mmol) of methylphenylcyanamide (mp 29.5–30.5 °C).[8b] Concentration gave a yellow liquid, TLC analysis (silica gel; 5:1:1 hexane–triethylamine–ethyl acetate) of which showed the presence of 4 (R_f 0.27), methylphenylcyanamide (R_f 0.37), and pseudourea **1g** (R_f 0.20). Immediate purification of this mixture by using a Waters Prep LC-500 and two Prep PAK-500 silica columns, using 5:1:1 hexane–triethylamine–ethyl acetate as the eluent, gave 1.35 g (74%) of pure **1g**: IR (film) 3360, 1630, 1050 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 6.7–7.6 (m, Ar H), 5.7 (br t, J = 6 Hz, CHOR), 5.35 (s, NH), 3.75 (s, two OCH_3), 3.25 (s, NCH_3), 0.7-2.2 (m, $CH_2CH_2CH_3$).

Thermal Rearrangement of Pseudourea 1g. Preparation of 3-Ethyl-6-(2,5-dimethoxyphenyl)-2(1*H*)-pyridinone (2g) and 4-[(2,5-Dimethoxyphenyl)methyl]-5-propyl-2-(*N*-methylanilinyl)oxazole (3g). A solution of 350 mg (0.96 mmol) of pseudourea **1g**, 493 mg (3.8 mmol) of *N,N*-diisopropylethylamine, and 96 mL of xylene was degassed[14] and heated at reflux under nitrogen for 24 h. Concentration afforded a yellow semisolid which was chromatographed (silica gel, 1:1 hexane–acetone) to yield two fractions. The first fraction (R_f 0.65, 1:1 hexane–acetone) gave 135 mg (38%) of oxazole **3g**, a light yellow liquid: IR (film) 1740, 1660, 1590, 1390, 1220, 1050 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.5–8.5 (m, Ar H), 3.7 (s, OCH_3 and $ArCH_2$), 3.4 (s, NCH_3), 2.4 (unsymm t, J = 7 Hz, $CH_2CH_2CH_3$), 1.1–1.9 (m, $CH_2CH_2CH_3$), 0.95 (unsymm t, J = 7 Hz, CH_3); mass spectrum (isobutane CI), m/z (relative intensity) 367 (100%, MH^+). The second fraction yielded 114 mg (46%) of 2-pyridone **2g**: mp 131–134 °C; TLC R_f 0.25 (1:1 hexane–acetone). An analytical sample was obtained by recrystallization from 1:2 chloroform–hexane: mp 136–137 °C; IR ($CHCl_3$) 3380, 1640, 1610, 1490, 1040 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.25 (d, J = 7 Hz, C_4H), 6.8–7.2 (m, Ar H) 6.40 (d, J = 7 Hz, C_5H), 3.83 (s, 2 OCH_3), 2.56 (q, J = 7.5 Hz, CH_2CH_3), 1.20 (t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 163.1 (C_2), 141.4 (C_6), 136.6 (C_4), 133.8 (C_3), 105.4 (C_5), and other peaks at 154.1, 150.8, 122.4, 115.9, 115.1, 113.2, 56.4, 55.9, 23.2, 12.7; mass spectrum (isobutane CI), m/z (relative intensity) 260 (100%, MH^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.47; H, 6.61; N, 5.40. Found: C, 69.51; H, 6.69; N, 5.37.

Thermal Rearrangement of Pseudourea 1b. Preparation of 3-Ethyl-6-phenyl-2(1*H*)-pyridinone (2b). A solution of 346 mg (1.13 mmol) of pseudourea **1b**, 583 mg (4.2 mmol) of *N,N*-diisopropylethylamine, and 113 mL of xylene was degassed[14] and heated at reflux under nitrogen for 28 h. Concentration gave a yellow residue which was dissolved in 15 mL of hot acetone and slowly allowed to cool to 0 °C to afford 132 mg (59%) of 2-pyridone **2b**, mp 164–166 °C. Purification of the mother liquor by chromatography on silica gel (4:1 hexane–ethyl acetate) gave an additional batch of **2b** which was recrystallized from ethyl acetate at −15 °C. The total yield of pure 2-pyridone **2b** was 155 mg (69%), mp 164–165 °C (lit.[1b] mp 164–166 °C), identical by TLC, ^1H NMR, and ^{13}C NMR with an authentic specimen.[1b] Careful chromatographic purification of the mother liquor from a comparable reaction which employed 140 mg (0.46 mmol) of **1b** resulted in the isolation of 16 mg (11%) of oxazole **3b**, a yellow oil which was ca. 90% pure by ^1H NMR: ^1H NMR (60 MHz, CCl_4) δ 7.0–7.7 (m, Ph), 3.67 (s, CH_2Ph), 3.45 (s, NCH_3), 2.40 (t, J = 8 Hz, $CH_2CH_2CH_3$), 1.2–1.9 (m, CH_2CH_3), 0.9 (t, J = 7 Hz, CH_3).

