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# The Synthesis of 3α-/3β- Cholesteryl and Cholestanyl Esters and Ethers - an Assessment of their Mesogenicity

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Several 3α- and 3β- esters and ethers of cholesterol and cholestanol have been prepared and their synthesis and mesogenicity is discussed.

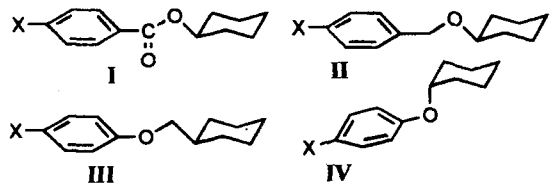
*Keywords:* cholesterol; cholestanol; chiral nematic; esters; ethers; inversion

With the preparation of cholesteryl benzoate in 1888, cholesteryl esters hold the unique distinction of defining the oldest known group of calamitic liquid crystals. Over the years, cholesteric liquid crystals have been used in many thermochromic applications, but since the 1980's, non-steroidal based derivatives have been preferred. Esters derived from cholesterol are difficult to purify, they vary in quality depending on the source of the cholesterol and are photochemically unstable; for these reasons, chiral nematics based on esters with (*S*)-2-methylbutylphenyl or (*S*)-2-methylbutylbiphenyl components have been produced commercially[1-4].

None the less, cholesterol- and cholestanol-derived thermochromic materials still have the advantage of being cheaper to prepare than other chiral nematics, and provided that their purity and photochemical stability is

acceptable they are valuable materials. In this article we report various attempts to improve the utility of steroid-based compounds as thermochromic materials and we discuss some synthetic problems encountered.

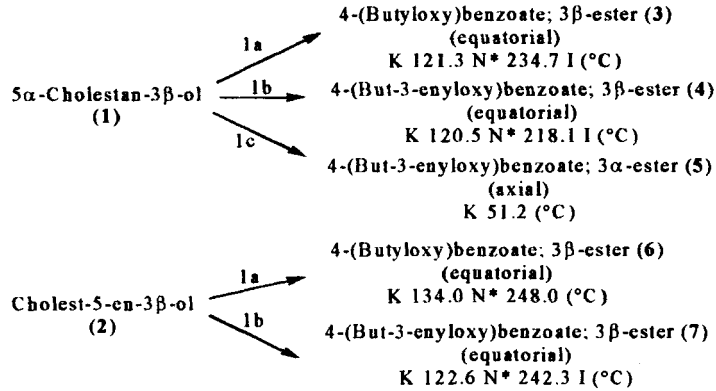
The approaches that we are considering with respect to improving the stability of steroid-based cholestrogens, are the replacement of the ester link to the steroid unit (**I**), (see figure 1), with a more stable ether link (**II-IV**), and an assessment of the potential mesogenicity of esters and ethers with axial versus equatorial connections. The derivatives **I-III**, with 3β-equatorial substituents and two linking atoms between the aryl unit and the steroid, still have approximately the required geometry to maintain the calamitic shape of the molecule. In addition structure **IV** with a 3α-axial substituent may still provide examples of molecules with acceptable shapes. A suitable way of obtaining an axial (3α-) attachment of esters and ethers to cholestanol is to use the diethyl azodicarboxylate (DEAD) in a substitution procedure with carboxylic acids or phenols in the Mitsunobu reaction[5]; this method proceeds with inversion of the stereochemistry of the alcohol. For cholesterol, however, the situation is less clear-cut because the C5-C6 double bond can interfere with reactions at the 3-position and side reactions can occur producing products that are formed with retention of stereochemistry at the reaction site[6].




X = R, RO, aryl *etc.*
The cyclohexane ring represents ring A of cholesterol or cholestanol

**Figure 1:** Steroid derivatives being studied

Another structural modification we have been investigating is the incorporation of an isolated (*i.e.*, non-conjugated) double bond in a terminal chain to assess its effect on the brightness of the selective reflection. A derivative of cholestanol, compound **4**, is one of the materials prepared for this aspect of the work and its transition temperatures (see Scheme 1), in comparison with those for compound **3**, with a saturated butyloxy chain, show that the double bond leads to a reduction of ~17 °C in the clearing point. Compounds **7** and **6**[7] are the analogous pair of compounds based on cholesterol and once again the effect of the double bond is to decrease the clearing point, in this case by ~6 °C. Comparison of the transition temperatures for **3** and **6** and for **4** and **7** shows the typical result that cholestanol derivatives have clearing points approximately 15-25 °C lower than for the cholesterol compounds. Thus the C5 double bond in cholesterol and the double bond in the terminal chain have opposite effects on the degree of mesophase stability.




