Synthesis of [1,3,5]Thiadiazino[3,2-*a*]benzimidazole-2,4(3*H*)-diones and their Sulphur Analogues

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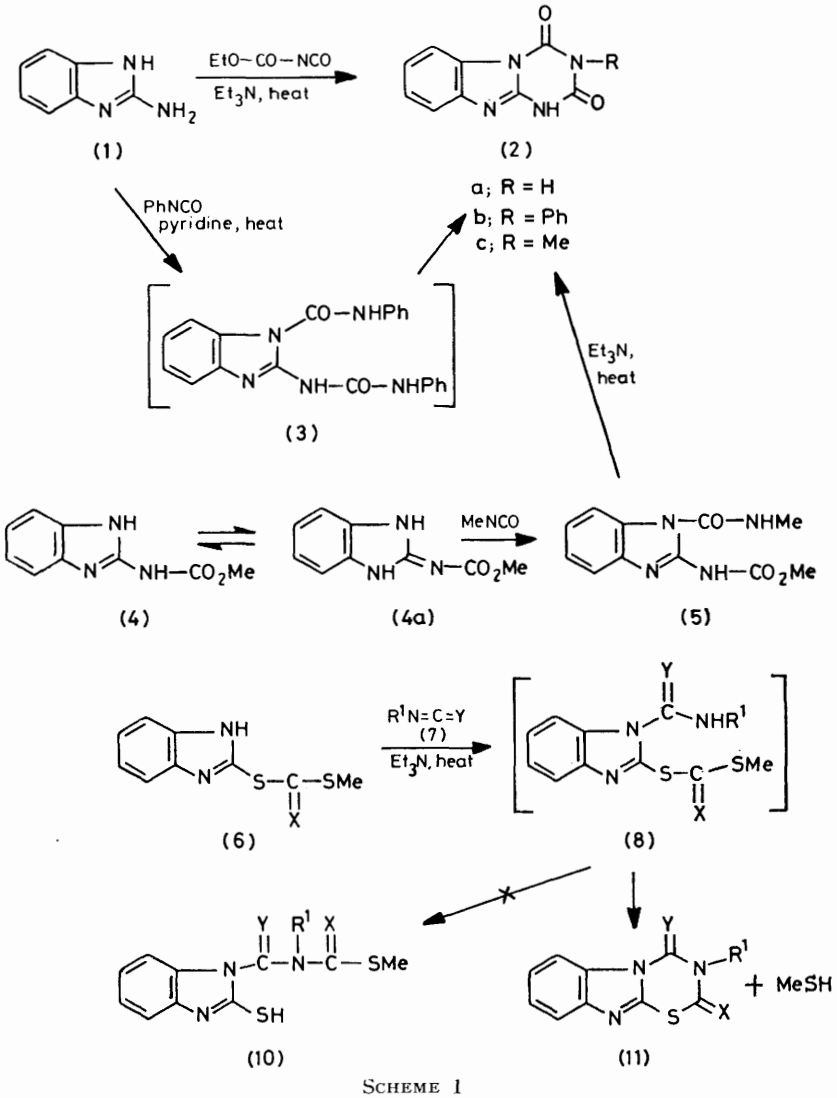
Benzimidazol-2-yl di- or tri-thiocarbonates and iso- or isothio-cyanates give, on heating in the presence of triethylamine, the novel [1,3,5]thiadiazino[3,2-*a*]benzimidazole-2,4(3*H*)-diones (11; X = Y = O) or their sulphur analogues (11; X = S, Y = O; or X = Y = S).

CYCLISATION of 2-amino-thiazole,[1] -thiazoline,[2] -selenazoline,[2] or -1,3-thiazine,[2] or 3-aminoindazole [3] with ethoxycarbonyl isothiocyanate to the corresponding thioxo-*s*-triazinones has been reported. Heterocyclic β-enaminoesters and isocyanates yielded hetero-condensed pyrimidines;[4] ethyl 2-aminoquinoline-3-carboxylate and phenyl isocyanate formed 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydropyrimido[4,5-*b*]quinoline.[5] On heating with ethoxycarbonyl isocyanate in the presence of a base, 2-aminobenzimidazole (1) cyclised to 2,4-dioxo-1,2,3,4-tetrahydrobenzimidazo[1,2-*a*]-*s*-triazine (2a).[6]

