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Unfused Heterobicycles as Amplifiers of Phleomycin. VI† Some Thienyl- and Thiazolyl-pyrimidines with Strongly Basic Side Chains

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Abstract

2-Chloro-4-(thien-2′-yl)pyrimidine (2a) and its thiazol-2′-yl analogue (2d) are prepared by condensation of 2-chloropyrimidine with thien-2-yl- and thiazol-2-yl-lithium, followed by oxidation of the dihydro intermediates. 4-Chloro-6-methyl-2-(thien-2′-yl)pyrimidine (3b), its 2-(2′,4′-dimethylthiazol-5′-yl) analogue (3f) and the 2-(2′-methylthiazol-4′-yl) analogue (4b) are made from the corresponding pyrimidinones, which are available by primary synthesis. Each chloro compound is converted by nucleophilic displacement into its β-dimethylaminoethylamino and β-dimethylaminoethylthio derivatives, for which activities as amplifiers of phleomycin are reported and discussed.

Of the unfused heterobicyclic systems tested *in vitro* for activity as amplifiers of phleomycin,[1–5] thiazolylpyridines carrying a strongly basic side chain have proven consistently effective.[1,3] Bearing in mind that replacement of a pyridine by a pyrimidine ring in fused heterobicyclic amplifiers usually improved activity and biostability,[6,7] we now report syntheses and activities for several thiazolylpyrimidines and some deaza (i.e. thienyl) analogues, each with a strongly basic side chain attached.

Syntheses

The 4-(thien-2′-yl)- and 4-(thiazol-2′-yl)-pyrimidines were approached by treating 2-chloropyrimidine with thien-2-yl- and thiazol-2-yl-lithium, respectively. The resulting dihydropyrimidines (1a) and (1b) were oxidized by permanganate in acetone to yield the chloro intermediates (2a) and (2d), each of which was allowed to react

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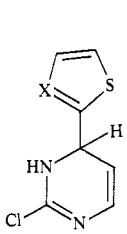
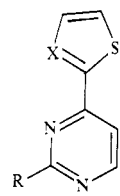
[1] Brown, D. J., Cowden, W. B., Grigg, G. W., and Kavulak, D., *Aust. J. Chem.*, 1980, **33**, 2291.
[2] Brown, D. J., Cowden, W. B., and Strekowski, L., *Aust. J. Chem.*, 1981, **34**, 1353.
[3] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423.
[4] Kowalewski, A., Strekowski, L., Szajda, M., Walenciak, K., and Brown, D. J., *Aust. J. Chem.*, 1981, **34**, 2629.
[5] Brown, D. J., and Cowden, W. B., *Aust. J. Chem.*, 1982, **35**, 1203.
[6] Brown, D. J., Dunlap, W. C., Grigg, G. W., Danckwerts, L., and Nagamatsu, T., *Aust. J. Chem.*, 1978, **31**, 397; Brown, D. J., Grigg, G. W., Iwai, Y., McAndrew, K. N., Nagamatsu, T., and van Heeswyck, R., *Aust. J. Chem.*, 1979, **32**, 2713; Brown, D. J., and Iwai, Y., *Aust. J. Chem.*, 1979, **32**, 2727.
[7] Brown, D. J., and Grigg, G. W., *Med. Res. Rev.*, 1982, **2**, 191.

in turn with 2-dimethylaminoethylamine and 2-dimethylaminoethanethiolate to give amplifiers (2b), (2c), (2e) and (2f).

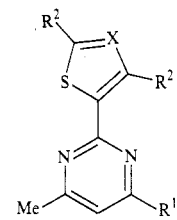
The 2-(thien-2′-yl)- and 2-(thiazol-5′-yl)-pyrimidines were made by initially treating ethyl thiophen-2-carboxylate and methyl 2,4-dimethylthiazole-5-carboxylate with 3-aminocrotonamide in alcoholic alkoxide to give the thienylpyrimidinone[5] (3a)† and the thiazolylpyrimidinone (3e). These were converted by phosphoryl chloride into the chloropyrimidines (3b) and (3f) from which were made the amplifiers (3c), (3d), (3g) and (3h).



