
**Journal of Sulfur Chemistry**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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**To cite this Article** Shawali, Ahmad Sami and Sayed, Abdelwahed R.(2007) 'A new convenient synthesis of alditol C-glycosides of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole', Journal of Sulfur Chemistry, 28: 1, 23 — 29
**To link to this Article: DOI:** 10.1080/17415990601101020
**URL:** http://dx.doi.org/10.1080/17415990601101020

*Journal of Sulfur Chemistry*
Vol. 28, No. 1, February 2007, 23–29

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# A new convenient synthesis of alditol C-glycosides of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole

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*(Received 17 September 2006; in final form 28 October 2006)*

Starting from bis(substituted methylene)carbonothioic dihydrazides, a series of the title compounds have been synthesized via their oxidative cyclization. The mechanism and regioselectivity of the reactions studied are discussed. The structures of the compounds prepared were elucidated on the basis of their elemental analyses, spectral data and alternate synthesis.

*Keywords*: Hydrazones; 1,5-Electrocyclization; Nitrilimines; Heterocycles



## 1. Introduction

A literature survey reveals that some 3,6-disubstituted s-triazolo[3,4-b][1,3,4]thiadiazole derivatives showed anti-HIV-1 activity at concentration slightly below cytotoxic levels [1]. Others possess significant to mild anti-inflammatory [2, 3], antibacterial and antifungicidal effects [4–6]. These findings led some authors to explore the synthesis of some alditol C-nucleoside analogs of such ring systems aiming at the improvement of their biological activity as a consequence of the hydrophilic nature of the alditolyl residue which may increase their transportation into biological systems [7]. The method adopted for the synthesis of such alditol C-nucleoside analogs involves the preparation of 3-alditolyl-4-amino-5-mercapto-1,2,4-triazole and then construct the 1,3,4-thiadiazole ring with the required substituent at C-6 [7]. Prompted by these results and in continuation of the work on utility of precursors of nitrilimines in organic synthesis [8–12], the authors wish to report herein a new convenient method for synthesis of alditol C-nucleoside analogs of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles via tandem 1,5-electrocyclizations of bis-nitrilimines (scheme 1).

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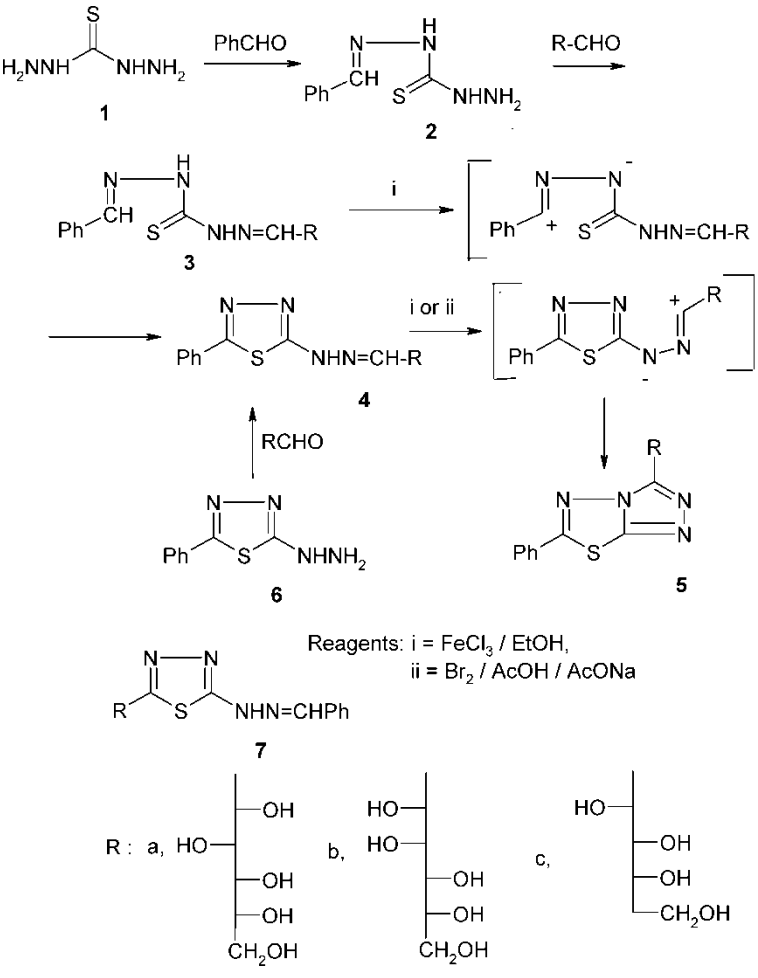
*Journal of Sulfur Chemistry*
ISSN 1741-5993 print/ISSN 1741-6000 online 
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990601101020