RESULTS AND DISCUSSION

Novel heterocyclic systems (11) resulted from the condensation of benzimidazol-2-yl di- or tri-thiocarbonate (6; X = O or S) and an iso- or isothio-cyanate (7; Y = O or S) on heating in the presence of triethylamine (Scheme 1). The reaction probably proceeded *via* intermediate (8) which rapidly lost methanethiol; the intermediate (8) could not be isolated under the conditions of the reaction. Cyclisation to (11) can be explained in terms of Baldwin's rules for ring closure which consider the '6-*Endo-Tet*' process [leading to



SCHEME 1

structures (10)] as disfavoured and the '*6-Exo-Tet*' [leading to structures (11)] as favoured.[7] However, an attempt to prepare thiadiazine (11; R^1 = Me, X = O, Y = S) from the dithiocarbonate (21) and methyl isothiocyanate resulted instead in the formation of (22). The rearrangement of (21) to (22) occurred with equal facility in the absence of methyl isothiocyanate. This failure to obtain the thiadiazine may be a consequence of (*a*) the lower dipole moment of the carbonyl group than that of the thiocarbonyl group,[8] leading to greater resistance of the SMe to act as a leaving group in dithiocarbonate (21) than in trithiocarbonate (6; X = S) [reflected also (Table 3) in the lower yield of, and more vigorous reaction conditions required for the formation of, thiadiazine (11; R^1 = Me, X = Y = O) than of thiadiazine (11; R^1 = Me, X = S, Y = O)], (*b*) low reactivity of methyl isothiocyanate [reflected (Table 3) in the lower yield of thiadiazine (11; R^1 = Me, X = Y = S) than of that of thiadiazine (11; R^1 = Me, X = S, Y = O)], and (*c*) the ease of rearrangement of dithiocarbonate (21).

Methyl chloroformate and the trithiocarbonate (6; X = S) gave, as expected, compound (9).

The ^{1}H n.m.r. spectra of compounds (11) were consistent with the assigned structures (Table 1). The signals for H_a in each case occurred downfield of H_b, H_c, and H_d (12) due to the influence of the *ortho* N:C group. In compound (11; R^1 = Ph, X = S, Y = O) signals for the *N*-phenyl protons could not be distinguished from those of the protons of the benzene ring of the benzimidazole part of the tricyclic structure. No signals which could be assigned to methylthio-protons were observed, thus ruling out any structure that contains the methylthio-group [such as (10)]. The i.r. spectra of (11; X = S, Y = O) exhibited absorption bands at 1 720—1 732 cm^{-1}. Compound (11; R^1 = Me, X = Y = O) exhibited an additional absorption band at 1 670 cm^{-1}.

No analogous displacement of methanethiol resulting in structure (14) occurred on heating in the presence of triethylamine of heterocyclic methyl trithiocarbonates (13; R^2 = benzimidazo-2-yl or benzothiazol-2-yl) and imidazole. The heterocyclic thiols were displaced in preference to methanethiol (Scheme 2) leading to the formation of (15), in conformity with the lower pK values of heterocyclic thiols and thus their greater ability to act as leaving groups in nucleophilic substitution reactions.

2-Aminobenzimidazole (1) and an excess of phenyl isocyanate gave, on heating in the presence of pyridine, a high yield of the triazine (2b),[9] probably *via* the intermediate (3) with loss of aniline [Omar *et al.*[10] reported the cyclisation on heating of *N*-*o*-aminophenyl-*N*'-phenylthiourea to benzimidazoline-2-thione in 95% yield with loss of aniline]. Methyl benzimidazol-2-ylcarbamate (4) interacted with methyl isocyanate to give the 1-methylcarbamoyl derivative (5) [14] which on heating in the presence of triethylamine * cyclised to the triazine (2c).[9]†

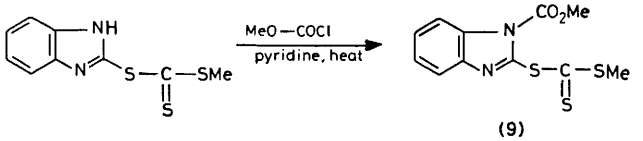
Under comparable experimental conditions benzimidazole-2-thiol (16) and an excess of phenyl isocyanate gave the carbamate (17), whereas the methyl carbamate (18) and methyl isocyanate gave a negligible yield of the

