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Synthesis of Some Derivatives of 2,5-Anhydro-D-mannitol

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Abstract

The synthesis of 2,5:3,4-dianhydro-D-allitol and of a variety of derivatives (sulfonyloxy, deoxy, azido, iodo, etc.) of 2,5-anhydro-D-mannitol is described.

Recently we described[1] some of the results of a structure–activity study on the enzyme invertase (β-D-fructofuranosidase, EC 3.2.1.26) from *Candida utilis.* It was noted that the non-glycosidic analogue of methyl β-D-fructofuranoside (1), namely 2,5-anhydro-D-mannitol (2), acted as a weak inhibitor (K_i 125) of the enzyme. Non-glycosidic analogues such as (2) cannot of course be 'hydrolysed' by invertase and it was considered worthwhile to synthesize some analogues of (2) that might be stronger inhibitors of the enzyme. We now report the synthesis of a number of previously unknown derivatives of compound (2). Several such derivatives have been prepared previously, namely the 1,6-di-*O*-trityl,[2]* 1,6-di-*O*-tosyl,[2] 1,6-dideoxy,[3] and 1-deoxy-1,1-difluoro[4,5] derivatives. The 1,6-dideoxy compound was prepared by Cope and Shen[3] from the reaction of hydrogen chloride with 1,4:2,5:3,6-trianhydro-D-mannitol. We have synthesized the 1,6-dideoxy compound by a different route, thus confirming their assignment and the mode of ring-opening.

Synthesis of compounds (3)–(23) has been by essentially conventional routes. The oxiran derivative (22) (2,5:3,4-dianhydro-D-allitol) was prepared directly from (2) in high yield by using triphenylphosphine and diethyl azodicarboxylate in dimethylformamide. Protection of the primary hydroxyl groups was not required and, as (2) has a twofold rotation axis, only one oxiran derivative is possible.

The effect of these compounds on invertase will be described elsewhere.

Experimental

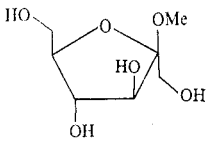
Melting points were determined on a Buchi 'Tottoli' melting point apparatus and are uncorrected. ^{1}H n.m.r. spectra were recorded at 60 MHz on a Varian EM-360 spectrometer, at 100 MHz on a

* Trityl (Tr) = triphenylmethyl.

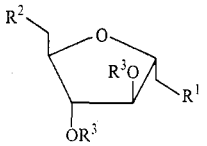
[1] Guthrie, R. D., Jenkins, I. D., Rogers, P. J., Sum, W. F., Watters, J. J., and Yamasaki, R., *Carbohydr. Res.*, 1979, **75**, C1.
[2] Akiya, S., and Osawa, T., *Yakugaku Zasshi*, 1954, **74**, 1259.
[3] Cope, A. C., and Shen, T. Y., *J. Am. Chem. Soc.*, 1956, **78**, 5912.
[4] Kent, P. W., Barnett, J. E. G., and Wood, K. R., *Tetrahedron Lett.*, 1963, 1345.
[5] Wood, K. R., and Kent, P. W., *J. Chem. Soc. C*, 1967, 2422.

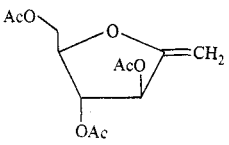
JEOL PX-100 spectrometer and at 270 MHz on a Bruker HX-270 spectrometer (through the courtesy of the Australian NMR Centre) and are for solutions in $CDCl_3$ unless otherwise stated. ^{13}C n.m.r. spectra were obtained at 22·3 MHz on a Bruker HX-90 spectrometer. Single frequency off-resonance decoupling and polarization transfer (p.t.) spectroscopy[6] were used to assist in the assignment of peaks. I.r. spectra were determined on a Perkin–Elmer 377 spectrometer. Optical rotations were measured at room temperature (25° ± 1) in a 1-dm tube on a Perkin–Elmer 241 polarimeter, in chloroform unless otherwise stated. Acetylation was carried out with acetic anhydride and pyridine for 24 h at room temperature.