SCHEME 1

## 2. Results and discussion

The required *bis*-hydrazones **3** were prepared by condensation of 2-phenylmethylene carbonothioic dihydrazide **2** [13] with the appropriate aldose sugar (scheme 1). The structures of the new *bis*-hydrazones **3a–c** were confirmed by their elemental analyses and spectral (MS, IR and $^1$H NMR) data (see Experimental). Their $^1$H NMR spectra in DMSO-$d_6$ exhibited, in each case, four characteristic signals: two signals due to −CH=N- protons in the regions $\delta$ 8.11–8.37 and 8.41–8.62 as well as two other signals due to −NHN=C protons in the regions 11.54–11.65 and 11.68–11.89. In addition, the spectra showed the signals of the protons of the sugar residue at $\delta$ 3.38–5.21 and that of the phenyl protons at $\delta$ 7.00–7.79.

Heating each of the latter *bis*-hydrazones **3** with ferric chloride in ethanol was found to give the respective D-aldose N-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazone **4** (scheme 1). The structures of these new derivatives **4a–c** were deduced from their combustion analyses, spectral (MS, IR and $^1$H NMR) data and their alternate synthesis by reaction of the appropriate aldose with 2-hydrazino-5-phenyl-1,3,4-thiadiazole [14] (see Experimental). Their $^1$H NMR spectra in DMSO-$d_6$ exhibited, in each case, the signals due to the protons of the sugar residue at $\delta$

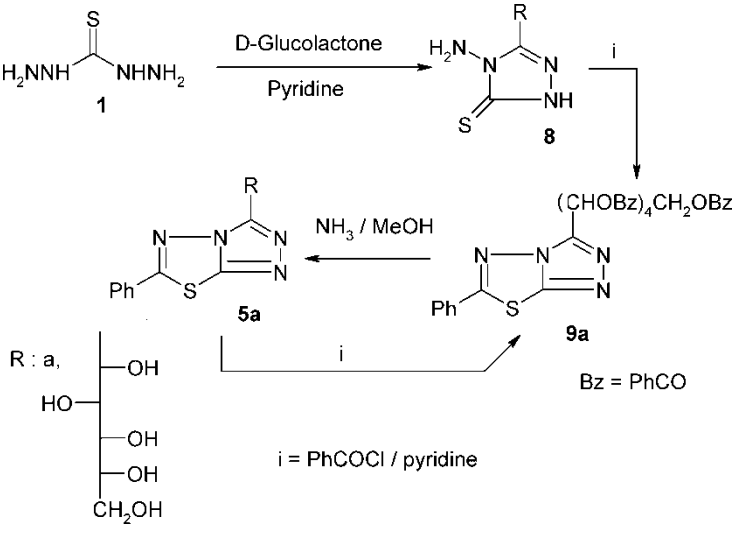
3.38–5.21, the phenyl protons at $\delta$ 7.00–7.79 in addition to two characteristic signals in the regions $\delta$ 8.59–8.63 and 11.75–11.89 due to −CH=N- and −NH-N=C protons, respectively. In no cases were the isomeric products of type **6** (scheme 1) produced.

