

$\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CCl}_4$ , 100 MHz, mixture of diastereomers)  $\delta$  0.96 (t, 3 H,  $\text{CH}_3\text{CH}_2$ ,  $J = 7$  Hz), 1.03 (d, 3 H,  $\text{CH}_3\text{CHCH}_2$ ,  $J = 7$  Hz), 1.16-1.40 (m, 6 H,  $\text{CH}_3\text{CHCOO}$  and  $\text{OCH}_2\text{CH}_3$ ), 1.60, 1.65 (2 s, 3 H,  $\text{C}=\text{CCH}_3$ ), 1.7-2.6 (m, 4 H,  $\text{CH}_2$ ), 2.90 (m, 1 H,  $\text{CHCO}$ ), 3.50 (m, 1 H,  $\text{CHCOO}$ ), 4.20 (q, 2 H,  $\text{OCH}_2$ ), 5.18 (br t, 1 H,  $\text{C}=\text{CH}$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{O}_3$ : C, 69.96; H, 10.07. Found: C, 69.86; H, 10.18.

**4,6-Dimethyl-(E)-6-nonen-3-one (6c).** A mixture of 150 mg (0.62 mmol) of **5c**, 400 mg (1.27 mmol) of  $\text{Ba}(\text{OH})\cdot 8\text{H}_2\text{O}$ , 0.7 mL of EtOH, and 1.4 mL of water was stirred under argon in a 100 °C oil bath for 2 h. The cooled mixture was overlaid with pentane, diluted with 8 mL of water, and treated with 4 N HCl until the white precipitate dissolved. The aqueous layer was extracted with four additional portions of pentane. The concentrated extracts gave upon bulb-to-bulb distillation (150 °C, 40 mm) 95 mg (91%) of **6c**. Spectra were obtained by using material which was further purified by PTLC ( $\text{CH}_2\text{Cl}_2$ ) and redistillation: IR (neat) 2960, 2930, 1707, 1460, 1450, 1375  $\text{cm}^{-1}$  (lit.<sup>9</sup> 1710  $\text{cm}^{-1}$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  0.92 (t, 3 H,  $\text{CH}_3\text{CH}_2$ ,  $J = 7.5$  Hz), 1.02 (d, 3 H,  $\text{CH}_3\text{CHCO}$ ,  $J = 6.8$  Hz), 1.03 (t, 3 H,  $\text{CH}_3\text{CH}_2\text{CO}$ ,  $J = 7.3$  Hz), 1.59 (s, 3 H,  $\text{C}=\text{CCH}_3$ ), 1.93 (m, 1 H,  $\text{CH}_2\text{CHCO}$ ), 1.98 (m, 2 H,  $\text{CH}_2\text{CH}=\text{C}$ ), 2.32 (dd, 1 H,  $\text{CH}_2\text{CHCO}$ ,  $J = 13.5, 7.0$  Hz), 2.44 (q, 2 H,  $\text{CH}_2\text{CO}$ ,  $J = 7.3$  Hz), 2.71 (m, 1 H,  $\text{CHCO}$ ), 5.13 (qt, 1 H,  $\text{C}=\text{CH}$ ,  $J = 7.1, 1.2$  Hz); mass spectrum (70 eV),  $m/e$  (relative

intensity) 168 (35), 139 (33), 111 (35), 86 (88), 83 (45), 69 (100), 57 (75), 55 (50), 41 (45); these spectra are in accord with those previously reported;<sup>9</sup>  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 22.62 MHz)  $\delta$  7.7, 14.2, 15.7, 16.2, 21.2, 34.5, 43.4, 44.4, 129.2, 131.5, 214.9.