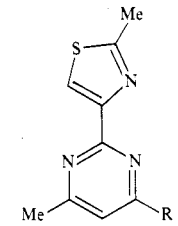
(1a) X = CH
(1b) X = N



	X	R
(2a)	CH	Cl
(2b)	CH	$NH(CH_2)_2NMe_2$
(2c)	CH	$S(CH_2)_2NMe_2$
(2d)	N	Cl
(2e)	N	$NH(CH_2)_2NMe_2$
(2f)	N	$S(CH_2)_2NMe_2$



	X	R^1	R^2
(3a)	CH	OH	H
(3b)	CH	Cl	H
(3c)	CH	$NH(CH_2)_2NMe_2$	H
(3d)	CH	$S(CH_2)_2NMe_2$	H
(3e)	N	OH	Me
(3f)	N	Cl	Me
(3g)	N	$NH(CH_2)_2NMe_2$	Me
(3h)	N	$S(CH_2)_2NMe_2$	Me



(4a) R = OH
(4b) R = Cl
(4c) R = $NH(CH_2)_2NMe_2$
(4d) R = $S(CH_2)_2NMe_2$

Table 1. Activities as amplifiers of phleomycin

Measured at 3·3 mM; for details see ref. 3

Compound	Activity	Compound	Activity	Compound	Activity
(2b)	**	(3c)	*	(4c)	*
(2c)	*****	(3d)	*	(4d)	**[B]
(2e)	*	(3g)	*[A]		
(2f)	**	(3h)	***		

[A] Almost **. [B] Almost ***.

The 2-(thiazol-4′-yl)pyrimidines were made rather similarly. Condensation of ethyl 2-methylthiazole-4-carboxylate with 3-aminocrotonamide gave the thiazolylpyrimidinone (4a) which was converted into the chloro analogue (4b) and thence into the strongly basic derivatives (4c) and (4d).

Activities as Amplifiers

Activities as amplifiers of phleomycin-G were measured against *Escherichia coli B* by an *in vitro* method recently described.[3] The results (Table 1) indicated that a sulfur-linked side chain was superior in most cases to the corresponding amine-linked

† This and other pyrimidinones are shown in their tautomeric hydroxy forms to avoid excessive illustrations.

side chain [cf. (2b) and (2c); (2e) and (2f); (3g) and (3h); (4c) and (4d)]. It was also evident that the relative orientation of the two rings could be important. Thus the 4-thienylpyrimidine (2c) was very highly active, whereas the 2-thienylpyrimidine (3d), which differed only in orientation (apart from a single extra *C*-methyl group) was but slightly active. On the other hand, the 2-(thiazol-5′-yl)pyrimidine (3h) differed very little in activity from the nearly isomeric 2-(thiazol-4′-yl)pyrimidine (4d), despite the difference in orientation. Another anomaly also became evident: replacement of the thien-2-yl ring in the amplifier (2c) by a thiazol-2-yl ring to give the analogue (2f) reduced activity from 5- to 2-star; in contrast, a similar replacement, (3d) → (3h), produced an increase in activity from 1- to 3-star.

In surveying the above and other results for such unfused amplifiers,[1–5] it emerged that optimal (5-star) activity had been achieved only in amplifiers characterized by one or two sulfur-linked basic side chains and by at least one six-membered heterocyclic ring with a basic centre (ring-nitrogen) *para* to the bond joining the two rings. However, these criteria were insufficient in themselves to ensure 5-star activity in a heterobicyclic system and other yet-undefined factors (such as the degree of coplanarity in the system) were clearly involved.

Experimental

Analyses were done by Analytical Service Units in the Australian National University and the Uniwersytet im Adama Mickiewicza. The n.m.r. spectra (chemical shifts in δ; J values in Hz) were measured (unless indicated otherwise) at 60 MHz and 33° in $CDCl_3$ against Me_4Si as internal standard. Melting points were uncorrected.

2-Chloro-4-(thien-2′-yl)pyrimidine (2a)

Thien-2-yllithium was prepared by adding 15% butyllithium in hexane (Fluka: 16·6 ml) to thiophen (2·1 g) in ether (50 ml) at 20°. This solution was maintained at *c.* −40° while a solution of 2-chloropyrimidine[8] (2·86 g) in ether (100 ml) was added slowly with stirring during 10 min. After the temperature had risen to *c.* 0°, the reaction mixture was stirred with water (50 ml) and extracted with ether (2 × 100 ml). Evaporation of the dehydrated extract gave crude 2-chloro-4-(thien-2′-yl)-3,4-dihydropyrimidine (1a) (4·7 g), ν_{max} 2900 cm^{-1} (NH).

