH_2CH_2NMe_2$
(8b)	O	H
(8c)	O	$CH_2CH_2NMe_2$

to the amplifier (4a); 2-methyl-4-thiazolecarbohydrazide was converted similarly into the thione (5a) and then the amplifiers (6a) and (6b). Other desirable variations included the conversions of the 5-thione (3b) and the corresponding oxadiazole (3c) into the alkylated derivatives (4b) and (4c); 5-(furan-2′-yl)-1,3,4-thiadiazole-2(3*H*)-thione and its isomer (5b) into their derivatives (7a) and (8a); and 5-(furan-2′-yl)-1,3,4-oxadiazole-2(3*H*)-thione and its isomer (8b) into the derivatives (7b) and (8c).

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.

2-(2″,4″-Dimethyl-4′,5″-bithiazol-2′-ylthio)-N,N-dimethylethylamine (1a)

To 2′,4′-dimethyl-4,5′-bithiazole-2(3*H*)-thione hydrobromide[6] (0·31 g, 1·0 mmol) in water (5 ml) was added 10 M sodium hydroxide to pH 9–10, followed by 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0·16 g, 1·1 mmol). The solution was readjusted to pH 9–10, stirred for 10 min at 20° and then for 20 min at 60°. On cooling, it was adjusted to pH 10–11. The mixture was extracted with ether (3 × 20 ml) and the combined extracts were dried over sodium sulfate. The weighed residue from evaporation was dissolved in ethanol (10 ml) and treated with dry hydrogen bromide (2 equiv.) The mixture was boiled briefly before cooling to give the *dihydrobromide* (0·27 g, 57%), m.p. 227–229° (dec.) (from ethanol) (Found: C, 31·4; H, 4·3; N, 9·1; S, 20·9. $C_{12}H_{19}Br_2N_3S_3$ requires

[6] Hibino, T., Suzuki, Y., Okano, S., Hara, Y., and Sato, E., Ger. Offen. 2,341,753 (1974) (*Chem. Abstr.*, 1974, **80**, 133421).

C, 31·3; H, 4·2; N 9·1; S 20·9%). N.m.r. (base) 7·00, s, H 5′; 3·33, t, H 2; 2·67, t, H 1; 2·26, s, NMe_2.

3-(2″,4″-Dimethyl-4′,5″-bithiazol-2′-ylthio)-N,N-*dimethylpropylamine* (*1b*)

As in the preceeding preparation, the same thione was alkylated with 3-chloro-*N*,*N*-dimethylpropylamine hydrochloride to give the *dihydrobromide* (48%), m.p. 225° (dec.) (Found: C, 33·0; H, 4·4; N, 8·8. $C_{13}H_{21}Br_2N_3S_3$ requires C, 32·9; H, 4·5; N, 8·8%). N.m.r. (base) 7·02, s, H 5′; 3·22, t, H 3; 2·58, s, Me; 2·53, s, Me; 2·17, s, NMe_2.

2-(2″,4″-Dimethyl-4′,5″-bithiazol-2′-yl)-N,N-*dimethylethylamine* (*1c*)

3-Dimethylamino(thiopropanamide) hydrochloride[7] (1·68 g, 10 mmol) and 5-bromoacetyl-2,4-dimethylthiazole hydrobromide[8] (3·15 g, 10 mmol) were stirred at 25° in ethanol (20 ml) for 20 min and then heated under reflux for 2 h. After cooling, the solid was filtered off and washed with acetone, followed by ether (2 × 20 ml). A suspension in water (20 ml) was adjusted to pH 10–11 with 10 M sodium hydroxide and extracted with ether (5 × 50 ml). The weighed residue from evaporation of the extracts was treated in ethanol (20 ml) with dry hydrogen bromide (2 equiv.), boiled briefly and cooled. The resulting solid recrystallized from ethanol to give the *dihydrobromide* (2·6 g, 60%), m.p. 200–201° (Found: C, 33·5; H, 4·5; N, 9·6; S, 14·8. $C_{12}H_{19}Br_2N_3S_2$ requires C, 33·6; H, 4·5; N, 9·8; S, 14·9%). N.m.r. (base) 7·02, s, H 5′; 3·12, t, H 2; 2·68, t, H 1; 2·60, s, Me; 2·53, s, Me; 2·25, s, NMe_2.