TABLE 1

I.r. absorption bands (cm^{-1}) for $CHBr_3$ solutions and ^{1}H n.m.r. signals (τ values) for $CDCl_3$ solutions

Compound	Compound R^1	X	Y	I.r. bands NH	C:O	C:S	^{1}H n.m.r. peaks [a] H_a	$H_{b,c,d}$	R^1	Me
(18)				3 420	1 770		1.9—2.8 (m) [b]			5.88 (s)
(6)		O		3 390	1 710		2.2—2.9 (m)			7.56 (s)
(6)		S		3 430		1 060	2.1—3.0 (m)			7.38 (s)
(11)	Me	S	O		1 720	1 084	1.6—2.0 (m)	2.2—2.8 (m)	6.06 (s)	
(11)	Ph	S	O		1 729	1 068	1.65—1.9 (m) [c]	2.0 —	2.7 (m)	
(11)	Me	O	O		1 732; 1 670		1.5—1.9 (m)	2.1—2.8 (m)	6.4 (s)	
(11)	Me	S	S			1 068	1.0—1.2 (m)	2.1—2.7 (m)	5.62 (s)	

[a] The designation of the protons on the benzene ring of the benzimidazole nucleus is as shown in (12). s = Singlet, m = multiplet. [b] $CDCl_3$ + ^{2}[H_6]DMSO solution. [c] Dimethylacetamide solution.



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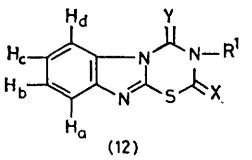

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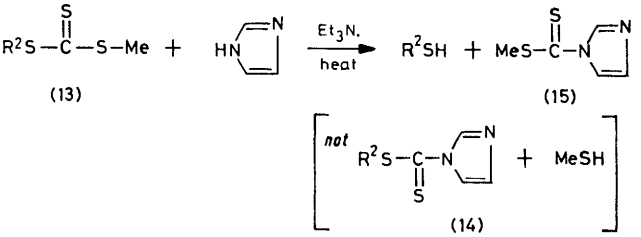
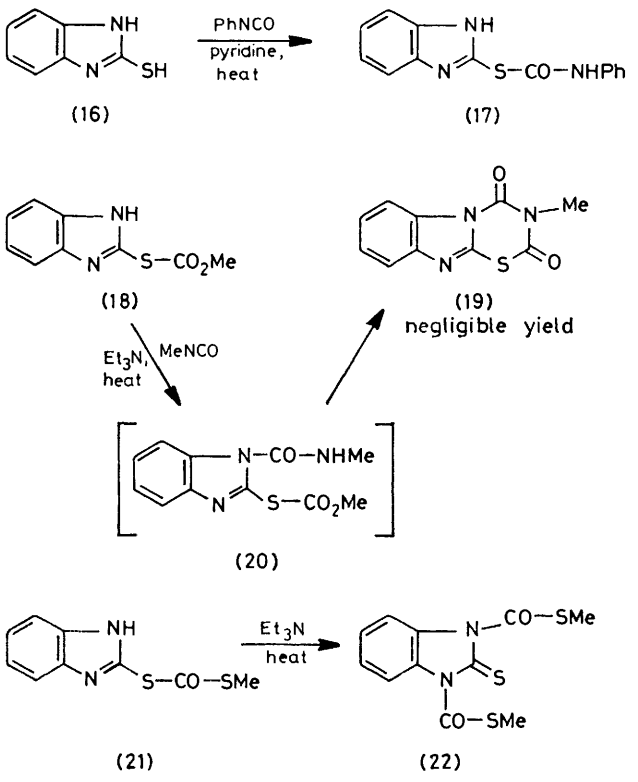


SCHEME 2

* Benomyl (1-butylcarbamoyl-2-methoxycarbonylaminobenzimidazole) underwent cyclisation to (2; R = Bu) on treatment with sodium hydroxide (J. M. Ogara, E. Bose, B. T. Manji, E. R. White, and W. W. Kilgare, *Phytopathology*, 1971, **61**, 905). Compound (2; R = Bu) was also obtained by K. H. Mayer, D. Lauerer, and H. Heitzer, *Synthesis*, 1977, 804, from 1-ethoxycarbonyl-2-[(*N*-ethoxycarbonyl-*N*-butylamino)carbonylamido)]benzimidazole on treatment with sodium hydroxide at 20 °C.