1a...DCC, DMAP, DCM, 4-butyloxybenzoic acid
1b...DCC, DMAP, DCM, 4-(but-3-enyloxy)benzoic acid
1c...DEAD, $PPh_3$, THF, 4-(but-3-enyloxy)benzoic acid

**Scheme 1**

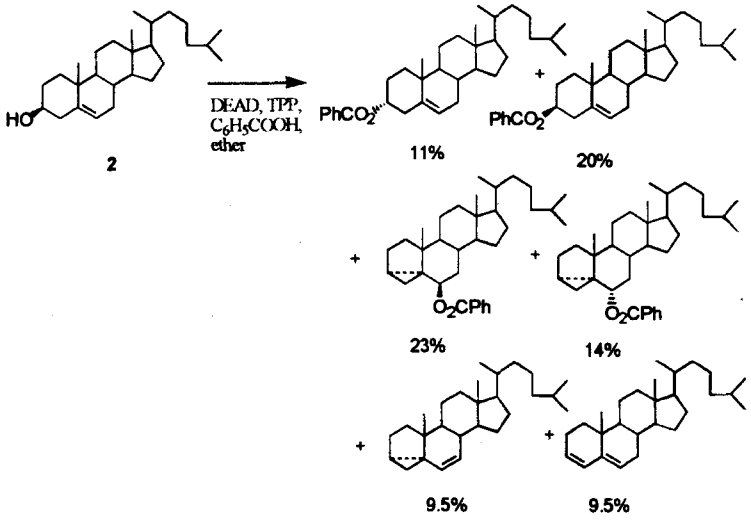
The axial (3α-) derivative (**5**) corresponding to the equatorial (3β-) compound **4** was prepared, to determine whether or not the molecule was able to overcome the severe distortion from linearity of its molecular shape and still be mesogenic. The melting point of compound **5** was lowered to 51.2 °C, but the compound was not mesogenic and did not exhibit a mesophase even on cooling down to -75 °C; the axial attachment of the ester has therefore caused a reduction in the $T_{N^*\text{-}I}$ value of more than 290 °C.

Another structural variation that was employed was to use an ether link (with a single atom between the aryl and steroid units) rather than the two-atom link of an ester. Molecular modelling of these systems shows that the axial ether has a more rod-like shape than the equatorial ether or the axial ester. The axial ethers of cholestanol (**15**, **18** and **19**) were therefore prepared but none of these compounds was found to be mesogenic above -75 °C.

## Discussion of synthesis

Bose *et al.*[8] have shown that inversion of stereochemistry at the 3-position of 5α-cholestan-3β-ol occurs in a quantitative esterification with benzoic acid using DEAD in THF in a Mitsunobu procedure; they confirmed this observation by converting 5α-cholestan-3β-ol, *via* its tosylate, into 5α-cholestan-3α-ol, which was then esterified using an acid chloride. The reverse reaction using 5α-cholestan-3α-ol (in THF) failed, but Loibner *et al.*[9] subsequently transformed 5α-cholestan-3α-ol into a 5α-cholestan-3β-yl benzoate (73% yield) with DEAD and benzoic acid in benzene, thus showing that the conversion of equatorial alcohol to axial ester or axial alcohol to equatorial ester is feasible in good yield, and that the role of the solvent is crucial. These reactions are straightforward for the 5α-cholestan-3-ols and they are also successful with cholest-4-ene-3β-ol[10] so that the 3α-benzoate is

