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SYNETHESIS AND CHARACTERIZATION OF DI- AND TETRASUBSTITUTED *p-tert*-BUTYLTHIACALIX[4]ARENES CONTAINING ISATIN MOIETY AT THE LOWER RIM

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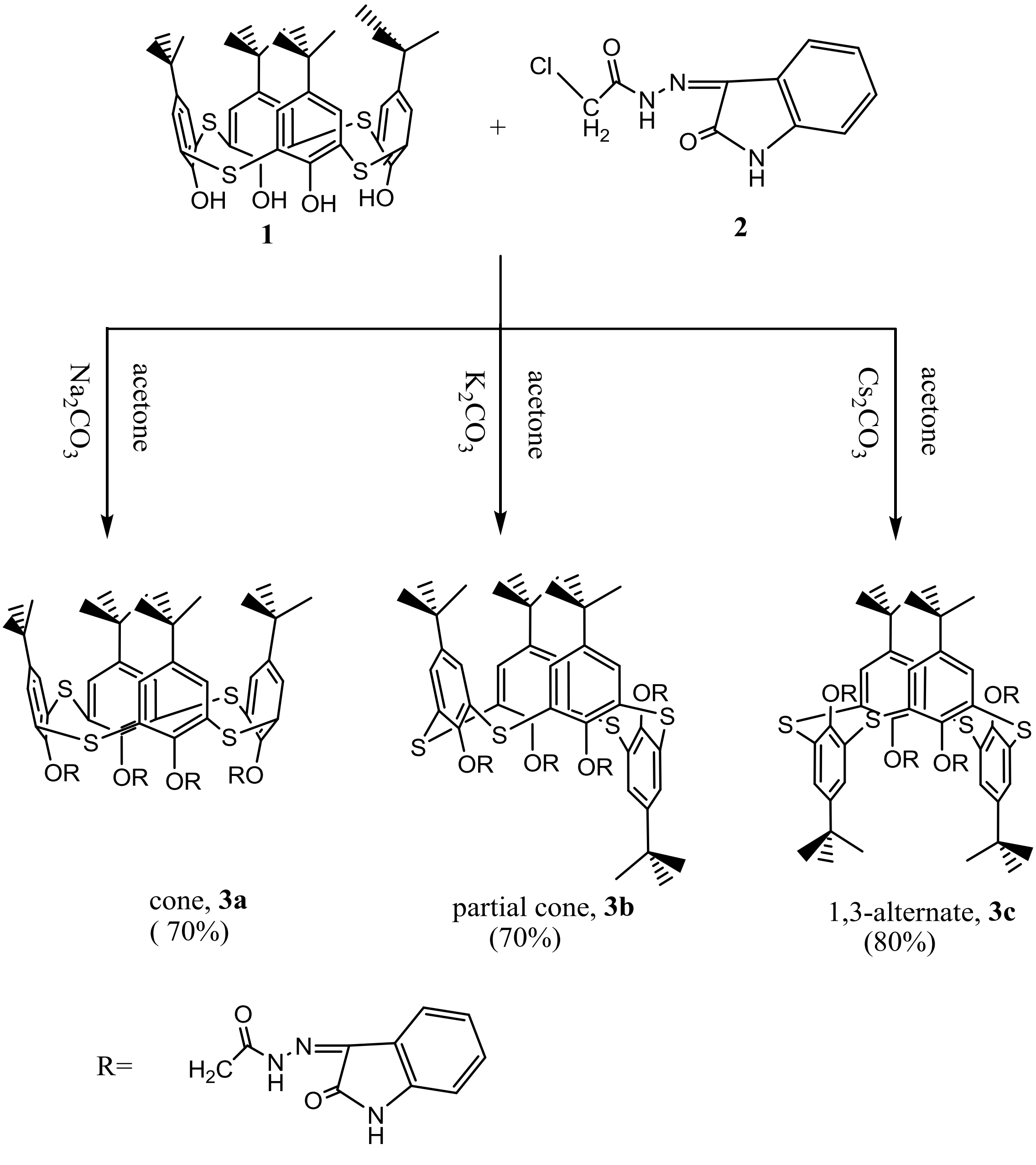
Abstract – Di- and tetrasubstituted *p-tert*-butylthiacalix[4]arene in three different conformers (cone, partial cone and 1,3-alternate) at lower rim, have been synthesized by the reaction of *p-tert*-butylthiacalix[4]arene and disubstituted *p-tert*-butylthiacalix[4]arene with isatin-3-[N^2-(chloroacetyl)]hydrazone in acetone or acetonitrile in the presence of different alkali metal carbonates or hydroxide. Structures of the new compounds were established by elemental analyses and spectral data IR, ^{1}H NMR, ^{13}C NMR.