N,N-*Dimethyl-2-(4′-methyl-2′,4″-bithiazol-2″-yl)ethylamine* (*2*)

Crude 2-bromoacetyl-4-methylthiazole hydrobromide[8] (2·11 g, 7·0 mmol) and 3-dimethylamino(thiopropanamide) hydrochloride[7] (1·18 g, 7·0 mmol) were boiled under reflux in ethanol (10 ml) for 3 h. The volume was reduced to *c.* 5 ml under diminished pressure and cooled. The solid was filtered off, dissolved in water (8 ml), adjusted to pH 10 and extracted with chloroform (3 × 10 ml). The combined extracts were dried (sodium sulfate), filtered and evaporated under reduced pressure. The weighed residue in ethanol (5 ml) was treated with dry hydrogen bromide (2 equiv.), boiled briefly and cooled. The resulting *dihydrobromide* (0·2 g, 7%) had m.p. 205–206° (from ethanol) (Found: C, 31·9; H, 4·2; N, 10·0; S, 15·3. $C_{11}H_{17}Br_2N_3S_2$ requires C, 31·8; H, 4·1; N, 10·1; S, 15·4%).

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

2,4-Dimethylthiazole-5-carbohydrazide[9] (4·0 g, 23·4 mmol) was dissolved in ethanol (50 ml) containing potassium hydroxide (85%; 1·54 g, 23·4 mmol) and to the stirred solution was added carbon disulfide (1·80 g, 23·7 mmol). After stirring for 30 min the solid was filtered off, washed with ether and dried to give the crude potassium dithiocarbazate (6·33 g) which was added in small portions to concentrated sulfuric acid (20 ml) at < 5°. The mixture was stirred for an additional 5 min and then poured into crushed ice (500 g); the solid was filtered off, washed well with water and recrystallized from methanol to give the *thione* (3a) (3·1 g, 54%), m.p. 254–256° (Found: C, 36·7; H, 3·1; N, 18·4. $C_7H_7N_3S_3$ requires C, 36·7; H, 3·1; N, 18·3%). N.m.r. [$(CD_3)_2SO$] 2·66, s, Me; 2·49, s, Me.

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

Ethyl 2-methylthiazole-4-carboxylate[10] (5·0 g, 29·2 mmol) and hydrazine hydrate (3·0 g, 60 mmol) were stirred in methanol (25 ml) at 60° for 1 h. The mixture was evaporated under reduced pressure and the solid recrystallized from propan-2-ol to give *2-methylthiazole-4-carbohydrazide* (3·52 g, 77%), m.p. 126–127°. Sublimation gave an analytical sample (Found: C, 38·5; H, 4·5; N, 26·5. $C_5H_7N_3OS$ requires C, 38·2; H, 4·5; N, 26·7%). N.m.r. [$(CD_3)_2SO$] 9·48, s, (br), NH; 8·06, s, H 5′; 4·48, s, (br), NH_2; 2·68, s, Me.

[7] Sallay, S., U.S. Pat. 3,474,100 (1969) (*Chem. Abstr.*, 1970, **72**, 3506).
[8] Okamiya, J., *Nippon Kagaku Zasshi*, 1966, **87**, 594.
[9] Takata, Y., Yamamoto, K., and Takata, Y., *Yakugaku Zasshi*, 1953, **73**, 126.
[10] Jones, E. R. H., Robinson, F. A., and Strachan, M. N., *J. Chem. Soc.*, 1946, 87.

This hydrazide was treated as in the preceding preparation to give the corresponding potassium dithiocarbazate (92%), from which was formed the *thione* (5a) (48%), m.p. 228–230° (Found: C, 33·7; H, 2·4; N, 19·5. $C_6H_5N_3S_3$ requires C, 33·5; H, 2·3; N, 19·5%). N.m.r. [$(CD_3)_2SO$] 8·22, s, H 5′; 2·71, s, Me.

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

The thione (3a) was alkylated with 2-chloro-*N,N*-dimethylethylamine and treated with dry hydrogen bromide, as for the preparation of (1a) above, to give the *hydrobromide* (40%), m.p. 199–202° (from ethanol) (Found: C, 34·5; H, 4·5; N, 14·5. $C_{11}H_{17}BrN_4S_3$ requires C, 34·6; H, 4·5; N, 14·7%). N.m.r. (base) 3·53, t, H 2; 2·75, t, H 1; 2·70, s, Me; 2·62, s, Me; 2·31, s, NMe_2.