This material (4·6 g) was dissolved in acetone (1200 ml) before treatment (cf.[9]) with potassium permanganate (2·35 g) to give the *chlorothienylpyrimidine* (3·7 g), m.p. 125–127° (after sublimation at 0·05 mm and subsequent recrystallization from acetone/hexane) (Found: C, 48·6; H, 2·4; N, 14·5. $C_8H_5ClN_2S$ requires C, 48·9; H, 2·6; N, 14·2%). N.m.r. [$(CD_3)_2CO$] 8·77, d, J 5·5, H6; 8·15, dd, J 4·0, 1·2, H3′; 7·97, d, J 5·5, H5; 7·93, dd, J 5·0, 1·2, H5′; 7·33, dd, J 5·0, 4·0, H4′.

N-(2″-Dimethylaminoethyl)-4-(thien-2′-yl)pyrimidin-2-amine (2b)

The chlorothienylpyrimidine (2a) (1·5 g), 2-dimethylaminoethylamine (2·0 ml) and ethanol (2·0 ml) were heated under reflux for 20 min. Chromatographic purification [three Merck silica gel plates (2 by 200 by 200 mm); benzene/triethylamine/ethanol (90 : 7 : 3)] gave the required amine (2b) as an oil (n.m.r. 8·35, d, J 5·5, H6; 7·75, dd, J 3·8, 1·2, H3′; 7·53, dd, J 5·0, 1·2, H5′; 7·17, dd, J 5·0, 3·8, H4′; 6·88, d, J 5·5, H5; 6·00, s, br, NH; 3·62, q, J 6·0, H1″; 2·60, t, J 6·0; H2″; 2·32, s, NMe_2). The oil (0·5 g) was added to a mixture of 40% hydrobromic acid (0·3 ml) and ethanol (20 ml) followed by benzene (20 ml). Removal of volatiles under reduced pressure gave the *hydrobromide*, m.p. 160–163° (from ethanol) (Found: C, 43·5; H, 5·1; N, 16·7. $C_{12}H_{17}BrN_4S$ requires C, 43·8; H, 5·2; N, 17·0%).

[8] Sperber, N., Papa, D., Schwenk, E., Sherlock, M., and Fricano, R., *J. Am. Chem. Soc.*, 1951, **73**, 5752.

[9] Bredereck, H., Gompper, R., and Herlinger, H., *Chem. Ber.*, 1958, **91**, 2832; Gronowitz, S., and Röe, J., *Acta Chem. Scand.*, 1965, **19**, 1741.

N,N-*Dimethyl-2-[4'-(thien-2''-yl)pyrimidin-2'-ylthio]ethylamine* (*2c*)

2-Dimethylaminoethanethiol hydrochloride (1·7 g) was added to ethanolic sodium ethoxide [from ethanol (100 ml) and sodium (0·55 g)]. This solution and the chlorothienylpyrimidine (2a) (2·1 g) were boiled under reflux for 5 h. Filtration from salt, evporation and subsequent chromatography [four Merck silica gel plates; benzene/triethylamine (3 : 1)] gave an oil (2c) (1·25 g) (n.m.r. 8·43, d, *J* 5·2, H6′; 7·73, dd, *J* 3·8, 1·2, H3″; 7·53, dd, *J* 5·0, 1·2, H5″; 7·18, d, *J* 5·2, H5′; 7·13, dd, *J* 5·0, 3·8, H4″; 3·35, t, *J* 7·0, H2; 2·73, t, *J* 7·0, H1; 2·37, s, NMe_2) which was converted as above into its *hydrobromide*, m.p. 207–209° (from ethanol) (Found: C, 41·5; H, 4·4; N, 12·1. $C_{12}H_{16}BrN_3S_2$ requires C, 41·6; H, 4·4; N, 12·1%).