INTRODUCTION

Calixarenes,[1,2] are easily accessible macrocyclic compounds from cheap materials (para-substituted phenol, formaldehyde and sodium hydroxide). They have attracted considerable attention to researchers because of their wide impacts on numerous science and technology fields, like separation science,[3] catalysis,[4] nuclear waste treatment,[5] medical applications,[6] supramolecular chemistry.[7] In 1997, Mayino and co-workers[8] reported a facile synthesis of *p-tert*-butylthiacalix[4]arene by based-catalyzed condensation of *p*-substituted phenols and elemental sulfur which are considered modified calixarenes in which the methylene subunits are replaced with sulfur atoms. Much attention has been focused on thiacalixarenes[9] because of their intriguing properties and their increased versatility over calixarenes. Thiacalixarenes have a different wide of applications in solution of environmental related problems,[10] catalysis and supramolecular chemistry.[11] Both calixarenes and thiacalixarenes applications are mainly depend on their structure modification by the introduction of different functional substituents at its active sites, lower and higher rims, bridging groups and extending cavity sizes. Isatin is a core constituent of many alkaloids and drugs as well as dyes, pesticides and analytical reagents.[12] In view of this fact and as continuation of our research on thiacalixarene,[13-19] we herein introduce of isatin moiety at the lower rim of *p*-*tert*-butylthiacalix[4]arene by its reaction with isatin-3-[N^2-(chloroacetyl)]hydrazone for the generation of new di- and tetrasubstituted *p*-*tert*-butylthiacalix[4]arenes in different conformers.