Column chromatography on silica gel was carried out over Merck Kieselgel 60 (70–230 mesh). Flash chromatography was conducted with Merck Kieselgel 7739 (230–400 mesh) according to the literature procedure.[7] Thin-layer chromatography was performed over Merck Kieselgel 60 GF_{254}. Organic solutions were evaporated in a vacuum at a bath temperature of less than 50°. Microanalyses were carried out by the Australian Microanalytical Service, Melbourne, or by the Department of Chemistry, Queensland University (Mr J. Kemp).



(1)





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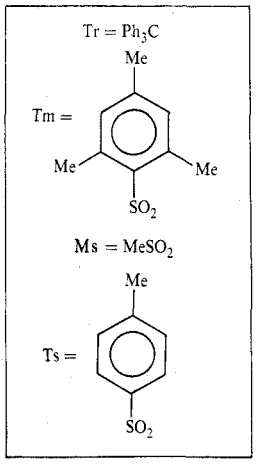
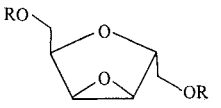


	R^1	R^2	R^3
(2)	OH	OH	H
(3)	OTr	OTr	H
(4)	OTr	OH	H
(5)	OTr	OTr	OTs
(6)	OTr	OAc	Ac
(7)	OH	OAc	Ac
(8)	OMe	OAc	Ac
(9)	OTm	OTm	H
(10)	OTm	OH	H
(11)	OMs	OMs	H
(12)	OMs	OH	H
(13)	OMs	OAc	Ac
(14)	OTs	OH	H
(15)	OTs	OTs	H
(16)	OTs	OTs	Ac
(17)	OTs	OAc	Ac
(18)	I	OAc	Ac
(20)	N_3	N_3	H
(21)	H	H	H



(22) R = H
(23) R = Ac

*Tritylation of 2,5-Anhydro-*D*-mannitol* (2)

A solution of compound (2) (200 mg) and trityl chloride (340 mg, 1 equiv.) in dry pyridine (2 ml) was heated on a boiling water bath for 2 h. After cooling, the mixture was poured into ice and water and extracted with chloroform. Evaporation gave a syrup which was separated into two components by p.l.c. (chloroform/methanol 97:3): *2,5-anhydro-1,6-di-*O*-trityl-*D*-mannitol* (3) (89 mg, 12%) and *2,5-anhydro-1-*O*-trityl-*D*-mannitol* (4) (153 mg, 33%).

The ditrityl ether (3) was characterized by tosylation in the usual manner to yield *2,5-anhydro-3,4-di-*O*-tosyl-1,6-di-*O*-trityl-*D*-mannitol* (5) (76%), m.p. 183° (chloroform/methanol), $[\alpha]_D$ +39°

[6] Doddrell, D. M., and Pegg, D. T., *J. Am. Chem. Soc.*, 1980, **102**, 6388.
[7] Still, W. C., Khan, M., and Mitra, A., *J. Org. Chem.*, 1978, **43**, 2923.

(*c*, 1·0) (Found: C, 72·5; H, 5·7. $C_{58}H_{52}O_9S_2$ requires C, 72·8; H, 5·4%). ^{1}H n.m.r.: δ 2·34, s, 6H, $2\times CH_3$; 3·12, m, 4H, H1,1′,6,6′; 4·14, m, 2H, H2,5; 5·17, d, 2H, H3,4, $J_{3,4}$ 3 Hz; 7·0–7·64, m, 23H, aromatic.

The mono-ether (4) was characterized by acetylation to give *3,4,6-tri-*O*-acetyl-2,5-anhydro-1-*O*-trityl-*D*-mannitol* (6) in 81% yield, m.p. 96–97° (methanol), $[\alpha]_D$ +34° (*c*, 1·0) (Found: C, 70·1; H, 6·3. $C_{31}H_{32}O_8$ requires C, 69·9; H, 6·1%). ^{1}H n.m.r. (60 MHz): δ 2·03, 2·10, 2·13, s, 3H each, $COCH_3$; 3·2–3·43, m, 2H, H6,6′; 4·29, s, 4H, H1,1′,2,5; 5·17, m, 1H, H4; 5·45, m, 1H, H3; 7·15–7·75, m, 15H, aromatic.