Rearrangement of Pseudourea 1d. Preparation of 3-Ethyl-2(1*H*)-pyridinone (2d) and 4-Methyl-5-propyl-2-(*N*-methylanilinyl)oxazole (3d). A solution of 200 mg (0.87 mmol) of pseudourea **1d**, 450 mg (3.5 mmol) of diisopropylethylamine, and 87 mL of xylene was degassed,[14] heated at reflux for 20 h, and concentrated. Purification of the residue by silica gel chromatography (5:1 to 1:1 hexane–acetone) gave in the first fraction 54 mg (27%) of oxazole **3d**, a pale yellow oil (R_f 0.45, 3:1 hexane–acetone). An analytical specimen was obtained by chromatography on silica gel (80:18:2 hexane–acetone–triethylamine): IR (film) 1675, 1590, 1390, 1200, 1035 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 6.8–7.4 (m, Ph), 3.45 (s, NCH_3), 2.5 (t, J = 7 Hz, $CH_2CH_2CH_3$), 1.95 (s, CH_3), 1.1–1.9 (m, CH_2CH_3), 0.9 (t, J = 7 Hz, CH_3); mass spectrum (isobutane CI), m/z (relative intensity) 231 (100%, MH^+); mol wt 230.140 (EI mass spectrum, $C_{14}H_{18}N_2O$ requires 230.142). A second fraction yielded a yellow solid (R_f 0.15, 3:1 hexane–acetone) which was recrystallized from 4:1 hexane–acetone to afford 44 mg (41%) of 2-pyridone **2d**, mp 120–121 °C. Recrystallization from hexane–acetone gave an analytical specimen, mp 121–121.5 C (lit.[1b] mp 120–121 °C), whose ^1H NMR spectra was identical with that of an authetic specimen.

Rearrangement of Pseudourea 1h. Preparation of 2-(9-Carbazolyl)-4-[(2,5-dimethoxyphenyl)methyl]-5-propyloxazole (3h). A dry Fisher–Porter bottle was charged with 25 mL of a xylene solution containing 106 mg (0.25 mmol) of pseudourea **1h** and 130 mg (1.0 mmol) of diisopropylethylamine. The bottle was degassed,[14] sealed, and heated at 205 °C for 12 h. Concentration afforded a yellow residue which did not show the presence of 2-pyridone **2h**[1b] by TLC analysis. Crystallization of this residue from acetone (−15 °C) gave 77 mg (73%) of white crystalline oxazole **3h**, mp 118–119 °C. An analytical specimen was obtained by recrystallization from acetone: mp 118.5–119.5 °C; IR ($CHCl_3$) 1590, 1450, 1240, 1045, 810 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.6–8.5 (complex m, Ar H), 3.88 (s, CH_2Ar), 3.82 (s, OCH_3), 3.72 (s, OCH_3), 2.7 (t, J = 7 Hz, $CH_2CH_2CH_3$), 1.5–2.1 (m, $CH_2CH_2CH_3$), 1.0 (t, J = 7 Hz, CH_2CH_3); CI mass spectrum (isobutane), m/z (relative intensity) 427 (100%, MH^+). Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14. Found: C, 75.83; H, 6.20.

Thermal rearrangements of pseudoureas **1e** and **1f** were conducted in a similar fashion and the results of these experiments are summarized in Table I.

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Registry No. 1a, 73267-71-7; **1b**, 75918-66-0; **1c**, 62969-93-1; **1d**, 75918-67-1; **1e**, 75918-68-2; **1f**, 75918-69-3; **1g**, 75918-70-6; **1h**, 75918-71-7; **2b**, 73252-79-6; **2d**, 62969-86-2; **2g**, 75918-72-8; **3a**, 73252-80-9; **3b**, 75918-73-9; **3c**, 73252-77-4; **3d**, 75918-74-0; **3f**, 75918-75-1; **3g**, 75918-76-2; **3h**, 75918-77-3; 4, 75918-78-4; methylphenylcyanamide, 18773-77-8.