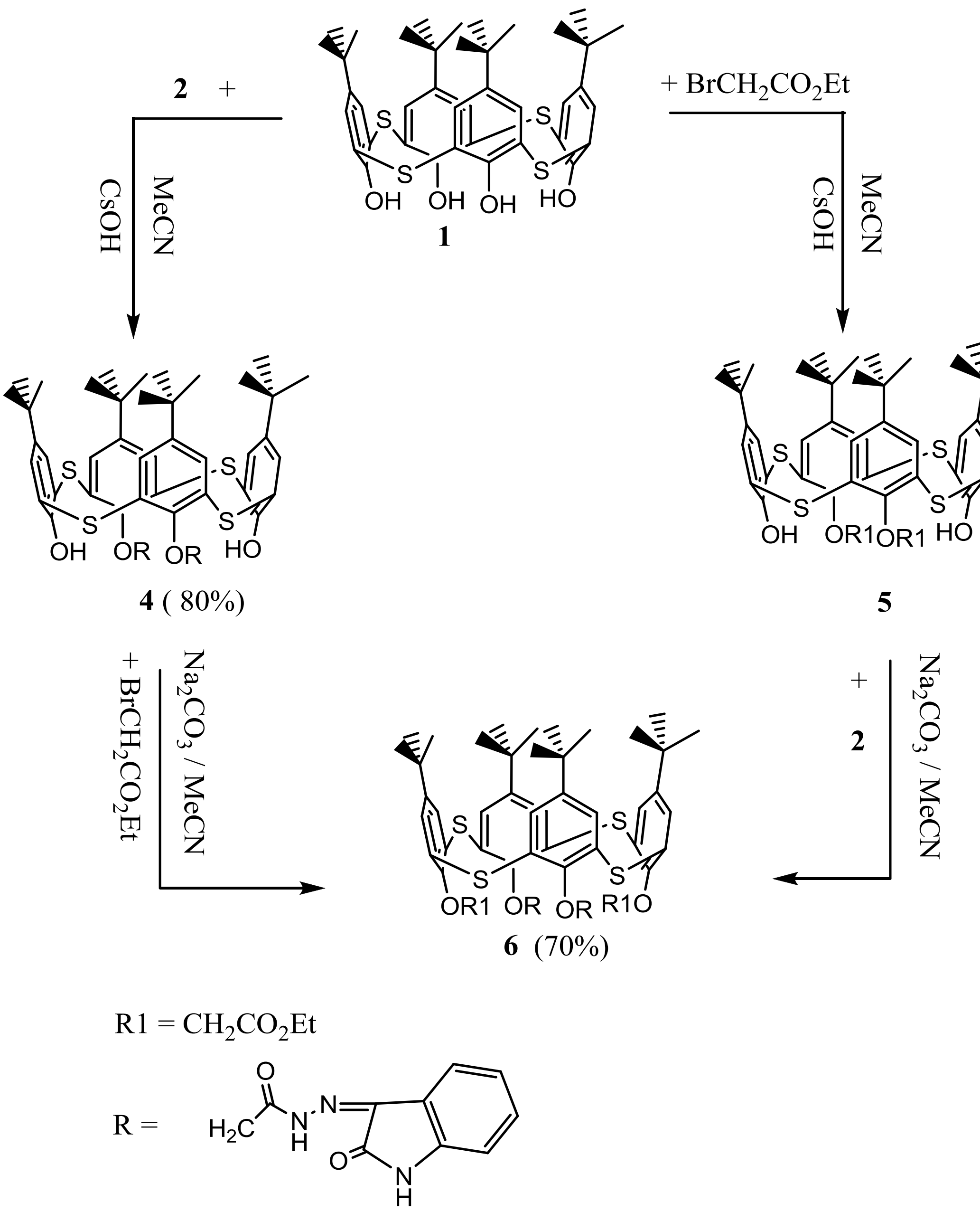
RESULTS AND DISCUSSION

p-*tert*-Butylthiacalix[4]arene **1** was reacted with fourfold excess of isatin-3-[N^2-(chloroacetyl)]-hydrazone **2**,[20] in acetone in the presence of different alkali metal carbonate (Na_2CO_3, K_2CO_3 and Cs_2CO_3) as a base leads to the formation of tetrasustituted *p*-*tert*-butylthiacalix[4]arenes **3a-c** in the different conformers *cone*, *partial cone* and *1,3-alternate* (Scheme 1) respectively.[13,21] The structures of the prepared compounds have elucidated by different physical spectroscopic methods (elemental analysis, IR and ^{1}H and ^{13}CNMR). The FT-IR spectral analysis of the product tetrasubstituted *p*-*tert*-butylthiacalix[4]arenes **3a-c** shows disappearing of -OH band characterized the starting material *p*-*tert*-butylthiacalix[4]arene **1** as well as appearing of the different proton peaks come from the isatin-3-[N^2-(chloroacetyl)]hydrazone fragment like two amidic carbonyls ranged from 1693 to 1712 cm^{-1}. The ^{1}HNMR shows a methylene group of -$COCH_2$- range from 4.5-4.8 ppm and aromatic proton of isatin from 6.72-7.44 ppm. Regarding the structure determination of the different conformers *cone*, *partial cone* and *1,3-alternate*, it depends on the chemical shift in ppm of the different groups as well as on their splitting (e.g., Bu^t group in case of *cone* **3a** and *1,3-alternate* **3c** conformers as singlet peak but at different chemical shift 1.04 and 1.18 ppm respectively as result of different shielding effect.)[13,21] In case of *partial cone* **3b**, Bu^t splits in three peaks types in 1:2:1 ratios at 1.06, 1.12 and 1.24 ppm. Disubstituted *p*-*tert*-butylthiacalix[4]arene **4** was prepared by reaction of *p*-*tert*-butylthiacalix[4]arene **1** with twofold excess of isatin-3-[N^2-(chloroacetyl)]hydrazone in acetonitrile in the presence of CsOH as a base catalyst (Scheme 2). FT-IR shows OH at 3232 cm^{-1} and two amidic carbonyls at 1701 and1693 cm^{-1}. The ^{1}HNMR of *p*-*tert*-butylthiacalix[4]arene **4** shows two Bu^t at 1.15 and 1.28 ppm as well as of two Ar-H of the thiacalixarene skeleton at 7.22 and 7.28 ppm. Finally mixed tetrasubstituted *p*-*tert*-butylthiacalix[4]arene **6** containing two different substituent fragments isatin and ester moiety (Scheme 2). It was prepared by two different pathways through the reaction of the reported disubstituted *p*-*tert*-butylthiacalixarene **5**,[22] by the reaction with two moles isatin-3-[N^2-(chloroacetyl)]hydrazone or by the reaction of compound **4** with two moles of ethyl bromoacetate in acetonitrile in the presence of Na_2CO_3 as a base. A FT-IR spectrum of *p*-*tert*-butylthiacalixarene **6** shows two different types of carbonyl groups, amidic carbonyl at 1694.95 cm^{-1} and ester carbonyl at 1741 cm^{-1}.