*3,4,6-Tri-*O*-acetyl-2,5-anhydro-*D*-mannitol* (7)

To a chilled solution of compound (6) (2·0 g) in acetic acid (5 ml), was added hydrogen bromide in acetic acid (1·0 ml, 45% w/v) dropwise with shaking. The mixture was shaken for a further 5 min and the yellow precipitate was collected. The filtrate was poured into ice and water containing sodium acetate (1·0 g), and extracted with chloroform. Evaporation gave a light-coloured syrup which was purified by p.l.c. (ether) to give the *title compound* as a syrup (0·7 g, 63%), $[\alpha]_D$ +32° (*c*, 1·0) (Found: C, 49·5, H, 6·0. $C_{12}H_{18}O_8$ requires C, 49·3, H, 6·2%). ^{1}H n.m.r. (100 MHz): δ 2·08, s, 9H, $COCH_3$; 3·74, bs, 2H, H6,6′; 4·07, m, 2H, H5, 6-OH; 4·21, s, 3H, H1,1′,2; 5·16, m, 2H, H3,4.

*3,4,6-Tri-*O*-acetyl-2,5-anhydro-1-*O*-methyl-*D*-mannitol* (8)

Methylation of compound (7) (200 mg) with methyl iodide and freshly prepared silver oxide (1·0 g) gave the *title compound* as a thin syrup, $[\alpha]_D$ +39° (*c*, 1·1) (Found: C, 51·4; H, 6·5. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·6%). ^{1}H n.m.r. (100 MHz): δ 2·08, s, 9H, $COCH_3$; 3·37, s, 3H, OCH_3; 3·53, m, 2H, H6,6′; 4·06–4·28, m, 4H, H1,1′,2,5; 6·14, m, 2H, H3,4.

Trimsylation of Compound* (2)

Compound (2) (328 mg) was treated with trimsyl chloride (437 mg, 0·72 equiv.) in pyridine (6 ml) at *c.* 3° overnight and then at room temperature for 5 h. The mixture was poured into ice and water (100 ml). The precipitate was collected and washed with water. Recrystallization from aqueous ethanol gave *2,5-anhydro-1,6-di-*O*-trimsyl-*D*-mannitol* (9) (156 mg, 15%), m.p. 96–97°, $[\alpha]_D$ +25·2° (*c*, 1·0) (Found: C, 54·6; H, 6·1. $C_{24}H_{32}O_9S_2$ requires C, 54·6; H, 6·1%). ^{1}H n.m.r. (60 MHz): δ 2·23, s, 6H, *p*-CH_3; 3·7–4·15, m, 10H, H1,1′,2,3,4,5,6,6′, 3-OH, 4-OH; 7·02, s, 4H, aromatic; ^{13}C n.m.r. ($CDCl_3$): 20·6, *p*-CH_3; 22·7, *o*-CH_3; 69·5, C1,6; 77·7, C3,4; 81·7, C2,5; 132·7, 140·6, 143·1, aromatic.

The filtrate was extracted with chloroform (5 × 50 ml). Evaporation gave a white solid which was recrystallized from chloroform and light petroleum to give *2,5-anhydro-1-*O*-trimsyl-*D*-mannitol* (10) (297 mg, 40%), m.p. 125°, $[\alpha]_D$ +30·1° (*c*, 1·0 in methanol) (Found: C, 52·1; H, 6·4. $C_{15}H_{22}O_7S$ requires C, 52·0; H, 6·4%). ^{1}H n.m.r. [60 MHz; $(CD_3)_2CO$]: δ 2·37, s, 3H, *p*-CH_3; 2·60, s, 6H, *o*-CH_3; 3·17–4·72, m, 11H, H1,1′,2,3,4,5,6,6′, 3-OH, 4-OH, 6-OH; 7·13, s, 4H, aromatic; ^{13}C n.m.r. ($CDCl_3$): 20·7, *p*-CH_3; 22·7, *o*-CH_3; 62·8, C6; 70·0, C1; 78·4, 78·6, C3, C4; 82·5, C2; 85·7, C5; 132·8, 140·6, 143·2, aromatic.