2-Chloro-4-(thiazol-2′-yl)pyrimidine (*2d*)

Thiazol-2-yllithium was made by adding 15% butyllithium in hexane (27 ml) to 2-bromothiazole[10] (6·95 g) in ether (150 ml) at −45°. Treatment of the solution with 2-chloropyrimidine[8] (4·85 g) in ether (150 ml), as for the thienyl analogue (2a) above, gave 2-chloro-4-(thiazol-2′-yl)-3,4-dihydropyrimidine (1b) (8·0 g), ν_{max} 2900 cm^{-1} (NH). Oxidation in acetone/dimethylformamide with permanganate (3·1 g) yielded the *chlorothiazolylpyrimidine* (3·5 g), m.p. 153–155° (after sublimation and recrystallization from acetone/hexane) (Found: C, 42·4; H, 2·0; N, 21·2. $C_7H_4ClN_3S$ requires C, 42·5; H, 2·0; N, 21·3%). N.m.r. [$(CD_3)_2CO$] 8·92, d, *J* 4·8, H6; 8·18, d, *J* 4·8, H5; 8·15, d, *J* 3·2, H4′; 8·02, d, *J* 3·2, H5′.

N-(*2″-Dimethylaminoethyl*)-*4-(thiazol-2′-yl)pyrimidin-2-amine* (*2e*)

The above chloro compound (2d) (1·42 g) and 2-dimethylaminoethylamine (2·0 ml) were allowed to stand at 25° for 4 h. Chromatography [three Merck silica gel plates; benzene/triethylamine (3 : 1)] gave the *amine* (0·88 g), m.p. 76–77·5° (from ether/light petroleum) (Found: C, 52·8; H, 6·1; N, 28·0. $C_{11}H_{15}N_5S$ requires C, 53·0; H, 6·1; N, 28·1%). N.m.r. 8·45, d, *J* 5·2, H6; 8·00, d, *J* 3·2, H4′; 7·52, d, *J* 3·2, H5′; 7·37, d, *J* 5·2, H5; 5·80, s, br, NH; 3·58, q, *J* 6·0, H1″; 2·57, t, *J* 6·0, H2″; 2·32, s, NMe_2.

N,N-*Dimethyl-2-[4′-(thiazol-2″-yl)pyrimidin-2′-ylthio]ethylamine* (*2f*)

Prepared as its thiethyl analogue (2c), but from the chlorothiazolylpyrimidine (2d) (2·1 g), the *product* (2f) (1·8 g) had m.p. 53–54·5° (from ether/light petroleum) (Found: C, 49·7; H, 5·3; N, 21·1. $C_{11}H_{14}N_4S_2$ requires C, 49·6; H, 5·3; N, 21·0%). N.m.r. 8·65, d, *J* 5·2, H6′; 8·03, d, *J* 3·2, H4″; 7·77, d, *J* 5·2, H5′; 7·60, d, *J* 3·2, H5″; 3·40, t, *J* 7·0, H2; 2·75, t, *J* 7·0, H1; 2·37, s, NMe_2.

4-Chloro-6-methyl-2-(thien-2′-yl)pyrimidine (*3b*)

6-Methyl-2-(thien-2′-yl)pyrimidin-4(3*H*)-one[5] (3a) (1·0 g) and phosphoryl chloride (10 ml) were heated under reflux for 2 h. The residue from evaporation of volatiles was stirred with crushed ice and extracted with ether. Removal of the ether gave the *chloro compound* (91%), m.p. 87–88° (after sublimation) (Found: C, 51·6; H, 3·5; N, 13·0; S, 14·9. $C_9H_7ClN_2S$ requires C, 51·3; H, 3·4; N, 13·3; S, 15·2%).

N-(*2″-Dimethylaminoethyl*)-*6-methyl-2-(thien-2′-yl)pyrimidin-4-amine* (*3c*)

The foregoing chloro compound (0·18 g) and 2-dimethylaminoethylamine (3·0 ml) were heated under reflux for 1·5 h. The residue from removal of the excess of amine under reduced pressure was suspended in 2 M sodium hydroxide (5 ml) and extracted with ether. Evaporation of the dehydrated extract gave an oil which was weighed, dissolved in ethanol (4 ml) and mixed with hydrogen bromide (2 equiv.) in ethanol (*c.* 2 ml). The mixture was raised to boiling point and then chilled to give the product (3c) as its *dihydrobromide* (36%), m.p. 288–289° (from ethanol) (Found: C, 36·9; H, 4·7; N, 13·1; S, 7·6. $C_{13}H_{20}Br_2N_4S$ requires C, 36·8; H, 4·8; N, 13·2; S, 7·6%). N.m.r. (base) 7·45, m, H3′–5′; 6·00, s, H5; 3·42, q, H1″; 2·66, t, H2″; 2·41, s, 6-Me.