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**Registry No.** **1a**, 62251-79-0; **1b**, 62251-80-3; ( $\pm$ )-**3a**, 83269-60-7; ( $\pm$ )-**3b** (isomer 1), 83269-61-8; ( $\pm$ )-**3b** (isomer 2), 83269-83-4; ( $\pm$ )-(*E*)-**3c**, 83269-62-9; ( $\pm$ )-**4a**, 83269-63-0; ( $\pm$ )-**4b** (isomer 1), 83269-64-1; ( $\pm$ )-**4b** (isomer 2), 83269-84-5; ( $\pm$ )-(*E*)-**4c**, 83269-65-2; **5a**, 83269-66-3; **5b**, 83269-67-4; ( $\pm$ )-(*E*)-**5c** (isomer 1), 83269-68-5; ( $\pm$ )-(*E*)-**5c** (isomer 2), 83269-85-6; ( $\pm$ )-**6a**, 83269-69-6; **6b**, 83269-70-9; **7a**, 83269-72-1; ( $\pm$ )-*trans*-**7b**, 83269-73-2; **7c**, 83269-74-3; **7d**, 83269-75-4; ( $\pm$ )-**7e**, 83269-76-5; **8a**, 10488-95-6; ( $\pm$ )-*trans*-**8b**, 83269-77-6; **8c**, 5248-18-0; **8d**, 83269-78-7; ( $\pm$ )-**8e**, 83269-79-8; ( $\pm$ )-(*E*)-**9**, 83269-71-0; (*Z*)-**10**, 83269-80-1; **11**, 61835-96-9; (*E*)-**12**, 83269-81-2; BnBr, 100-39-0; BuLi, 542-69-8; MeI, 74-88-4;  $\text{Ph}_3\text{P}=\text{CHCOOEt}$ , 1099-45-2; BuLi, 109-72-8; PhLi, 591-51-5; EtI, 75-03-6;  $\text{Bu}_3\text{SnCl}$ , 1461-22-9; 3-chloropropanoyl chloride, 625-36-5; crotonoyl chloride, 10487-71-5; ethyl 5-chloro-3-oxo-2-(triphenylphosphoranylidene)pentanoate, 83269-82-3; hexanoyl chloride, 142-61-0.

## Synthesis of Nonachloro-4-phenoxyphenol

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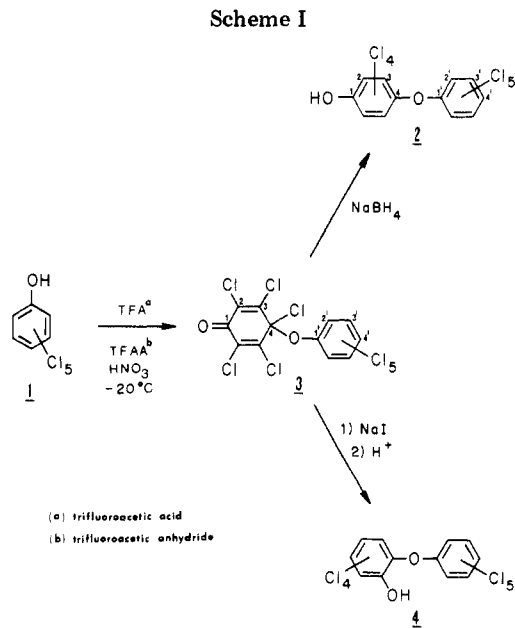
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Reduction of 2,3,4,5,6-pentachloro-4-(pentachlorophenoxy)-2,5-cyclohexadienone (**3**) yields nonachloro-4-phenoxyphenol (**2**) and nonachloro-2-phenoxyphenol (**4**) in varying amounts, depending on the nature of the reaction scheme. Mechanistic pathways for the formation of **2** and **4** from **3** are suggested. The structure of **3** was confirmed by X-ray crystallography. The carbon-13 NMR spectrum of **2** is described.

Analysis of technical pentachlorophenol (**1**) indicates the presence of numerous chlorinated byproducts that arise in the manufacturing process.<sup>2</sup> The potential health hazards from exposure to these chemicals are of some concern. It has been shown, for example, that nonachloro-4-phenoxyphenol (**2**), a contaminant of **1**,<sup>3</sup> has a hemolytic potency at least a hundred times greater than that of **1**.<sup>4</sup> The need to evaluate other toxicological properties of this compound is apparent. Therefore, a convenient procedure for preparing this compound is needed. We report here our methods for synthesizing and purifying **2**.