Mesylation of Compound (2)

(A) *With two equivalents.*—Compound (2) (100 mg) was dissolved in pyridine (2 ml) and the solution was cooled in an acetone/dry ice bath. A chilled solution (ice bath) of mesyl chloride (100 μl) in pyridine (2 ml) was added to the solution of compound (2). After being kept at −20° for 48 h and at 0° for 24 h, the mixture was evaporated to a syrup which was chromatographed (chloroform/methanol 4:1). The major product was recrystallized from ethanol to give *2,5-anhydro-1,6-di-*O*-mesyl-*D*-mannitol* (11) (75 mg, 38%), m.p. 104–106°, $[\alpha]_D$ +40° (*c*, 0·5 in H_2O) (Found: C, 30·3; H, 5·1. $C_8H_{16}O_9S_2$ requires C, 30·0; H, 5·0%). ^{1}H n.m.r. [100 MHz, $(CD_3)_2SO$]: δ 3·15, s, 6H, CH_3; 3·25, s, 2H, 3-OH, 4-OH; 3·60–4·02, m, 4H, H1,1′,6,6′; 4·02–4·38, m, 4H, H2,3,4,5.

* Trimsyl (Tm) = 2,4,6-trimethylbenzenesulfonyl.

(B) *With one equivalent.*—Mesyl chloride (1·0 ml) in pyridine (9 ml) was added dropwise to a solution of compound (2) (2·0 g) in pyridine (15 ml) at −40°, and the mixture was allowed to stand for 24 h at 0°. The mixture was evaporated to a syrup which was chromatographed (ethyl acetate/methanol 9:1) to give compound (11) (585 mg, 15%) and *2,5-anhydro-1-O-mesyl-D-mannitol* (12) (1·7 g, 52%), $[\alpha]_D$ +42° (*c*, 2·3 in H_2O) (Found: C, 34·9; H, 6·1. $C_7H_{14}O_7S$ requires C, 34·7; H, 5·8%). ^{1}H n.m.r. (100 MHz, CD_3OD): δ 3·06, s, 3H, CH_3; 3·64, m, 2H, H1,1′; 3·72–4·08, m, 5H, H3,4, 3-OH, 4-OH, 6-OH; 4·31, m, 2H, H2,5; ^{13}C n.m.r. [$(CD_3)_2CO$]: 37·4, CH_3; 62·9, C6; 70·9, C1; 78·5, C3,4; 82·4, C2; 85·4, C5.

3,4,6-Tri-O-acetyl-2,5-anhydro-1-O-mesyl-D-mannitol (*13*)

Acetylation of compound (12) (5·0 g) followed by chromatography (acetone/hexane 1:4) gave the *title compound* as a syrup (6·5 g, 84%), $[\alpha]_D$ +18·3° (Found: C, 42·2; H, 5·6. $C_{13}H_{20}O_{10}S$ requires C, 42·4; H, 5·5%). ^{1}H n.m.r. (100 MHz): δ 2·11, s, 9H, $COCH_3$; 3·08, s, 3H, CH_3SO_2; 4·23–4·48, m, 6H, H2,3,4,5,6a,6b; 5·17, s, 2H, H1,1′; ^{13}C n.m.r. [$(CD_3)_2CO$]: δ 20·7, Ac-CH_3; 37·5, Ms-CH_3; 63·2, C6; 68·7, C1; 78·2, C3,4; 81·3, C2,5; 170·1, C=O.

2,5-Anhydro-1-O-tosyl-D-mannitol (*14*)

A solution of tosyl chloride (570 mg, 0·9 equiv.) in pyridine (5 ml) was cooled to the point of crystallization and added dropwise to compound (2) (490 mg) dissolved in pyridine (5 ml), the temperature being maintained between −40 and −35°. After being set aside at 0° for 16 h and then at room temperature for 48 h, the solution was poured into ice and water. The precipitate was collected, and recrystallized from ethanol to give *2,5-anhydro-1,6-di-O-tosyl-D-mannitol* (15) (118 mg, 8%), m.p. 131–133° (lit.[2] 133·5°). The filtrate was evaporated and the syrup obtained was purified by p.l.c. (chloroform/methanol 9:1) to give the *title compound* (350 mg, 37%), m.p. 107–109° (water), $[\alpha]_D$ +36° (*c*, 1·0 in water) (Found: C, 48·5; H, 6·0. $C_{13}H_{18}O_7S$ requires C, 49·0; H, 5·7%). ^{1}H n.m.r. [60 MHz, $(CD_3)_2CO$]: δ 2·46, s, 3H, CH_3; 3·40–4·8, m, 11H, H1,1′,2,3,4,5,6,6′, 3-OH, 4-OH, 6-OH; 7·42–7·93, m, 4H, aromatic. This was further characterized as the diacetate (16), as repeated analyses failed to improve the carbon analysis. Traces of water of hydration may mean that the reported $[\alpha]_D$ is slightly low.