Further oxidation of the latter compounds **4a–c** with ferric chloride in ethanol or with bromine in acetic acid in the presence of anhydrous sodium acetate led to the target alditol C-nucleoside analogs **5a–c** (scheme 1). The structures of the isolated products **5a–c** were compatible with their combustion analyses, spectra (MS, IR and $^1$H NMR). For example, their $^1$H NMR spectra showed the absence of the signals characteristic of the −NH-N=CH- that appeared in the spectra of their precursors **3** and **4**. The $^1$H NMR spectrum of **5** showed, in each case, exchangeable proton signals corresponding to the hydroxyl protons of the sugar residue in the region $\delta$ 3.20–5.24. Finally, the structural assignment for the products **5** and in turn the regioselectivity of the **3** → **4** conversion were confirmed by their conversion into know derivatives and alternate synthesis. For example, treatment of **5a** with benzoyl chloride in pyridine afforded a product that proved identical in all respects (m.p., mixed m.p. and spectra) with an authentic sample of 3-(1,2,3,4,5-penta-O-benzoyl-D-gluco-pentitol-1-yl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole **9a** prepared by literature method (scheme 2) [7]. Furthermore, treatment of the latter authentic sample of **9a** [7] (scheme 2) with ammonia solution in methanol afforded a product which proved identical in all respects with **5a** prepared in this work by oxidation of **4a**.

As depicted in scheme 1, the pathway leading to **5**, involves two tandem *in situ* 1,5-electrocyclizations of the intermediate nitrilimines. This suggested pathway is reminiscent of other related oxidative cyclization of aldehyde thiosemicarbazones [15] and aldehyde N-heteroaryl hydrazones reported recently by Shawali *et al.* [16] and by others [17–19].

In conclusion, the regioselective oxidative cyclization of 2,2'-(substituted methylene)-carbonothioic dihydrazides **3** has proven to be of general utility for synthesis of sugar N-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazones **4a–c** allowing easier preparation of 3-acyclo C-nucleoside analogs **5a–c**, respectively. In addition, the method described herein has the advantages of higher overall yields, shorter reaction time and utilization of safe and easily handled chemicals (aldehydes and ferric chloride).






SCHEME 2

## 3. Experimental

All melting points were determined with a Gallenkamp melting point apparatus and are reported uncorrected. The IR spectra were recorded in KBr on Pye Unicam SP3-300 infrared spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ using a Varian Gemini 300 NMR spectrometer using tetramethylsilane as internal standard. The mass spectra were recorded on GCMS-Q P1000-EX Varian MAT 711 spectrometer. Elemental analyses were carried out at Microanalytical Laboratory, University of Cairo, Giza, Egypt. The starting carbonothioic dihydrazide **1** [20], 5-phenyl-2-hydrazino-1,3,4-thiadiazole [14] and 2-phenylmethylene carbonothioic dihydrazide **2** [13] and 3-(1,2,3,4,5-penta-O-benzoyl-D-gluco-pentitol-1-yl)-6-phenyl-1,2,4-triazolo[3,4-b][1,2,4]thiadiazole **9a** [7] were prepared as previously described.

### 3.1 *Synthesis of the bis-hydrazones 3a–c*

To a solution of carbonothioic dihydrazide **2** (1.06 g, 0.01 mol) in ethanol (200 ml) was added the solution of the respective aldose sugar (0.01 mol) in water (5 ml) and few drops of acetic acid. The mixture was heated in boiling water bath for 4 h, then benzaldehyde (0.70 ml, 7 mmol) was added to the reaction mixture and heating was continued for 5 min, then cooled. The solid product that separated was filtered off, washed with ethanol and dried. Attempts to recrystallize these products resulted in their conversion to the respective **4a–c**. Accordingly, they have been used directly. The physical properties of the compounds **3a–c** prepared are listed below.