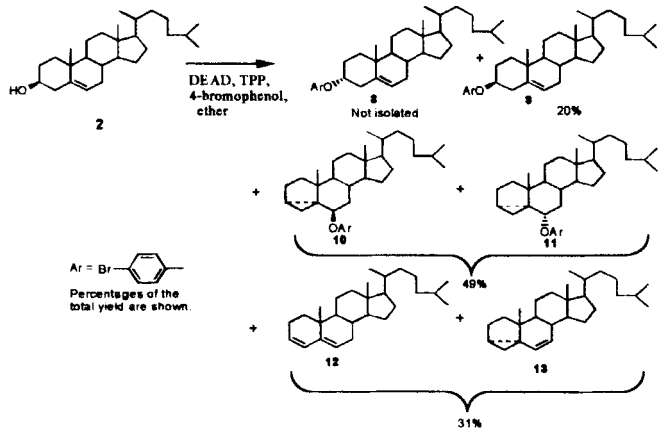
obtained in 81% yield. However, if cholest-5-ene-3β-ol (**2**) (normal cholesterol) is used, the corresponding inversion product is not obtained because of the intervention of the 5-ene double bond. Aneja *et al.*[6] have reported that cholesterol esterified with benzoic acid using DEAD gave all possible products resulting from intermediate homoallylic carbocation formation (see Scheme 2).



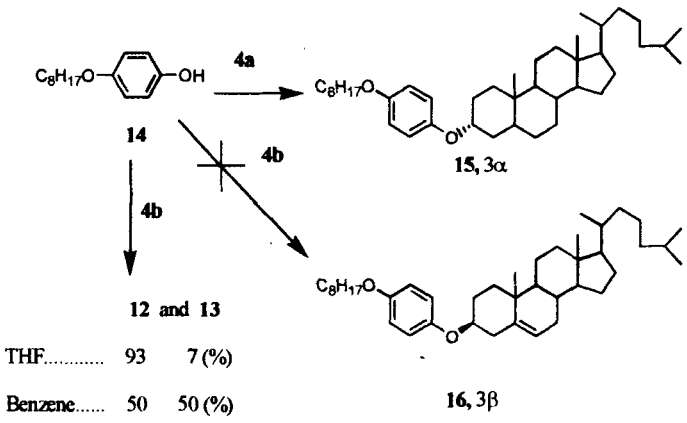

**Scheme 2:** Products from the esterfication of cholesterol (**2**)[6]

Etherification and esterification can both be achieved in Mitsunobu conditions, simply by using either a phenol or an acid; Manhas *et al.*[11] have reported a convenient synthesis of aryl ethers based on this procedure. Using phenol and 4-bromophenol in a Mitsunobu reaction with cholestan-3β-ol in THF, they prepared the 3α-phenyl and 3α-(4-bromo)phenyl ethers (with inversion of configuration) in 80 and 65% yields respectively, and using cholesterol the 3β-phenyl and 3β-(4-bromo)phenyl ethers (with retention of

configuration) were obtained in 65 and 60% yields respectively. We attempted to prepare compound **9** (see Scheme 3) so that coupling at the bromo site would allow a variety of more elaborate 3β-cholesteryl ethers to be prepared. However, our reaction of 4-bromophenol and cholesterol in ether, in contrast to the work of Manhas *et al.*[11] in THF, gave all the products resulting from homoallylic carbocation formation; in addition only a poor yield of compound **9** was obtained (see Scheme 3). The pKa or nucleophilicity of the phenol appears to be important in the Mitsunobu formation of aryl ethers of cholesterol. The reaction using cholesterol and 4-octyloxyphenol (pKa ~10.5) (Scheme 4) failed whereas phenol (pKa 9.9) and 4-bromophenol (pKa 9.25) (ref. 11 and Scheme 3) were successful. It is unwise to make generalisations on the results from reactions involving only three different phenols, but our findings showing that the most acidic phenol gives the best yield of aryl ether are in keeping with reports on reactions using 5α-cholestan-3α-ol, 5α-cholestan-3β-ol and (-)-menthol[12].