Scheme1. Synthesis of tetrasubstituted *p*-*tert*-butylthiacalix[4]arenes **3a-c**

^{1}HNMR analysis shows two Bu^t peaks at 1.15 and 1.20 ppm, two different methylene group –CH_2CO- as singlet peak at 5.20 ppm of the ester moiety and doublet of - CH_2CONHN= - at 4.24 ppm of isatin moiety. Furthermore, there were two singlet of Ar-H of thiacalixarene skeleton at 7.60 and 7.62 ppm. In addition to the above mentioned of some physical characterization of the new prepared thiacalix[4]arenes, fully spectral analysis are presented in details in the experimental section.



Scheme 2. Synthesis of di- and mixed tetrasubstituted *p*-*tert*-butylthiacalix[4]arenes **4** and **6** respectively.

CONCLUSIONS

The reaction of isatin-3-[*N*^{2}-(chloroacetyl)]hydrazone with *p*-*tert*-butylthiacalix[4]arene and disubstituted *p*-*tert*-butylthiacalix[4]arene in acetonitrile or acetone in the presence of different alkali metal hydroxide and alkali metal carbonates (M_2CO_3, M = Na , K or Cs and CsOH) was studied in this research article. The reaction was successful in preparing of five new *p-tert*-butylthiacalix[4]arene derivatives containing isatin moiety in different conformers which is expected to add a new features to the thiacalixarene skeleton.

EXPERIMENTAL

All chemicals were used without further purification. Melting points (°C, uncorrected) were measured in open glass capillaries using a Barnstead 9001 electrothermal melting point apparatus. A Perkin Elmer Spectrum 1000 FT-IR Spectrometer was used for recording infrared (IR) spectra of the prepared compounds as KBr pellets. Elemental analyses were performed on a Perkin-Elmer 2,400 CHN/O analyzer model. ^{1}H- and ^{13}C-NMR spectra of compounds were run on JEOL ECP-400 MHz and 300 MHz NMR spectrometers, in dimethyl sulfoxide (DMSO-d_6) or chloroform ($CDCl_3$) at room temperature. The chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane (TMS) used as reference. The instruments are located at King Saud University, College of Science and Chemistry Department.

General methods for preparation of tetrasustituted *p-tert*-butylthiacalix[4]arenes **3a-c**:

A mixture of *p-tert*-butylthiacalix[4]arene (**1**) 1g (1.38 mmol), isatin-3-[*N*^{2}-(chloroacetyl)]hydrazone (**2**) 1.35 g (5.6 mmol) and an appropriate alkali metal carbonate (M_2CO_3, M= Na, K, or Cs) was suspended in 60 mL dry acetone. The reaction mixture was heated under reflux for 6 days. The reaction mixture was filtered on hot and the solid carbonate layer was diluted by HCl solution, filtered, washed with distilled water, and dried. The solid product (**3a**, **3b** or **3c**) recrystallized from mixture solvent (DMSO-EtOH).