3,4-Di-O-acetyl-2,5-anhydro-1,6-di-O-tosyl-D-mannitol (*16*)

Acetylation of compound (15) gave the *title compound* (85%), m.p. 142–143° (ethanol), $[\alpha]_D$ +40° (*c*, 1·0) (Found: C, 51·8; H, 5·3. $C_{24}H_{28}O_{11}S_2$ requires C, 51·8; H, 5·1%). ^{1}H n.m.r. (60 MHz): δ 2·03, s, 6H, $COCH_3$; 2·43, s, 6H, 2×CH_3; 4·15, s, 6H, H1,1′,2,5,6,6′; 5·11, m, 2H, H3,4; 7·31–7·90, m, 8H, aromatic.

3,4,6-Tri-O-acetyl-2,5-anhydro-1-O-tosyl-D-mannitol (*17*)

(A) Acetylation of compound (14) gave the *title compound* as a syrup (66%), $[\alpha]_D$ +40° (*c*, 1·0) (Found: C, 51·0; H, 5·2. $C_{19}H_{24}O_{10}S$ requires C, 51·3; H, 5·4%). ^{1}H n.m.r. (60 MHz): δ 2·1, s, 9H, $COCH_3$; 2·4, s, 3H, Ts-CH_3; 4·2, s, 6H, H1,1′,2,5,6,6′; 5·1, s, 2H, H3,4; 7·2–7·8, m, 4H, aromatic.

(B) Treatment of compound (7) (63 mg) with tosyl chloride (70 mg) in pyridine (3 ml) at room temperature for 3 days, followed by purification by p.l.c. (ether/light petroleum 3:2), gave a syrup (56 mg, 53%), identical (t.l.c.) to that prepared in (A).

3,4,6-Tri-O-acetyl-2,5-anhydro-1-deoxy-1-iodo-D-mannitol (*18*)

Compound (13) (6·0 g) was treated with sodium iodide (3·6 g, 3 equiv.) in dimethylformamide (50 ml) for 4 h at 90°. Evaporation of the mixture gave a syrup which was chromatographed (acetone/hexane 1:4) to give the *title compound* as a syrup (5·2 g, 81%), $[\alpha]_D$ +3·7° (Found: C, 36·0; H, 4·5. $C_{12}H_{17}IO_7$ requires C, 36·0; H, 4·3%). ^{1}H n.m.r. (60 MHz): δ 2·14, s, 9H, $COCH_3$; 3·36–3·42, m, 2H, H1,1′; 4·03–4·36, m, 4H, H2,5,6,6′; 5·10–5·30, m, 2H, H3,4; ^{13}C n.m.r. [$(CD_3)_2CO$]: 6·15, C1; 20·7, CH_3; 63·7, C6; 79·6, C4; 81·6, C3,5; 82·9, C2; 170·2, C=O.

3,4,6-Tri-O-acetyl-2,5-anhydro-D-arabino-*hex-1-enitol* (*19*)

Compound (18) was shaken with silver fluoride (2 g) in dry pyridine (40 ml) for 7 h. The mixture was diluted with chloroform (60 ml) and passed through Celite. The filtrate was washed with water, aqueous sodium thiosulfate solution, and water. Evaporation gave a syrup which was chromatographed (ethyl acetate/hexane 1:3) to give the *title compound* as an unstable syrup, $[\alpha]_D$ −3·4° (Found: C, 52·8; H, 6·0. $C_{12}H_{16}O_7$ requires C, 52·9; H, 5·9%). ^{1}H n.m.r. (60 MHz): δ 2·13, s, 9H, $COCH_3$; 4·18–4·65, m, 5H, H3,4,5,6,6′; 5·15, t, 1H, H1, $J_{1,1'}$ *c.* 1·5 Hz, $^3J_{1',3}$ *c.* 1·5 Hz; ^{13}C n.m.r. [$(CD_3)_2CO$]: 20·6, CH_3; 63·2, C6; 75·3, 76·5, C3,4; 82·4, C5; 86·6, C1; 159·3, C2; 169·8, 170·1, 170·5, C=O.