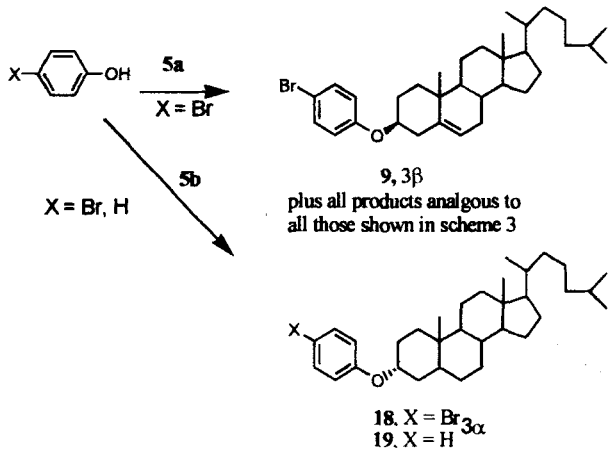



**Scheme 3:** Etherification of cholesterol (**2**)




**4a...** DEAD, $PPh_3$, THF, 5α-cholestan-3β-ol (**1**)
**4b...** DEAD, $PPh_3$, THF or benzene, cholest-5-en-3β-ol (**2**)

**Scheme 4:** Etherification of cholestanol (**1**) and cholesterol (**2**) using 4-octyloxyphenol (**14**)




**5a...** DEAD, $PPh_3$, THF, cholest-5-en-3β-ol (**2**)
**5b...** DEAD, $PPh_3$, THF, 5α-cholestan-3β-ol (**1**)

**Scheme 5:** Etherification of cholestanol (**1**) and cholesterol (**2**) using phenol and 4-bromophenol.

## SUMMARY

The double bond in the terminal chain of compounds **4** and **7** reduces melting points and clearing points compared to the values for compound **3** and **6** respectively; the double bond in cholesteryl systems raises melting points and clearing points (compare **6** and **3**, **7** and **4**). Axial esters (**5**), equatorial ethers (**9**) and axial ethers (**15**, **18**, **19**) of cholestanol or cholesterol have been prepared and they are non-mesogenic. The Mitsunobu reactions of cholesterol and phenols are critically dependent on the solvent and the acidity of the phenol.


## EXPERIMENTAL

**5α-Cholestan-3β-yl 4-(butyloxy)benzoate (3)**

*N,N'*-Dicyclohexylcarbodiimide (DCC) (0.01 mol) was added to a stirred solution of 5α-cholestan-3β-ol (**1**) (0.01 mol), 4-butyloxybenzoic acid (0.01 mol), 4-*N,N*-(dimethylamino)pyridine (DMAP) (0.001 mol) in dichloromethane (30 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred overnight (TLC analysis revealed a complete reaction), filtered, and the solvent removed from the filtrate *in vacuo* to give a white solid. The crude product was purified by column chromatography [silica gel/HPLC grade hexane:ethyl acetate, 5.66:1], followed by recrystallisation (ethyl acetate) to give white crystals that were dried *in vacuo*.

Yield 30%, transition temperatures K 121.3 N* 234.7 I °C; $^1$HNMR ($CDCl_3$) δ 0.65 (3H, s), 0.83–1.98 (50H, m), 3.99 (2H, t), 4.86 (1H, m), 6.89 (2H, d), 7.92 (2H, d) ; IR (KBr) $\nu_{max}$ 2930, 2910, 2880, 1720, 1620, 1290, 1165, 840, 770 cm$^{-1}$; MS *m/z*: 564($M^+$), 522, 328 (100%), 257, 192, 135, 121, 69, 55.

**5α-Cholestan-3β-yl 4-(but-3-enyloxy)benzoate (4)**

Compound **4** was prepared by a similar procedure to that described for the preparation of compound **3**, using 2.6 mmol of DCC, 5α-cholestan-3β-ol (**1**), 4-(but-3-enyloxy)benzoic acid and DMAP (0.002 mmol).

Yield 30%, transition temperatures K 120.5 N* 218.1 I °C; $^1$HNMR ($CDCl_3$) δ 0.69 (3H, s), 0.83–2.02 (43H, m), 2.57 (2H, q), 4.08 (2H, t), 4.91 (1H, m), 5.13 (1H, dt), 5.21 (1H, quart), 5.90 (1H, m), 6.89 (2H, d), 7.98 (2H, d) ; IR (KBr) $\nu_{max}$ 2940, 2920, 2880, 2860, 1720, 1620, 1290, 1165, 840, 770 cm$^{-1}$; MS *m/z*: 562($M^+$), 521, 371, 356, 328, 257, 192 (100%), 135, 121, 69, 55.