3a, cone, reddish brown crystal, mp > 300 °C, IR (KBr ν/ cm^{-1}), 3240 (NH), 3053 cm^{-1} (Ar-H), 2962 cm^{-1} (CH), 1701 cm^{-1} (C=O), 1693 cm^{-1} (C=O); ^{1}H NMR (300 MHz, TMS, δ= 0 ppm, DMSO-d_6), 1.04 (36H, s, Bu^t), 4.5 (8H, d, CH_2CO), 6.72-7.44 (8H +16H, m, Ar-H and isatin-H), 8.4 (4H, s, CONH-), 11.3 (4H, s, CNHCO); ^{13}C NMR (75 MHz, DMSO) 28.52, 29.40, 29.98, 30.18, 33.52, 69.59, 97.87, 102.62, 117.47, 121.87, 122.92, 128.92, 133.21, 155.53, 167.54, 169.45. El. Anal. Calcd for $C_{80}H_{76}N_{12}O_{12}S_4$: C, 62.97; H, 5.02; N, 11.02. Found: C, 63.30; H, 5.45; N, 10.90.

3b, partial cone, reddish brown, crystal, mp 290 °C, IR (KBr ν/ cm^{-1}), 3241.41 cm^{-1} (NH), 3053 cm^{-1} (Ar-H), 2962.66 cm^{-1} (Ar-H), 1701 cm^{-1} (CO), 1693 cm^{-1} (CO); ^{1}H NMR (300 MHz, TMS, δ = 0 ppm, DMSO-d_6), 1.06 (9H, s, Bu^t), 1.12 (18H, s, Bu^t), 1.24 (9H, s, Bu^t), 4.20-6.12 (8H, m, -$COCH_2$-), 6.90-7.52 (8H +16H, m, Ar-H and isatin-H), 8.9-9.2 (4H, m, CONH), 10.6-10.9 (4H, m, CNHCO); ^{13}C NMR (75 MHz, DMSO), 28.51, 29.98, 30.12, 31.45, 32.73, 34.73, 59.60, 60.54, 65.93, 69.26, 70.61, 105.50, 117.43, 118.50, 119.82, 121.21, 122.38, 123.50, 124.16, 125.24, 126.53, 127.12, 128,24, 131.52, 132.03, 133.95, 138.56, 139.46, 143.20, 144.50, 146.46, 147.50, 148.30, 149,60, 150.45, 151,20, 156.12, 157.30, 158,30, 159.04, 160.01, 161.27, 166.35, 166.90, 167.50, 168.23, 169.01, 169.92. El. Anal. Calcd for $C_{80}H_{76}N_{12}O_{12}S_4$: C, 62.97; H, 5.02; N, 11.02. Found: C, 63.39; H, 5.35; N, 10.70.

3c, 1,3-alternate, yellow crystal, mp > 300 °C, IR (KBr ν/ cm^{-1}), 3282.84 (NH), 3060 cm^{-1} (Ar-H), 2962 cm^{-1} (CH), 1701 cm^{-1} (C=O), 17012 cm^{-1} (C=O); ^{1}H NMR (400 MHz, TMS, δ = 0 ppm, DMSO-*d*$_6$), 1.18 (36H, s, Bu^t), 4.8 (8H, d, CH_2CO), 7.23-7.72 (8 H +16H, m, Ar-H and isatin-H), 8.3 (4H, s, CONH), 9.9 (4H, s, CNHCO); ^{13}C NMR (100 MHz, DMSO) 28.70, 29.40, 29.98, 30.50, 33.52, 69.59, 97.87, 102.62, 117.47, 121.50, 122.92, 128.92, 133.01, 152.53, 166.50, 169.55. El. Anal. Calcd for $C_{80}H_{76}N_{12}O_{12}S_4$: C, 62.97; H, 5.02; N, 11.02; Found: C, 63.41; H, 4.80; N, 11.42.