N,N-*Dimethyl-2-[5′-(2″-methylthiazol-4″-yl)-1′,3′,4′-thiadiazol-2′-ylthio]ethylamine (6a)*

The thione (5a) was alkylated, as for (1a) above, to give the free *ethylamine* (68%), m.p. 66–68° (from light petroleum, b.p. 60–80°) (Found: C, 42·1; H, 5·0; N, 19·3. $C_{10}H_{14}N_4S_3$ requires C, 41·9; H, 4·9; N, 19·6%). N.m.r. 7·95, s, H 5′; 3·51, t, H 2; 2·73, t, H 1; 2·75, s, Me; 2·31, s, NMe_2. This was treated with dry hydrogen bromide in ethanol to give the *hydrobromide*, m.p. 214–215° (from ethanol) (Found: C, 32·6; H, 4·1; N, 15·2. $C_{16}H_{15}BrN_4S_3$ requires C, 32·7; H, 4·1; N, 15·2%).

N,N-*Diethyl-2-[5′-(2″-methylthiazol-4″-yl)-1′,3′,4′-thiadiazol-2′-ylthio]ethylamine (6b)*

Alkylation of the thione (5a) with 2-chloro-*N,N*-diethylethylamine, as for (1a) above, gave the *ethylamine* (6b) (83%), m.p. 52–53° (from light petroleum, b.p. 40–60°) (Found: C, 45·9; H, 5·7; N, 17·7. $C_{12}H_{18}N_4S_3$ requires C, 45·8; H, 5·8; N, 17·8%). N.m.r. 7·94, s, H 5′; 3·47, t, H 2; 2·88, t, H 1; 2·75, s, Me; 2·60, q, CH_2; 1·05, t, Me. This was treated with dry hydrogen bromide in ethanol to give the corresponding *hydrobromide*, m.p. 204–206° (from ethanol) (Found: C, 36·6; H, 4·8; N, 14·2. $C_{12}H_{19}BrN_4S_3$ requires C, 36·5; H, 4·8; N, 14·2%).

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

5-(Thien-2′-yl)-1,3,4-thiadiazol-2(3*H*)-thione[11] (3b) was alkylated with 2-chloro-*N,N*-dimethylethylamine and treated with dry hydrogen bromide (1 equiv.), as for (1a) above, to give the *hydrobromide* (29%), m.p. 164–165° (Found: C, 34·4; H, 4·0; N, 11·9. $C_{10}H_{14}BrN_3S_3$ requires C, 34·1; H, 4·0; N, 11·9%).

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

5-(Thien-2′-yl)-1,3,4-oxadiazole-2(3*H*)-thione[12] (3c) alkylated with 2-chloro-*N,N*-dimethylethylamine and treated with dry hydrogen bromide, as for the preparation of (1c) above, to give the *hydrobromide* (21%), m.p. 125–127° (from propan-2-ol/acetone) (Found: C, 36·0; H, 4·4; N, 12·3. $C_{10}H_{14}BrN_3OS_2$ requires C, 35·7; H, 4·2; N, 12·5%).

2-[5′-(Furan-2″-yl)-1′,3′,4′-thiadiazol-2′-ylthio)]-N,N-dimethylethylamine (7a)

5-(Furan-2′-yl)-1,3,4-thiadiazole-2(3*H*)-thione[13] was alkylated with 2-chloro-*N,N*-dimethylethylamine in the usual manner and the product treated with dry hydrogen bromide to give the *hydrobromide* (47%), m.p. 163–164° (Found: C, 35·7; H, 4·3; N, 12·4. $C_{10}H_{14}BrN_3OS_2$ requires C, 35·7; H, 4·2; N, 12·5%).