***5α-Cholestan-3α-yl 4-(but-3-enyloxy)benzoate* (5)**

Compound **5** was prepared by a similar procedure to that described for the preparation of compound **15** using 2.6 mmol of DEAD, 5α-cholestan-3β-ol (**1**), 4-(but-3-enyloxy)benzoic acid and triphenylphosphine.

The crude product was purified by column chromatography [silica gel/HPLC grade hexane:ethyl acetate, 19:1] and recrystallisation (ethyl acetate) to give white crystals which were dried *in vacuo*. Yield 25%, mp 51.2 °C; $^1$HNMR ($CDCl_3$) δ 0.65 (3H, s), 0.73–2.02 (43H, m), 2.57 (2H, quart), 4.07 (2H, t), 5.13 (1H, dt), 5.21 (1H, quart), 5.24 (1H, m), 5.90 (1H, m), 6.92 (2H, d), 8.00 (2H, d); IR (KBr) $\nu_{max}$ 2940, 2920, 2880, 2860, 1720, 1620, 1290, 1170 840, 770 cm$^{-1}$; MS *m/z*: 562($M^+$), 490, 371, 356, 302, 257, 215, 192 (100%), 164.

**Cholest-5-en-3β-yl 4-(but-3-enyloxy)benzoate (7)**

Compound **7** was prepared by a similar procedure to that described for the preparation of compound **4**, using 7.81 mmol of DCC, 4-(but-3-enyloxy)benzoic acid, DMAP (0.781 mmol) and cholest-5-en-3β-ol (**2**). Yield 41%, transition temperatures K 122.6 N* 242.3 I °C; $^1$HNMR ($CDCl_3$) δ 0.69 (3H, s), 0.90–2.02 (40H, m), 2.57 (2H, d), 4.08 (2H, t), 4.91 (1H, m), 5.13 (1H, dt), 5.21 (1H, quart), 5.44 (1H, d), 5.90 (1H, m), 6.89 (2H, d), 7.98 (2H, d) ; IR (KBr) $\nu_{max}$ 2920, 1710, 1600, 1250, 1165, cm$^{-1}$; MS *m/z*: 560($M^+$), 368(100%), 353, 347, 260, 147,121.

***1-Bromo-4-(cholest-5-en-3β-yl)benzene* (9)**

Compound **9** was prepared by a similar procedure to that described for the preparation of compound **15** using the quantities stated.

DEAD (5.05 g, 0.029 mol), cholest-5-en-3β-ol (**2**) (11.22 g, 0.029 mol), 4-bromophenol (5.00 g, 0.029 mol), triphenylphosphine (7.60 g, 0.029 mol).

The crude product was purified by column chromatography [silica gel/petroleum fraction (bp 40-60 °C):dichloromethane, 49:1] to give white crystals, recrystallised (ethyl acetate) and dried *in vacuo*. Compound **9** and several other products (**10**–**13**) were also isolated. Total yield 5.97 g (38%); yield of compound **9** 1.17 g (20%), mp 162-164 °C, lit.[11] 162–164 °C; $^1$HNMR ($CDCl_3$) δ 0.69 (3H, s), 0.84–2.08 (38H, m), 2.30–2.50 (2H, m), 4.06 (1H, m), 5.44 (1H, d), 6.77 (2H, d), 7.34 (2H, d); IR (KBr) $\nu_{max}$ 2960, 2940, 1490, 1230 cm$^{-1}$; MS *m/z*: 540($M^+$), 370, 287. Compound **10** and **11**, combined yield 2.93 g (49%); $^1$HNMR ($CDCl_3$) shows signals at δ 3.75 (C6-H; compound **10**), 4.50 (C6-H; compound **11**), 0.58 and 0.30 (C3-H, C4-H); IR (KBr) $\nu_{max}$ 2890, 2960, 1490, 1220, 1360, 640 cm$^{-1}$; MS *m/z*: 370, 354, 185, 161, 145, 105, 91, 79, 69, (100%)

Compounds **12** and **13,** combined yield 1.87 g (31%) (see preparation of compound **16** for $^1$HNMR details).