2,5-Anhydro-1,6-diazido-1,6-dideoxy-D-*mannitol* (*20*)

Compound (15) (1·7 g) was treated with sodium azide (1·0 g) in dry DMF (10 ml) for 4 h at 95°. Evaporation and purification of the product by p.l.c. (chloroform/methanol 9:1) gave the *title compound* as a syrup (367 mg, 48%), $[\alpha]_D$ +114° (*c*, 2·0) (Found: C, 33·4; H, 4·6. $C_8H_{10}N_6O_3$ requires C, 33·6; H, 4·7%). ^{1}H n.m.r. (60 MHz): δ 6·5, m, 6H, H1,1′,6,6′, 3-OH, 4-OH; 4·1, m, 4H, H2,3,4,5.

2,5-Anhydro-1,6-dideoxy-D-*mannitol* (*21*)

Treatment of compound (9) (140 mg) with lithium aluminium hydride (1 g) in ether (20 ml) for 2·5 h under reflux, followed by p.l.c. (methylene chloride/methanol 9:1), gave the *title compound* as a syrup, $[\alpha]_D$ +30° (*c*, 1·5 in methanol). ^{1}H n.m.r. [60 MHz, $(CD_3)_2CO$]: δ 1·32, d, 6H, H1,6, $J_{1,2}$, $J_{5,6}$ *c.* 6 Hz; 3·60–4·05, m, 4H, H2,3,4,5; 4·36, s, 2H, 3-OH, 4-OH.

The product was characterized as its known diacetate (61%), $[\alpha]_D$ +14° (*c*, 2·75 in MeOH), [lit.[3] $[\alpha]_D$ +15° (*c*, 8·2 in MeOH)]. The same product could be obtained by a similar reaction sequence on 2,5-anhydro-1,6-di-*O*-tosyl-D-mannitol.

2,5:3,4-Dianhydro-D-*allitol* (*22*)

To a solution of compound (2) (1·1 g) and triphenylphosphine (3·5 g, 2 equiv.) in dimethylformamide (18 ml) diethyl azodicarboxylate (2·2 ml, 2 equiv.) in dimethylformamide (2 ml) was added dropwise with stirring at 0°. After warming to room temperature with stirring for 2 h, the mixture was evaporated to a thick syrup. Flash chromatography (3 × 15 cm, acetone/dichloromethane 1:1) of the mixture gave the *title compound* as a syrup (815 mg, 83%), $[\alpha]_D$ −67·6° (methanol). ^{13}C n.m.r. [$(CD_3)_2CO$]: 57·2, 58·2, C3,4; 62·3, 63·4, C1,6; 78·9, 79·8, C2,5. The compound was characterized as its diacetate (23).

Acetylation of compound (22) (100 mg) followed by flash chromatography (2 × 15 cm, acetone/hexane 1:2) gave *1,6-di-O-acetyl-2,5:3,4-dianhydro*-D-*allitol* (23) an oil (160 mg, 83%), $[\alpha]_D$ −53·5° (Found C, 51·9; H, 6·1. $C_{10}H_{14}O_6$ requires C, 52·2; H, 6·1%). ^{1}H n.m.r. (270 MHz, C_6D_6): δ 1·65, 1·67, s, 3H each, $COCH_3$; 3·05, d, 1H, H4, $J_{3,4}$ 2·9 Hz, $J_{4,5}$ 0 Hz; 3·20, d, 1H, H3, $J_{2,3}$ 0 Hz; 3·72, dd, 1H, H6, $J_{5,6}$ 6·2 Hz, $J_{6,6'}$ −10·7 Hz; 3·79, dd, 1H, H6′, $J_{5,6'}$ 5·7 Hz; 3·89, dd, 1H, H5; 3·90, dd, 1H, H2, $J_{1,2}$ 6·2 Hz, $J_{1',2}$ 5·7 Hz; 4·23, dd, 1H, H1′, $J_{1,1'}$ −11·7 Hz; 4·36, dd, 1H, H1.

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