*5-(Furan-3′-yl)-1,3,4-thiadiazole-2(3*H*)-thione (5b)*

Furan-3-carbohydrazide[14] (5·5 g, 43·6 mmol) was dissolved in methanol containing potassium hydroxide (85%; 2·87 g, 43·6 mmol) and to this solution was added carbon disulfide (3·31 g, 43·6 mmol) and the mixture was stirred for 45 min. The solid was filtered off, washed with ether

[11] Kochhar, M. M., Salahi-Asbahi, M., and Williams, B. B., *J. Pharm. Sci.*, 1973, **62**, 336.
[12] Debourge, J. C., Pillon, D., and Trinh, S., Ger. Offen. 2,361,613 (1974) (*Chem. Abstr.*, 1974, **81**, 91537).
[13] Baron, M., and Wilson, C. V., *J. Org. Chem.*, 1958, **23**, 1021.
[14] Burtner, R. R., *J. Am. Chem. Soc.*, 1934, **56**, 666.

and dried to give the corresponding potassium dithiocarbazate (9·84 g, 94%). This material (2·4 g, 10 mmol) was added in small portions to concentrated sulfuric acid (25 ml) at $< 5°$. After the final addition the mixture was stirred for a further 5 min and poured onto crushed ice (200 g). The solid was filtered off, washed with water and recrystallized from ethanol to give the *thione* (5b) (0·59 g, 34%), m.p. 177–180° (dec.) (Found: C, 39·4; H, 2·2; N, 15·0. $C_6H_4N_2OS_2$ requires C, 39·1; H, 2·2; N, 15·2%).

2-[5′-(Furan-3″-yl)-1′,3′,4′-thiadiazol-2′-ylthio)]-N,N-dimethylethylamine (8a)

The thione (5b) was alkylated and converted into the salt, as in the preparation of (1a) above, to give the *hydrobromide* (39%), m.p. 167–168° (Found: C, 35·9; H, 4·4; N, 12·4. $C_{10}H_{14}BrN_3OS_2$ requires C, 35·7; H, 4·2; N, 12·5%).

2-[5′-(Furan-2″-yl)-1′,3′,4′-oxadiazol-2′-ylthio)]-N,N-dimethylethylamine (7b)

5-(Furan-2′-yl)-1,3,4-oxadiazole-2(3*H*)-thione[15] was alkylated in the usual manner with 2-chloro-*N*,*N*-dimethylethylamine and treated with dry hydrogen bromide to give the *hydrobromide* (45%), m.p. 132–133° (Found: C, 37·6; H, 4·4; N, 13·0. $C_{10}H_{14}BrN_3O_2S$ requires C, 37·5; H, 4·4; N, 13·1%).

5-(Furan-3′-yl)-1,3,4-oxadiazole-2(3H)-thione, Tautomer (8b)

The potassium dithiocarbazate, from the preparation of (5b) above, (1·0 g, 4·17 mmol) was heated under reflux in 95% ethanol (25 ml) with 10 M sodium hydroxide (2 drops) for 3·5 h. The ethanol was removed under reduced pressure and the residue was dissolved in water (10 ml) and adjusted to pH 3 with concentrated hydrochloric acid. Chilling gave the *thione* (81%), m.p. 153–154° (Found: C, 43·4; H, 2·5; N, 16·9. $C_6H_4N_2O_2S$ requires C, 43·4; H, 2·4; N, 16·9%).

2-[5′-(Furan-3″-yl)-1′,3′,4′-oxadiazol-2′-ylthio)]-N,N-dimethylethylamine (8c)

The thione (8b) was alkylated and converted into the salt in the usual manner to give the *hydrobromide* (57%), m.p. 146–148° (Found: C, 37·6; H, 4·4; N, 13·0. $C_{10}H_{14}BrN_3O_2S$ requires C, 37·5; H, 4·4; N, 13·1%).

Activities as Amplifiers

When screened[4] at 0·5–3·3 mM concentration for amplification of phleomycin-G against an *in vitro* culture of *Escherichia coli*, compounds (1a) and (1b) showed 5-star activity; compounds (1c) and (2) showed 3- and 2-star activities, respectively; the thiadiazoles (4a), (4b), (6a), (6b), (7a) and (8a) showed 2-star activity; and the oxadiazoles (4c), (7b) and (8c) showed 1-star activity.

Acknowledgments

We thank Dr G. W. Grigg and Mrs D. Kavulak, CSIRO Division of Molecular Biology, for screening the amplifiers.

Manuscript received 3 May 1985

[15] Young, R. W., and Wood, K. H., *J. Am. Chem. Soc.*, 1955, **77**, 400.