### Results and Discussion

Synthesis of **2** was accomplished by reduction of 2,3,4,5,6-pentachloro-4-(pentachlorophenoxy)-2,5-cyclohexadienone (**3**), prepared from **1**.<sup>5</sup> In addition to the desired product **2**, the 2-hydroxy isomer (**4**) was obtained in varying yield, depending on the nature of the reduction used (Scheme I). When sodium borohydride was used to reduce **3**, isomers **2** and **4** were formed in a ratio of 2:1. In



contrast, when sodium iodide in methanol and chloroform was used to reduce **3**, the ratio of **2** to **4** was 1:20.<sup>5</sup> Reduction of **3** in a neutral methanolic solution with sodium iodide has been reported to produce **2**.<sup>6</sup> However, a

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Table I. Carbon-13 NMR Chemical Shifts (ppm) for Nonachloro-4-phenoxyphenol and 2,3,5,6-Tetrachloro-4-(pentachlorophenoxy)anisole

| carbon | phenol <sup>a</sup> | anisole <sup>b</sup> | $\Delta\delta$ |
|--------|---------------------|----------------------|----------------|
| 1      | 141.32              | 145.19               | 3.87           |
| 2, 6   | 120.80              | 127.70               | 6.90           |
| 3, 5   | 123.75              | 124.07               | 0.32           |
| 4      | 148.08              | 150.35               | 2.27           |
| 1'     | 148.48              | 147.54               | -0.94          |
| 2', 6' | 124.59              | 124.59               | 0.00           |
| 3', 5' | 131.81              | 131.84               | 0.03           |
| 4'     | 128.46              | 129.00               | 0.54           |
| 7      |                     | 60.28                |                |

<sup>a</sup> 80 mg of sample in 0.5 mL of CCl<sub>4</sub>, 5 mg of chromium acetylacetonate, and 20  $\mu$ L of Me<sub>2</sub>SO-*d*<sub>6</sub>. <sup>b</sup> 74 mg of sample in 0.5 mL of CCl<sub>4</sub>, 5.5 mg of chromium acetylacetonate, and 20  $\mu$ L of Me<sub>2</sub>SO-*d*<sub>6</sub>.

mixture of 2 and 4 was obtained in poor yield by this method. The major product of the reaction was 1.

Structural proof of 2 was based on mass spectrometry<sup>3</sup> and <sup>13</sup>C NMR spectrometry. The <sup>13</sup>C NMR spectrum of 2 was obtained in the presence of chromium acetylacetonate, a spin-relaxation agent.<sup>7</sup> Assignment of resonances to the appropriate carbon atoms (Table I) was facilitated by preparing the methyl ether derivative (5) and comparing changes in chemical shifts,  $\Delta\delta$ , for each carbon atom. Similar comparisons have been made for 1 and pentachloroanisole and for nonachloro-3-phenoxyphenol and 2,4,5,6-tetrachloro-3-(pentachlorophenoxy)anisole.<sup>8</sup> Assignments of C2' and C6', C3', and C5', and C4' were made by comparison of the spectrum of 2 with the spectrum of nonachloro-3-phenoxyphenol (C2' and C6' = 124.5; C3' and C5' = 131.4; C4' = 128.3 ppm). As expected, small  $\Delta\delta$ 's were observed upon methylation of the hydroxy group.

The three peaks farthest downfield are obviously associated with oxygen linkages. Comparison of  $\Delta\delta$ 's for 1 and pentachloroanisole ( $\Delta\delta$ 's: C1 = 5.7; C2 and C6 = 9.9; C3 and C5 = 1.7; C4 = 5.8 ppm)<sup>8</sup> lead to the assignment of C1 and C4 in 2. The carbon farthest from the site of substitution, C1', has the smallest  $\Delta\delta$ .

The two remaining resonances (120.80 and 123.75 ppm) have the same intensities as those assigned to C2' and C6', and C3' and C5', approximately twice the intensity of the other peaks. Assignment of the peak at 123.75 ppm to C3 and C5 was made on the basis of the small  $\Delta\delta$  (0.32 ppm) arising on conversion of the hydroxy to a methoxy group. This is consistent with previous reports that meta carbons are not greatly influenced when a hydroxy group is replaced with a methoxy group.<sup>9</sup> The large  $\Delta\delta$  (6.90 ppm) exhibited by the remaining peak (120.80 ppm) is consistent with the behavior of carbons ortho (C2 and C6) to the site of this type of substitution.