[10] Ganapathi, K., and Venkataraman, A., *Proc. Indian Acad. Sci., Ser. A*, 1945, **22**, 362.

N,N-*Dimethyl-2-[6'-methyl-2'-(thien-2''-yl)pyrimidin-4'-ylthio]ethylamine* (*3d*)

The chloro compound (3b) (0·21 g), 2-dimethylaminoethanethiol hydrochloride (0·16 g), potassium t-butoxide (0·25 g) and ethanol (8·0 ml) were heated under reflux for 2·5 h. Workup as for the foregoing analogue (3c) gave the product (3d) as *dihydrobromide* (48%), m.p. 291–292° (from ethanol) (Found: C, 35·6; H, 4·6; N, 9·5; S, 14·4. $C_{13}H_{19}Br_2N_3S_2$ requires C, 35·4; H, 4·3; N, 9·5; S, 14·5%).

2-(2',4'-Dimethylthiazol-5'-yl)-6-methylpyrimidin-4(3H)-one (*3e*)

Methyl 2,4-dimethylthiazole-5-carboxylate[11] (3·42 g), fresh 3-aminocrotonamide (3·0 g) and methanolic sodium methoxide [from methanol (35 ml); sodium (1·15 g)] were heated under reflux for 3·5 h. The residue from evaporation was dissolved in water (20 ml) and adjusted to pH 6 with concentrated hydrochloric acid. Chilling gave the required *pyrimidinone* (37%), m.p. 227–230° (from ethanol) (Found: C, 54·5; H, 5·0; N, 19·2; S, 14·4. $C_{10}H_{11}N_3OS$ requires C, 54·3; H, 5·0; N, 19·0; S, 14·5%). N.m.r. (90 MHz, 30°) 6·20, s, H5; 2·71, s, 4'-Me; 2·69, s, 2'-Me; 2·34, s, 6-Me.

4-Chloro-2-(2',4'-dimethylthiazol-5'-yl)-6-methylpyrimidine (*3f*)

The foregoing pyrimidinone (0·8 g) and phosphoryl chloride (7·0 ml) were heated under reflux for 3 h. The residue from evaporation was added to ice and the mixture was adjusted at 0–3° to pH 8–9 by means of 10 M sodium hydroxide. Ether extraction and evaporation of the extract gave a crude product which was dissolved in cyclohexane and filtered. Removal of the solvent gave the *chloro compound* (95%), m.p. 135–136° (after sublimation) (Found: C, 50·2; H, 4·3; N, 17·5; S, 13·7. $C_{10}H_{10}ClN_3S$ requires C, 50·1; H, 4·2; N, 17·5; S, 13·4%).

N-(*2''-Dimethylaminoethyl*)-*2-(2',4'-dimethylthiazol-5'-yl)-6-methylpyrimidin-4-amine* (*3g*)

The chloro compound (3f) (0·36 g) and 2-dimethylaminoethylamine (3 ml) were treated as described for the thienyl analogue (3c) to give the *thiazolylpyrimidinamine dihydrobromide* (74%), m.p. 276–278° (from ethanol) (Found: C, 37·3; H, 5·3; N, 15·1; S, 6·8. $C_{14}H_{23}Br_2N_5S$ requires C, 37·1; H, 5·1; N, 15·4; S, 7·1%). N.m.r. (base in $CDCl_3+D_2O$; 90 MHz, 30°) 6·01, s, H5; 3·45, t, H1''; 2·84, s, 4'-Me; 2·65, s, 2'-Me; 2·53, t, H2''; 2·32, s, 6-Me; 2·26, s, NMe_2.