† Compound (2*c*) was also obtained by the reaction of 2-aminobenzimidazole with 2,4-dimethylallophanoyl chloride [G.D.R. Patent 127.636/1977 (*Chem. Abs.*, 1978, **88**, 136680w)].

thiadiazine (19). Several effects may be responsible for these differences: (*a*) since SMe is a better leaving group than OMe, compounds (11) formed readily from the proposed intermediate (8) in good yield, whereas only a



negligible yield of (19) was obtained from the proposed intermediate (20) [cyclisation of *S*-aminocarbonylmethyl-*S*-phenyl-*N*-methoxycarbonylsulphoximide (or its *S*-methylamino-derivative) to 1-phenyl-4,6-dihydro-1,2,4-thiadiazine-3,5-dione 1-oxide (or its 4-methyl derivative) required the generation of the $-CONR^-$ species with sodium methoxide or sodium hydride];[11] (*b*) the ring nitrogens of 2-aminobenzimidazole derivatives are more reactive than those of 2-thiolobenzimidazole derivatives and thus facilitate cyclisation [guanidino-structures $-NH-C(NH_2)=N-$ are more nucleophilic than isothiouronium structures $-NH-C(SR)=N-$; also primary amines are *ca.* five times as reactive as thiols (towards *e.g.* diethyl pyrocarbonate)];[12] (*c*) there may be participation of structure (4a) which would offer an additional site for the reaction with the isocyanate.

EXPERIMENTAL

Chromatographic separations were carried out using a column packed with Merck silica gel 60. T.l.c. was carried out using plates pre-coated with silica gel 60 F_{254}. Melting points were determined on a Mettler apparatus. I.r. spectra were recorded with a Perkin-Elmer 521 spectrophotometer. ^1H N.m.r. spectra were recorded with a Varian A-60D or Varian HA100 instrument. The protons of the benzene nucleus of the benzimidazole part of compounds (17) and (22) are designated as shown in structure (12).

Preparation of Benzimidazol-2-yl Thiocarbonates (*Table* 2).—Benzimidazole-2-thiol (4.52 g, 25 mmol) in acetone (100 ml) and a solution of potassium hydroxide (1.54 g, 27.5 mmol) in methanol (50 ml) were heated under reflux for 1 h. The solution was evaporated to dryness. Acetone (50 ml) was added to the residue, then a solution of the chloroformate (25 mmol) in acetone (10 ml), and the mixture was heated under reflux for 3 h. The mixture was then cooled and filtered, the filtrate was evaporated to dryness, and the residue crystallised from a suitable solvent.

Preparation of [1,3,5]*Thiadiazino*[3,2-a]*benzimidazole*-2,4(3H)-*diones and their Sulphur Analogues* (*Table* 3).—Benzimidazol-2-yl thiocarbonate (6) or (18) (7.5 mmol), iso- or isothio-cyanate (7) (17 mmol), triethylamine (5 drops), and acetone (100 ml) were heated under reflux until the evolution of methanethiol ceased (2 h). The mixture was evaporated to dryness and the residue crystallised from a suitable solvent.

Rearrangement of Carbonate (21).—(*a*) Dithiocarbonate (21) (2.24 g, 10 mmol), methyl isothiocyanate (1.46 g, 20 mmol), and triethylamine (10 drops), in toluene (150 ml), were heated under reflux in an atmosphere of nitrogen for 4 h. The solution was evaporated to dryness. The residue was eluted with toluene yielding 1,3-*bis*[(*methylthio*)*carbonyl*]-*benzimidazoline-2-thione* (22) (0.55 g, 18%) as a white crystalline solid, m.p. 217.4 °C (from toluene); $\nu_{max.}$ ($CHBr_3$) 1 660 cm^{-1} (carbonyl); τ($CDCl_3$ + [$^2H_6$]DMSO) 1.76 (1 H, dd, H_a), 2.50—2.80 (3 H, m, $H_{b,c,d}$), 7.48 (6 H, s, 2 × Me) (Found: C, 44.1; H, 3.4; N, 9.4; S, 32.5. $C_{11}H_{10}N_2O_2S_3$ requires C, 44.3; H, 3.4; N, 9.4; S, 32.2%). Further elution with acetone–toluene (10% v : v) yielded benzimidazole-2-thiol, m.p. 297 °C (18.5%).