Since earlier attempts to confirm the structure of the starting material, 3, by <sup>13</sup>C NMR analysis had failed,<sup>5</sup> the structure was determined and confirmed by X-ray crystallographic techniques. The results of the structure solution of 3 show two independent molecules both with the same conformation. The two rings in each molecule are nearly planar with a maximum deviation from the least-squares planes of 0.04 Å. The dihedral angles formed between the least-squares planes are 68.1 and 66.5 Å in

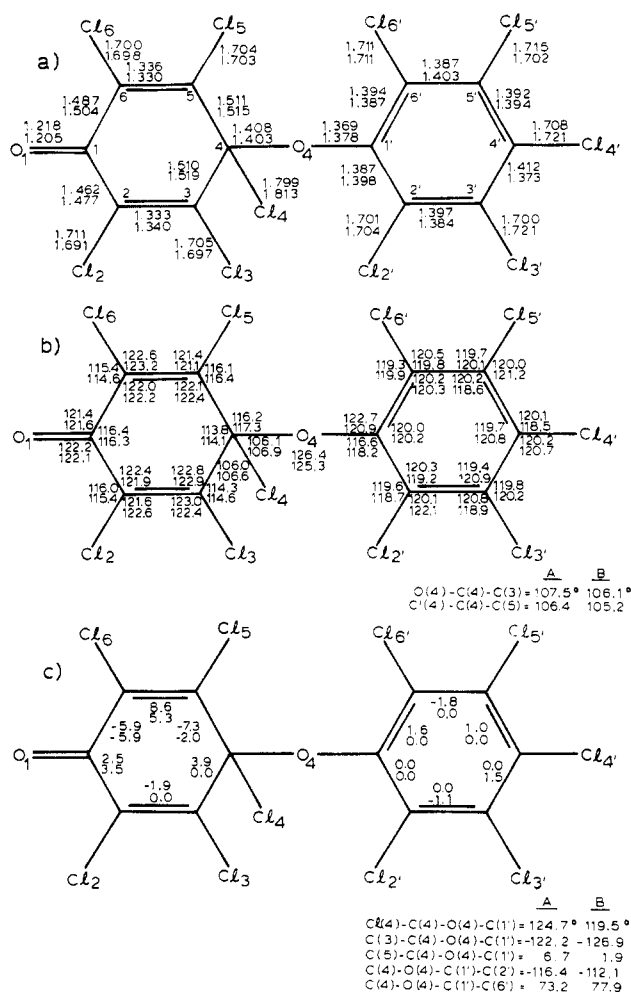


Figure 1. Intramolecular dimensions for 3. The upper values are for molecule A and the lower values for molecule B: (a) bond distances (angstroms); (b) bond angles, (degrees); (c) torsion angles (degrees).

molecules A and B, respectively. The intramolecular structural data are given in Figure 1. Here the excellent agreement between the structural parameters is evident.

Electron paramagnetic resonance spectra of 3 in carbon tetrachloride and benzene were measured. One broad band [ $g(\text{CCl}_4) = 2.0066$ ;  $g(\text{C}_6\text{H}_6) = 2.0070$ ] was observed in the resulting spectra. The pentachlorophenoxy radical exhibits a spectrum that consists of one broad band.<sup>10,11</sup> A number of chlorinated phenoxy radicals in carbon tetrachloride show  $g$  values ranging from 2.0062 to 2.0076.<sup>11</sup> In the presence of the spin trapping agent, 5,5-dimethyl-1-pyrroline 1-oxide, 3 produced a six-line spectrum ( $a_N = 12$ ;  $a_H = 7$ ;  $g = 2.0049$ ). This is consistent with values reported<sup>12</sup> for oxy radicals ( $a_N \approx 12$ -13;  $a_H \approx 7$ -9). It has been reported that dimers of polyhalogenated phenoxy radicals undergo partial dissociation in solution.<sup>10</sup> Thus, when 3 is in solution, it is in equilibrium with pentachlorophenoxy radical. In the presence of sodium iodide, the EPR spectrum of 3 is gradually altered to a single broad band ( $g = 2.0055$ ). This suggests the formation of a new radical species.