**3.1.1 2-[(D-gluco-pentitol-1-yl)methylene]-2'-(Phenylmethylene)-carbonothioic dihydrazide (3a).** Pale yellow solid, yield 55%, mp. 203–205 °C; IR(KBr) $\nu$ (cm$^{-1}$) 3282, 3155 1601; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.40–5.20 (sugar HO), 7.00–7.78 (m, 5H), 8.11 (s, 1H, N=CH), 8.62 (s, 1H, N=CH), 11.65 (s, 1H, NH), 11.75 (s, 1H, NH); MS m/z (%) 357 ($M^+$+1, 63), 356 ($M^+$, 56), 239 (79), 135 (10), 121 (21), 89 (44), 91 (81), 90 (100). Anal. Calcd. for $C_{14}H_{20}N_4O_5S$ (356.40): C, 47.18; H, 5.66; N, 15.72. Found: C, 47.20; H, 5.51; N, 15.81%.

**3.1.2 2-[(D-Manno-pentitol-1-yl)methylene]-2'-(phenylmethylene)-carbonothioic dihydrazide (3b).** Pale yellow solid, yield 55%, mp. 200 °C; IR(KBr) $\nu$ (cm$^{-1}$) 3445, 3304; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.38–5.21 (sugar HO), 7.45–7.86 (m, 5H), 8.13 (s, 1H, N=CH), 8.62 (s, 1H, N=CH), 11.64 (s, 1H, NH), 11.89 (s, 1H, NH); MS m/z (%) 357 ($M^+$+1, 4), 356 ($M^+$, 3), 278 (77), 264 (20), 239 (79), 177 (33), 146 (11), 121 (100), 118 (20), 90 (16), 77 (25). Anal. Calcd. for $C_{14}H_{20}N_4O_5S$ (356.40): C, 47.18; H, 5.66; N, 15.72. Found: C, 47.21; H, 5.59; N, 15.81%.

**3.1.3 2-[(D-Arabino-tetritol-1-yl)methylene]-2'-(phenylmethylene)-carbonothioic dihydrazide (3c).** Pale yellow solid, yield 60%, mp. 209–210 °C; IR(KBr) $\nu$ (cm$^{-1}$) 3444, 3282; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.96–5.29 (sugar HO), 7.44–7.81 (m, 5H), 8.37 (s, 1H, N=CH), 8.41 (s, 1H, N=CH), 11.59 (s, 1H, NH), 11.68 (s, 1H, NH); MS m/z (%) 327 ($M^+$+1, 35), 326 ($M^+$, 2), 306 (10), 247 (12), 233 (63), 131 (30), 104 (43), 90 (100), 77 (78). Anal. Calcd. for $C_{13}H_{18}N_4O_4S$ (326.38): C, 47.84; H, 5.56; N, 17.17. Found: C, 47.82; H, 5.59; N, 17.22%.

### 3.2 *Synthesis of D-sugar N-(5-aryl-1,3,4-thiadiazol-2-yl)hydrazones (4a–c)*

Method A: To a solution of the appropriate **3** (14 mmol) in ethanol (100 ml) was added a solution of iron(III) chloride (5 ml, 5 M). The reaction mixture was refluxed for 5 min, and the excess solvent was distilled under reduced pressure and the solid left was collected, washed with water, dried and finally crystallized from ethanol-water mixture to give the respective **4**.

Method B: To a solution of 5-phenyl-2-hydrazino-1,3,4-thiadiazole [14] (1.84 g, 0.01 mol) in ethanol (50 ml) were added a solution of the appropriate D-sugar (0.01 mol) in water (5 ml) and few drops of acetic acid. The reaction mixture was heated on a water-bath for 1 h and cooled. The solid that separated was filtered off, dried and finally crystallized from aqueous ethanol. The physical properties of the products **4a–c** are given below.