2-[2'-(2'',4''-Dimethylthiazol-5''-yl)-6'-methylpyrimidin-4'-ylthio]-N,N-dimethylethylamine (*3h*)

The chloro compound (3f) (0·45 g), 2-dimethylaminoethanethiol hydrochloride (0·27 g), sodium hydroxide (0·16 g) and ethanol (15 ml) were boiled under reflux for 2·5 h. The residue from evaporation was added to 2 M sodium hydroxide (8 ml) and subsequent workup as for the analogue (3d) gave the product (3h) as *dihydrobromide* (58%), m.p. 243–245° (from ethanol) (Found: C, 36·1; H, 4·9; N, 11·8; S, 13·6. $C_{14}H_{22}Br_2N_4S_2$ requires C, 35·8; H, 4·7; N, 11·9; S, 13·6%). N.m.r. (base; 90 MHz, 30°) 6·75, s, H5'; 3·36, t, H2; 2·86, s, 4''-Me; 2·67, s, 2''-Me; 2·66, t, H1; 2·40, s, 6'-Me; 2·31, s, NMe_2.

6-Methyl-2-(2'-methylthiazol-4'-yl)pyrimidin-4(3H)-one (*4a*)

Ethyl 2-methylthiazole-4-carboxylate[12] (2·57 g) and fresh 3-aminocrotonamide (2·7 g) were condensed, as described for the analogue (3e), to give the *pyrimidinone* (27%), m.p. 189–190° (from water then ethanol) (Found: C, 52·2; H, 4·2; N, 20·5; S, 15·7. $C_9H_9N_3OS$ requires C, 52·2; H, 4·4; N, 20·3; S, 15·5%). N.m.r. 10·80, s, br, NH; 8·11, s, H5'; 6·10, s, H5; 2·72, s, 2'-Me; 2·28, s, 6-Me.

4-Chloro-6-methyl-2-(2'-methylthiazol-4'-yl)pyrimidine (*4b*)

The foregoing pyrimidinone (1·2 g) and phosphoryl chloride (20 ml) were heated under reflux for 2 h and then treated as for the analogue (3f) to give the *chloro compound* (4b) (84%), m.p. 78–79°

[11] Hantzsch, A., *Justus Liebigs Ann. Chem.*, 1888, **250**, 257.
[12] Jones, E. R. H., Robinson, F. A., and Strachan, M. N., *J. Chem. Soc.*, 1946, 87.

(from light petroleum followed by sublimation) (Found: C, 48·2; H, 3·6; N, 18·6. $C_9H_8ClN_3S$ requires C, 47·9; H, 3·6; N, 18·6%).

N-(*2″-Dimethylaminoethyl*)-*6-methyl-2-(2′-methylthiazol-4′-yl)pyrimidin-4-amine* (*4c*)

The above chloropyrimidine was treated with 2-dimethylaminoethylamine as described for the analogue (3g) to give the product (4c) as its *dihydrobromide* (74%), m.p. >225° (from ethanol) (Found: C, 35·7; H, 4·8; N, 15·8. $C_{13}H_{21}Br_2N_5S$ requires C, 35·6; H, 4·8; N, 15·9%). N.m.r. (base in $CDCl_3+D_2O$; 90 MHz, 30°) 8·06, s, H5′; 6·11, s, H5; 3·40, t, H1″; 2·79, s, 2′-Me; 2·52, t, H2″; 2·42, s, 6-Me; 2·25, s, NMe_2.

N,N-*Dimethyl-2-[6′-methyl-2′-(2″-methylthiazol-4″-yl)pyrimidin-4′-ylthio]ethylamine* (*4d*)

The chloropyrimidine (4b) was converted, by the method used for the analogous product (3h), into the required *pyrimidinylthioethylamine dihydrobromide* (53%), m.p. >200° (dec.) (from ethanol) (Found: C, 34·1; H, 4·6; N, 12·0; S, 13·9. $C_{13}H_{20}Br_2N_4S_2$ requires C, 34·2; H, 4·4; N, 12·3; S, 14·1%). N.m.r. (base; 90 MHz, 30°) 8·16, s, H5″; 6·87, s, H5′; 3·35, t, H2; 2·78, s, 2″-Me; 2·59, t, H1; 2·46, s, 6′-Me; 2·26, s, NMe_2.

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