(*b*) The carbonate (21) (1.12 g, 5 mmol), triethylamine (10 drops), and toluene (100 ml) were heated under reflux

TABLE 2

Compounds obtained by heating potassium benzimidazole-2-thiolates or benzothiazole-2-thiolate with chloroformates

Compound	From chloroformate	M.p. (°C)	Yield (%)	Appearance	Analysis (%) Found C	H	N	S	Formula	Required C	H	N	S
(18)	Methyl	167—168 (decomp.) [a]	61	White crystals	52.1	3.9	13.6		$C_9H_8N_2O_2S$	51.9	3.9	13.5	
(21)	Methyl thiolo-	199.5 [b]	49	White needles	48.2	3.8	12.2	28.5	$C_9H_8N_2OS_2$	48.2	3.6	12.5	28.6
(6; X = S)	Methyl dithio-	188.9 [a]	57	Yellow leaves	45.0	3.4	11.7	39.9	$C_9H_8N_2S_3$	45.0	3.35	11.7	40.0
(13; R^2 = Benzothiazol-2-yl)	Methyl dithio-	80.2 [c]			42.0	2.8	5.4		$C_9H_7NS_4$	42.0	2.8	5.4	

[a] From toluene. [b] From acetone. [c] From light petroleum, b.p. 60—80 °C.

for 5 h. T.l.c. monitoring on silica gel using 10% v : v acetone–toluene showed the gradual disappearance of the carbonate and the concomitant formation of compounds (22) and (16).

Methyl 1-Methoxycarbonylbenzimidazol-2-yl Trithiocarbonate (9).—Trithiocarbonate (6; X = S) (1.20 g, 5 mmol), methyl chloroformate (0.472 g, 5 mmol), and pyridine (0.395 g, 5 mmol), in acetone (125 ml), were heated under reflux for 6 h and then set aside at room temperature for 3 d. The solvent was removed and the residue purified by column chromatography using toluene as eluant. The compound was obtained as a yellow crystalline solid (0.51 g, 34%), m.p. 63.8 °C; $\nu_{max.}$ ($CHBr_3$) 1 745 cm^{-1} (carbonyl) and 1 070 cm^{-1} (thiocarbonyl); τ($CDCl_3$) 1.8—2.7 (4 H, m, Ar-H), 5.92 (3 H, s, OMe), and 7.32 (3 H, s, SMe) (Found: C, 44.0; H, 3.6; N, 9.4; S, 31.7. $C_{11}H_{10}N_2O_2S_3$ requires C, 44.3; H, 3.4; N, 9.4; S, 32.3%).

Reaction of Heterocyclic Methyl Trithiocarbonates and Imidazoles.—(a) *Methyl benzimidazol-2-yl trithiocarbonate and imidazole.* A solution containing trithiocarbonate (6; X = S) (0.960 g, 4 mmol), imidazole (0.3 g, 4.4 mmol), and triethylamine (10 drops) in acetone (60 ml) was heated under reflux until t.l.c. examination of the reaction mixture, using a mixture of toluene and dichloromethane as eluants, indicated the complete disappearance of the trithiocarbonate (6; X = S). The solvent was removed under reduced pressure and the residue was chromatographed using chloroform as eluant to give *methyl imidazole-1-carbodithioate* (15) as a yellow oil (0.59 g, 93%); $\nu_{max.}$ ($CHBr_3$) 1 070 cm^{-1} (thiocarbonyl); τ($CDCl_3$) 1.52 (1 H, s, N–CH=N), 2.24 (1 H, d, HC=C), 2.90 (1 H, d, HC=C), and 7.24 (3 H, s, SMe) (Found: C, 38.2; H, 4.05; N, 17.7; S, 40.5. $C_5H_6N_2S_2$ requires C, 37.95; H, 3.8; N, 17.7; S, 40.5%). Further elution with ethyl acetate afforded benzimidazole-2-thiol as a white crystalline solid (0.515 g, 86%), m.p. 303.2 °C (lit.,[13] m.p. 303—304 °C).