Formation of 4 in the sodium iodide reduction of 3 probably results from the transfer of an electron from iodide to pentachlorophenoxy radical to form an anion.

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The anion may attack another radical in the 2-position with displacement of chloride to form 3,4,5,6-tetrachloro-2-(pentachlorophenoxy)phenoxy radical, which may then abstract a hydrogen atom from chloroform. Alternatively, formation of 3,4,5,6-tetrachloro-2-(pentachlorophenoxy)phenoxy radical may result from attack by the anion in the 2-position of a molecule of **3**. The trimer formed may undergo electron transfer from iodide with elimination of pentachlorophenoxide ion from the 4-position. Only about 5% **2** is formed, and this may be attributed to attack in the 4-position, rather than the 2-position, of the pentachlorophenoxy radical by the anion.

Formation of **2** in the sodium borohydride reduction of **3** probably occurs through reduction of the carbonyl group, followed by 1,4-conjugate elimination of hydrogen chloride. An analogous process has been suggested for the reaction of 10 $\beta$ -fluoro- $\Delta^1$ -dehydro-19-nortestosterone with sodium borohydride to produce estradiol.<sup>13</sup> Pentachlorophenoxy radical in the benzene solution of **3** probably accounts for the formation of **4**. Compound **2** is formed in a ratio of 2 to 1 with **4**.

### Experimental Section

Gas chromatography-mass spectrometry analyses were carried out on a Finnigan 4023 instrument. A Pyrex column (0.32 cm  $\times$  4.88 m) packed with 3% OV-101 on 80-100 mesh high-performance Chromosorb W (John-Manville Co.) was used for separation. Carbon-13 NMR spectra were obtained on a Varian CFT-80 spectrometer. EPR measurements were made on degassed solutions ( $2 \times 10^{-2}$  M) with a Varian E-4 spectrometer. The diphenylpicrylhydrazyl radical was used as a standard for determination of *g* values. Infrared measurements were made on a Perkin-Elmer 457 instrument. Melting points (uncorrected) were determined on a Fisher-Jones melting point apparatus.

**Nonachloro-4-phenoxyphenol (2)**. A methanol (25 mL) solution of sodium borohydride (0.57 g, 15 mmol) was added dropwise to a benzene (2 L) solution of **3** (2 g, 3.8 mmol) over a period of 30 min under constant stirring. The reaction mixture was stirred at room temperature for an additional hour and then washed three times with water (250 mL). Aqueous layers were combined and acidified with sulfuric acid and extracted three times with benzene (100 mL). The combined benzene layers were dried over anhydrous sodium sulfate and concentrated to dryness on a rotary evaporator. Purity of the product was determined by HPLC analysis with a 4.6  $\times$  250 mm silica gel (5  $\mu$ m Lichrosorb Si 60, E. Merck) column and a 4.6  $\times$  250 mm reverse-phase (7-8  $\mu$ m Zorbax ODS, DuPont) column. Analysis of the residue (1.8 g, 94.7%) indicated a composition of **2** (66%), **4** (26%), and **1** (4%).

**Purification of 2**. Purification of **2** was achieved by anion-exchange chromatography, followed by silica gel chromatography.

**Ion-Exchange Chromatography**. Anion-exchange resin (50-100 mesh Dowex 21 K, Dow Chemical Co.) was soaked overnight in 1 N sodium hydroxide and washed with water until neutral. After a final wash with methanol to remove the water, the resin was added to a 2.5  $\times$  33 cm Glenco 3500 column. The column was equilibrated with 1.50 N acetic acid in methanol (750 mL).

A solution of the reduction product (1.8 g) in 3:2 toluene/methanol (50 mL) was pumped onto the column. The column was eluted at 7 mL/min with (A) 1.5 N acetic acid in methanol (3 L) and (B) 4.0 N acetic acid in methanol (500 mL). The eluent was monitored at 280 nm. Solvent A eluted **2**, followed by **4**. Compound **1** was eluted with solvent B. Fractions containing **2** were collected and concentrated.