**3.2.1 D-Glucose N-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazone (4a).** Yellow brown solid, yield 50%, mp. 180 °C; IR(KBr) $\nu$ ($cm^{-1}$) 3447, 3279, 1584; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.36–5.21 (sugar HO), 7.46–7.83 (m, 5H), 8.59 (s, 1H, N=CH), 11.85 (s, 1H, NH); MS m/z (%) 355 ($M^+$+1, 5), 354 ($M^+$, 6), 207 (12), 185 (12), 177 (16), 144 (34), 139 (65), 118 (27), 103 (100), 84 (62), 77 (56), 71 (50), 66 (33), 55 (87). Anal. Calcd. for $C_{14}H_{18}N_4O_5S$ (354.39): C, 47.45; H, 5.12; N, 15.81. Found: C, 47.50; H, 5.11; N, 15.85%.

**3.2.2 D-Mannose N-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazone (4b).** Yellowish green solid, yield 60%, mp. 195 °C; IR(KBr) $\nu$ ($cm^{-1}$) 3384, 3237; 1601; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.38–5.22 (sugar HO), 7.45–8.13 (m, 5H), 8.62 (s, 1H, N=CH), 11.89 (s, 1H, NH); MS m/z (%) 355 ($M^+$+1, 4), 354 ($M^+$, 2), 256 (17), 229 (13) 207 (35), 171 (12), 149 (85), 131 (55), 113 (34), 97 (50), 85 (42), 77 (33), 71 (50), 69 (100), 55 (80). Anal. Calcd. for $C_{14}H_{18}N_4O_5S$ (354.39): C, 47.45; H, 5.12; N, 15.81. Found: C, 47.53; H, 5.14; N, 15.78%.

**3.2.3 D-Arabinose N-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazone (4c).** Yellowish brown solid, yield 60%, mp. 190 °C; IR(KBr) $\nu$ ($cm^{-1}$) 3381, 3277, 1600; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.27–5.24 (sugar HO), 7.38–7.83 (m, 5H), 8.63 (s, 1H, N=CH), 11.75 (s, 1H, NH); MS m/z (%) 325 ($M^+$+1, 3), 324 ($M^+$, 17), 194 (18), 162 (24) 104 (49), 103 (23), 91 (12), 77 (100), 64 (11), 55 (4), 51 (71). Anal. Calcd. for $C_{13}H_{16}N_4O_4S$ (324.36): C, 48.14; H, 4.97; N, 17.27. Found: C, 47.16; H, 4.85; N, 17.30%.

### 3.3 *Synthesis of alditol C-nucleoside analogs 5a–c*

Method A: To a stirred solution of the appropriate **4** (5 mmol) in glacial acetic acid containing anhydrous sodium acetate (1.2 g, 15 mmol) was added dropwise a solution of bromine (0.44 g, 5 mmol) in acetic acid (5 ml) at room temperature. After the addition was complete, the reaction mixture was stirred for further 12 hr at room temperature. The mixture was poured onto ice-cold water while being stirred. The solid precipitate was filtered off and washed with aqueous solution of sodium bicarbonate (5%), then with water, dried and finally crystallized from the appropriate solvent to give the respective **5**.

Method B: To a solution of the appropriate **4** (14 mmol) in ethanol (40 ml) was added a solution of iron(III) chloride (5 ml, 5 M). The reaction mixture was refluxed for 30 min and then left while being stirred overnight at room temperature. The excess solvent was distilled under reduced pressure and the solid residue left was collected and washed with water several times, dried and finally crystallized from the proper solvent to give the respective **5**.

The physical properties of the compounds **5a–c** are listed below.

**3.3.1 3-(D-Gluco-pentitol-1-yl)-6-phenyl-s-triazolo[3,4-b][1,3,4]-thiadiazole (5a).** Yellow brown solid, yield 46%, mp. 240 °C (EtOH), IR(KBr) $\nu$ ($cm^{-1}$) 3424, 1611 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.39–5.21 (sugar moiety), 7.39–7.84 (m. 5H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 62.77, 67.65, 70.57, 71.21, 71.64 (C-5', C-1', C-4', C-3', C-2' of sugar residue, respectively) 130.70 (C-6), 144.11 (C-3), 161.37 (C-7a) of the heterocyclic ring, 128.71, 129.27, 130.30, 130.46 (C-atoms of the phenyl group); MS m/z (%) 353 ($M^+$+1, 1), 352 ($M^+$, 6), 350 (36), 233 (34), 148 (12), 132 (10) 122 (12), 118 (23), 107 (14), 91 (79), 90 (100), 89 (33), 79 (11), 77 (47), 51 (71). Anal. Calcd. for $C_{14}H_{16}N_4O_5S$ (352.37): C, 47.72; H, 4.58; N, 15.90. Found: C, 47.65; H, 4.61; N, 15.88%.