***1-(5α-Cholestan-3α-yloxy)-4-octyloxybenzene* (15)**

Diethyl azodicarboxylate (DEAD) (0.78 g, 4.5 mmol) in dry THF (40 ml) was added dropwise to a stirred solution of 5α-cholestan-3β-ol (**1**) (1.75 g, 4.5 mmol), 4-octyloxyphenol (**14**) (1.00 g, 4.5 mol) and triphenylphosphine (1.18 g, 4.5 mmol) in THF (50 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred overnight, (TLC analysis revealed a complete reaction). The solvent was removed *in vacuo* (< 40°C) to give a white solid which was purified by column chromatography [silica gel/petroleum fraction (bp 40-60 °C):dichloromethane, 49:1], followed by recrystallisation (ethyl acetate) to give white crystals that were dried *in vacuo*. Yield 0.68 g (25%), mp 95.2 °C; $^1$HNMR ($CDCl_3$) δ 0.65 (3H, s), 0.75–2.00 (58H, m), 3.89 (2H, t), 4.39 (1H, m), 6.83 (4H, m); IR (KBr) $\nu_{max}$ 2920, 1860, 1500, 1230, 1000, 820 cm$^{-1}$; MS *m/z*: 592($M^+$), 370, 314, 222 (100%), 174, 149, 123, 110, 95, 69.

***Attempted preparation of 1-(cholest-5-en-3β-yloxy)-4-octyloxybenzene* (16)**

The preparation of compound **16** was attempted by a similar procedure to that described for the preparation of compound **15** using 4.5 mmol of DEAD, cholest-5-en-3β-ol (**2**), 4-octyloxyphenol (**14**) and triphenylphosphine.

The crude product was purified by column chromatography [silica gel/petroleum fraction (bp 40-60 °C):dichloromethane, 49:1] to give white crystals, recrystallised (ethyl acetate) and dried *in vacuo*. The product was found to be a mixture of two isomeric compounds. Yield of compounds **12** and **13** from THF were 9.5% and from benzene 12.5%. $^1$HNMR ($CDCl_3$) shows signals at δ 0.44 (C3-H, C4-H; compound **13**), 5.18, 5.53 (C6-H, C7-H; compound **13**), 5.39, 5.59, 5.94 (C3-H, C4-H, C6-H; compound **12**); IR (KBr) $\nu_{max}$ 2940, 2860, 1470, 1380, 1370, 1360, 640 cm$^{-1}$; MS *m/z*: 368 (100%)($M^+$), 354, 340, 314, 297, 274, 227, 213, 199, 173.

***1-Bromo-4-(5α-cholestan-3α-yl)benzene* (18)**

Compound **18** was prepared by a similar procedure to that described for the preparation of compound **15** using 0.01 mol of DEAD, 5α-cholestan-3β-ol (**1**), 4-bromophenol and triphenylphosphine.

The crude product was purified by column chromatography [silica gel/petroleum fraction (bp 40-60 °C):dichloromethane, 49:1] to give white crystals, recrystallised (ethyl acetate) and dried *in vacuo*. Yield 60%, mp 109-110 °C, lit. [11] 109-110 °C; $^1$HNMR ($CDCl_3$) δ 0.69 (3H, s), 0.90–1.96 (43H, m), 4.39 (1H, m), 7.10 (4H, m); IR (KBr) $\nu_{max}$ 2950, 1480, 1245, 1160,

995, 820 $cm^{-1}$; MS *m/z*: 542($M^+$), 370, 314, 222 (100%), 174, 149, 123, 110, 95, 69.

***(5α-Cholestan-3α-yl)benzene* (19)**

Compound **19** was prepared by a similar procedure to that described for the preparation of compound **15** using 0.01 mol of DEAD, 5α-cholestan-3β-ol (**1**), phenol and triphenylphosphine. The crude product was purified by column chromatography [silica gel/petroleum fraction (bp 40-60 °C):dichloromethane, 49:1] to give white crystals, recrystallised (ethyl acetate) and dried *in vacuo*. Yield 80%, mp 76-78 °C, lit.[11] 76-78°C; $^1$HNMR ($CDCl_3$) δ 0.69 (3H, s), 0.90–1.96 (43H, m), 4.39 (1H, m), 7.00 (5H, m); IR (KBr) $\nu_{max}$ 1595, 1580, 1490, 1160, 995, 820 $cm^{-1}$; MS *m/z*: 464, 370, 314, 222 (100%), 174, 149, 123, 110, 95, 69.

**Acknowledgements**

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