**Silica Gel Chromatography**. Product **2** from the ion-exchange chromatography procedure underwent additional purification on a 3.7  $\times$  25 cm column packed with silica gel (230-400 mesh Lichrosorb Si 60, E. Merck). The column was equilibrated with 96.7:3:0.3 hexane/ethyl acetate/2-propanol (500 mL). A

portion of the product (0.5 g) was dissolved in 7:1 toluene/ethyl acetate (4 mL) and applied to the column. Hexane/ethyl acetate/2-propanol (2 L), 96.7:3:0.3, was used to elute the sample. The eluent was monitored at 280 nm. A heart cut of the emerging peak was taken. Edge fractions were collected and rechromatographed. The column was cleansed of impurities by eluting with 1:1 hexane/ethyl acetate (500 mL) before reuse. Fractions containing pure **2** were combined and concentrated to dryness: yield 1.0 g (52.6%); mass spectra corresponded to that of **2**:<sup>3</sup> mp 215-216  $^{\circ}$ C, IR (KBr pellet)  $\nu$  3495, 1435, 1400, 1381, 1358, 1283, 1190 (broad), 1131, 1035, 974, 870, 790, 710  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{HCl}_9\text{O}_2$ : C, 29.05; H, 0.20; Cl, 64.30. Found: C, 29.12; H, 0.26; Cl, 64.63.

**2,3,5,6-Tetrachloro-2-(pentachlorophenoxy)anisole (5)**. Compound **2** was dissolved in carbon tetrachloride and treated with an ethereal solution of diazomethane prepared from Diazald (Aldrich Chemical Co.) to form **5**.

**2,3,4,5,6-Pentachloro-4-(pentachlorophenoxy)-2,5-cyclohexadienone (3)**. Compound **3** was prepared from **1** according to the method of Reed<sup>14</sup> and purified as previously published.<sup>5</sup> In order to remove residual chloranil, **3** was eluted from a silica gel (Mallinckrodt SilicAR CC-7) column with carbon tetrachloride.

**Crystal Structure Determination**. Single crystals of **3**,  $\text{C}_{12}\text{O}_2\text{Cl}_{10}$ , grown from a chloroform/hexane solution were used for the X-ray measurements of the crystal data. The systematic absences in the diffraction data were consistent with the space group *Cc*, and the unit cell dimensions were determined from a least-squares analysis of the  $2\theta$  values for 25 reflections to be  $a = 14.178$  (1),  $b = 8.6429$  (8),  $c = 28.665$  (3)  $\text{\AA}$ , and  $\beta = 98.869$  (8) $^{\circ}$ . The unit cell volume is 3470.6  $\text{\AA}^3$ . Integrated intensities for 5095 independent reflections having  $2\theta < 60^{\circ}$  were measured on a Nicolet P3 diffractometer with Nb-filtered Mo  $K\alpha$  radiation ( $\lambda = 0.71069$   $\text{\AA}$ ). The structure was solved by a straightforward application of direct methods techniques. The structure was found to have two independent molecules, molecular weight 530.66 per asymmetric unit ( $Z = 8$ ), resulting in a calculated density for the crystal of 2.031  $\text{g cm}^{-3}$ .

The positional and anisotropic thermal parameters of all the atoms were refined by full-matrix least squares analysis using 4813 reflections, for which the structure factor amplitude was greater than three times its calculated standard deviation. The weights used during refinement were the quantities  $(1/\sigma F^2)$ . The final reliability index, *R* (defined as  $\sum ||F_o| - |F_c|| / \sum |F_o|$ ), was 6.2% for the 4813 reflections used in the refinement and 7.4% for all data. Table II (see paragraph at the end of paper concerning supplementary material) contains the final fractional paragraph.

The following library of crystallography programs were used: MULTAN 78, University of York, England (1978); ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN (1970).

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**Supplementary Material Available**: The positional and thermal parameters from the X-ray structure of **3** (2 pages). Ordering information is given on any current masthead page.

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