**3.3.2 3-(D-Manno-pentitol-1-yl)-6-phenyl-s-triazolo[3,4-b][1,3,4]-thiadiazole (5b).** Yellow brown solid, yield 50%, mp. 185 °C (EtOH), IR(KBr) $\nu$ ($cm^{-1}$) 3322, 1565; $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.20–5.23 (sugar moiety), 7.43–8.14 (m. 5H); MS m/z (%) 353 ($M^+$+1, 1), 352 ($M^+$, 6), 280 (91), 279 (22), 202 (32), 179 (67) 162 (16), 148 (7), 121 (82), 118 (73), 103 (25), 91 (20), 90 (100), 89 (39), 77 (52). Anal. Calcd. for $C_{14}H_{16}N_4O_5S$ (352.37): C, 47.72; H, 4.58; N, 15.90. Found: C, 47.80; H, 4.60; N, 15.85%.



**3.3.3 3-(D-Arabino-tetritol-1-yl)-6-phenyl-s-triazolo[3,4-b][1,3,4]-thiadiazole (5c).** Yellow brown solid, yield 40%, mp. 235 °C (EtOH), IR(KBr) $\nu$ ($cm^{-1}$) 3447, 1585; $^1H$ NMR (DMSO-$d_6$) $\delta$ 3.44–5.24 (sugar moiety), 7.43–7.81 (m. 5H); MS m/z (%) 323 ($M^+$+1, 1), 322 ($M^+$, 4), 283 (13), 178 (24), 148 (4), 120 (41), 106 (31), 91 (13), 90 (33), 77 (100), 76 (31), 51 (71). Anal. Calcd. for $C_{13}H_{14}N_4O_4S$ (322.34): C, 48.44; H, 4.38; N, 17.38. Found: C, 48.41; H, 4.40; N, 17.33%.

### 3.4 *Alternate synthesis of 3-(D-Gluco-pentitol-1-yl)-6-phenyl-s-triazolo[3,4-b][1,3,4] thiadiazole (5a)*

A solution of 3-(1,2,3,4,5-penta-O-benzoyl-D-gluco-pentitol-1-yl)-6-phenyl-1,2,4-triazolo-[3,4-b][1,2,4]thiadiazole **9a**, prepared by literature method [7] (1.75 g, 0.001 mol) in methanol (20 ml) was treated with ammonia solution (20%, 15 ml) and kept at room temperature for 16 h. The resulting solution was evaporated under reduced pressure and the solid product was crystallized from ethanol to give 6-Phenyl-3-(D-gluco-pentitol-1-yl)-s-triazolo[3,4-b][1,3,4]thiadiazole (**5a**) as yellowish brown solid, yield 30%, m.p. 240 °C, identical in all respects with that one obtained from oxidative cyclization of **4a**.

### 3.5 *Benzoylation of 5a (alternate synthesis of 9a)*

To a suspension of compound **5a** (3.52 g, 0.01 mol) in dry pyridine (50 ml) was added benzoyl chloride (6.43 g, 0.06 mol) and the reaction mixture was refluxed for 2 h and left to cool. The solid produced was filtered, washed with water and crystallized from ethanol to give 3-(1,2,3,4,5-penta-O-benzoyl-D-gluco-pentitol-1-yl)-6-phenyl-1,2,4-triazolo-[3,4-b][1,2,4]-thiadiazole **9a** as white needles in 65% yield, m.p. 159–160 °C) (Lit. m.p. 158–160 °C [7]).

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