(b) *Methyl benzothiazol-2-yl trithiocarbonate and imidazole.* A solution of trithiocarbonate (13; R^2 = benzothiazol-2-yl) (1.3 g, 5 mmol), imidazole (0.33 g, 5 mmol), and triethylamine (0.5 ml) in acetone (25 ml) was heated under reflux. The reaction mixture was monitored by t.l.c. using toluene–ethyl acetate (4 : 1) as eluant. The trithiocarbonate (13; R^2 = benzothiazol-2-yl) disappeared and two compounds with R_F values identical with those of compound (15) and of benzothiazole-2-thiol were formed.

2-{[(Phenylamino)carbonyl]thio}benzimidazole (17).—The conditions used were identical with those reported for the preparation of the triazine (2b) from 2-aminobenzimidazole and phenyl isocyanate.[9] To benzimidazole-2-thiol (1) (4.5 g, 30 mmol) suspended in pyridine (5 ml) phenyl isocyanate (10.71 g, 90 mmol) was added. An exothermic reaction ensued. The solution was heated under reflux for 3 h at 140 °C and allowed to cool. The crystalline mass was triturated with ether and the white solid was eluted with 30% (v : v) chloroform–toluene. The compound was obtained as white needles (5.65 g, 70%), m.p. 261.3 °C (from toluene); $\nu_{max.}$ ($CHBr_3$) 3 413 cm^{-1} (NH), 1 724, 1 560 cm^{-1} (amide); τ($CDCl_3$ + [$^2H_6$]DMSO) −2 to −3.5 (2 H, br, 2 × NH), 1.5—1.8 (1 H, m, H_a), and 2.2—3.1 (8 H, m, $H_{b,c,d}$ + Ph) (Found: C, 62.5; H, 4.1; N, 15.7; S, 11.9. $C_{14}H_{11}N_3OS$ requires C, 62.4; H, 4.1; N, 15.6; S, 11.9%).

TABLE 3

Compounds obtained by heating benzimidazole-2-thiocarbonates and iso- or isothio-cyanates

								Analysis (%)								
				Derived from				Found					Required			
Compd.	R^1	X	Y	Thio-carbonate	Isocyanate (7)	M.p. (°C)	Yield (%)	C	H	N	S	Formula	C	H	N	S
(11)	Me	S	O	(6) X = S	R^1 = Me, Y = O	178.5	69 [a]	47.9	2.8	16.8	25.9	$C_{10}H_7N_3OS_2$	48.2	2.8	16.9	25.7
(11)	Ph	S	O	(6) X = S	R^1 = Ph, Y = O	254.7 [b]	55	57.8	2.9	13.55	20.65	$C_{15}H_9N_3OS_2$	57.8	2.9	13.5	20.6
(11)	Me	O	O [c]	(6) X = O	R^1 = Me, Y = O	165.9 [d]	48	51.4	3.0	18.2	14.2	$C_{10}H_7N_3O_2S$	51.5	3.0	18.0	13.75
(11)	Me	S	S [e]	(6) X = S	R^1 = Me, Y = S	159.9	30 [f]	45.3	2.6	16.1	36.6	$C_{10}H_7N_3S_3$	45.25	2.7	15.8	36.25
(19) [g]				(18)	R^1 = Me, Y = O		negligible									

[a] The residue was eluted with toluene and the compound was obtained as yellow plates. Dimethyl trithiocarbonate was also obtained (12%). [b] Lemon-yellow needles from toluene. [c] Reaction was carried out in dimethylformamide at 100 °C. [d] White needles from acetone. [e] 15 drops of Et_3N and a heating period of 5 h were used. [f] The residue was eluted with chloroform and the compound was obtained as yellow crystals. In another experiment in which equimolar amounts of the thiocarbonate and isocyanate were used the compound was obtained in 10% yield and 81% of the starting thiocarbonate was recovered. [g] The reaction was also carried out in dimethylformamide at 100 °C. The compound could not be isolated, but was detected by t.l.c.; its R_F value was similar to that of the other thiadiazines (11).

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