Synthesis of disustituted *p*-*tert*-butylthiacalix[4]arene **4**:

A mixture of *p*-*tert*-butylthiacalix[4]arene (**1**) 1 g (1.38 mmol), isatin-3-[*N*^{2}-(chloroacetyl)]hydrazone (**2**) 0.67g (2.8 mmol) and cesium hydroxide (CsOH) 0.42 g (2.77 mmol) was suspended in 60 mL dry MeCN. The reaction mixture was heated under reflux for 3 days. The reaction mixture was filtered on hot; the precipitate was dissolved in diluted HCl solution, filtered. The solid residue was washed with distilled water, dried and recrystallized from mixture solvent (DMSO-EtOH).

4, reddish brown crystal, mp >300 °C, IR (KBr, ν/ cm^{-1}), 3310, (OH), 3244.27 cm^{-1} (NH), 3059 cm^{-1} (Ar-H), 2958 cm^{-1} (CH), 1701 cm^{-1} (C=O), 1693 cm^{-1} (C=O); ^{1}H NMR (400 MHz, TMS, δ = 0 ppm, DMSO-*d*$_6$), 1.15 (18H, s, Bu^t), 1.32 (18H, s, Bu^t), 5.2 (4H, d, CH_2CO), 6.90-7.90 (8H + 8H, m, Ar-H and isatin-H), 8.0(2H, s, CONH), 8.5(2H, s, OH), 9.8 (2H, s, CNHCO); ^{13}C NMR (100 MHz, DMSO), 28.60, 29.30, 30.98, 31.18, 34.1, 34.2, 34.52, 69.87, 98.87, 103.62, 117.80, 120.87, 122.41, 123.92, 129.92, 132.5, 134.45, 142.30, 155.7, 156.58, 160.54, 167.45, El. Anal. Calcd for $C_{60}H_{62}N_6O_8S_4$: C, 64.15; H, 5.56; N, 7.48. Found: C, 64.45; H, 5.46; N, 7.18.

Synthesis of tetrasustituted *p*-*tert*-butylthiacalix[4]arene **6**.

A mixture of disubstituted *p*-*tert*-butylthiacalix[4]arene (**5**) 0.5 g (0.56 mmol), isatin-3-[*N*^{2}-(chloroacetyl)]hydrazone (**2**) 0.26g (1.2 mmol) and sodium carbonate (Na_2CO_3) 0.23 g (2.18 mmol) was suspended in 50 mL dry MeCN. The reaction mixture was heated under reflux for 3 days. The reaction mixture was filtered on hot and the solid carbonate layer was washed with diluted HCl solution filtered, and was washed with distilled water. The solid residue dried and calculated the yield.

6, cone, yellow crystal mp 260 °C, IR (KBr ν/ cm^{-1}), 3228 cm^{-1} (NH), 3062 cm^{-1} (Ar-H), 2961 cm^{-1} (CH), 1750 cm^{-1} (CO), 1696 cm^{-1} (CO); ^{1}H NMR (300 MHz, TMS, δ = 0 ppm, $CDCl_3$), 1.15 (18H, s, Bu^t), 1.20 (18H, s, Bu^t), 1.42 (6H, t, $CH_2\mathit{CH_3}$), 4.24 (4H, d, $CO\mathit{CH_2}NH$), 4.42 (4H, q, $\mathit{CH_2}CH_3$), 5.20 (4H, s, $COCH_2O$-), 6.70-7.59 (10H, m, isatin-H + CONH), 9.9 (4H, s, CNHCO). 12.6, 29.60, 29.80, 30.98, 31.18, 34.1, 34.2, 34.52, 69.87, 98.87, 103.62, 117.80, 119.08, 121.87, 122.41, 124.62, 130.92, 132.5, 134.45, 134.9, 142.30, 154.1, 155.7, 156.58, 167.54, 169.45; Anal. Calcd for $C_{68}H_{76}N_6O_{12}S_4$: C, 62.94; H, 5.90; N, 6.48. Found: C, 62.45; H, 5.49; N, 6.28.

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