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Aromatization of Arene 1,2-Oxides. 1-Cyanobenzene Oxide

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Previous investigations of the aromatization of arene 1,2-oxides in our laboratory have provided examples of arene 1,2-oxide aromatization reactions proceeding by all the possible general routes to ortho-substituted phenols and phenol with substituent loss.[1-3] Substituents at C_1 that are electron withdrawing, such as CO_2CH_3 and CHO, favor C_2–O cleavage of the arene 1,2-oxide. The ratio of C_2–O cleavage/C_1–O cleavage of 1-(carbomethoxy)benzene oxide in 1:1 tetrahydrofuran–water is 70:30 at pH 0.1 and 83:17 at pH 7, and C_2–O cleavage results in substituent

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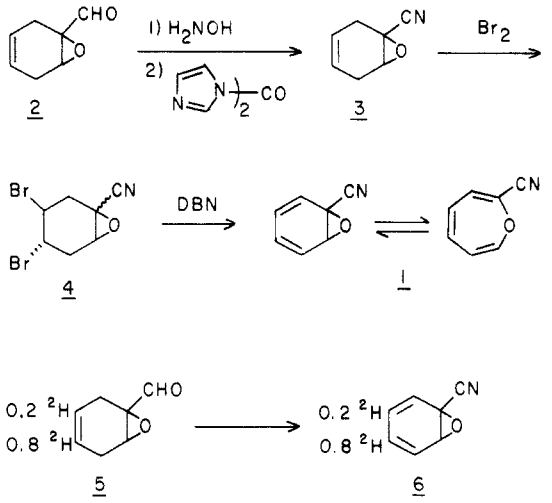
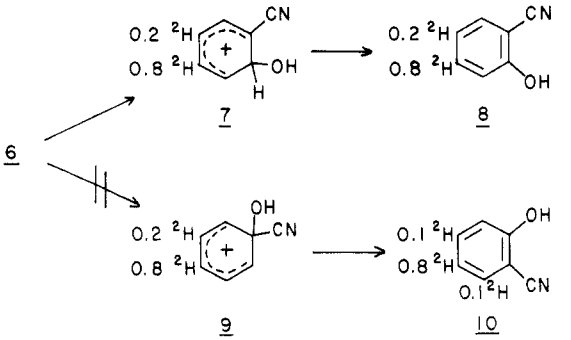
0022-3263/81/1946-0813$01.00/0

Scheme I



Scheme II



migration in formation of the aromatic product.[2] A smaller pH effect is observed in the aromatization of 1-formylbenzene oxide under similar conditions. The ratio of C_2–O cleavage/C_1–O cleavage is approximately 9:1, and C_2–O cleavage leads to substituent loss (H^+ + CO) in the aromatic product.[2]

The aromatization pathway for 1-cyanobenzene oxide (1) represents a particularly interesting case since, inductively, the cyano group is strongly electron withdrawing; but the importance of mesomeric stabilization of a cationic center α to a cyano group has been demonstrated by Gassman and co-workers.[4,5] Acid-catalyzed reactions of α-cyano epoxides commonly occur by C–O bond cleavage β to the cyano group to afford β-substituted cyanohydrins, and it is claimed that α-cyano epoxides formed during reaction of α-halocyanohydrins with base are converted to α-cyano ketones by a pathway involving migration of the cyano group.[6] With aryl substitution on each oxirane carbon atom, products from C–O cleavage α to the cyano group and subsequent aryl migration have been observed.[6] We have prepared 1 and, with deuterium labeling, have established the effect of the cyano group on the direction of oxirane ring opening during aromatization.

The synthesis of 1 is outlined in Scheme I. Aldehyde **2**[2] formed a relatively unstable oxime that was dehydrated to nitrile **3** with 1,1′-carbonyldiimidazole according to literature procedure.[7] Bromination of **3** afforded a crystalline, sharp-melting dibromide (**4**), the stereochemistry of which was not investigated. Dehydrobromination of **4** with 1,4-diazabicyclo[4.3.0]non-5-ene (DBN) gave 1 as a remarkably stable yellow, crystalline substance. Spectral data (see Experimental Section) indicate that 1 exists predominantly as the oxepin valence tautomer. Deuterium-labeled 1 (**6**) that contained 80% ^2H at C_4 and 20% ^2H at C_5 was prepared from **5**[2] by the same procedure for preparation of 1 from **2**.

Aromatization of 1 in $CF_3CO_2{}^2H$ at room temperature was complete after 3 h. The only product formed was *o*-hydroxybenzonitrile, and no deuterium exchange of aromatic protons with solvent was observed after a period of 3 days. Only 10% conversion of 1 to aromatic products was observed after 22 days at room temperature in 1:1 tetrahydrofuran–water at pH 1.1, and the aromatization product mixture was complex due to hydrolysis of the cyano group. No aromatization of 1 occurred in 1:1 tetrahydrofuran–water at pH 7.0 over a period of 22 days at room temperature. Aromatization did occur at pH 7.0 when heated under reflux for 2 days. *o*-Hydroxybenzonitrile was the major product (75%), but salicylamide (18%) and phenol (7%) were also observed. Since phenol and salicylamide are the products from aromatization of 1-carboxamidobenzene oxide,[8] the phenol formed from 1 may arise by hydrolysis of the nitrile group of 1 and subsequent aromatization to salicylamide and phenol rather than by loss of the cyano group during aromatization of 1.

Deuterium-labeled arene oxide **6** was aromatized in CF_3CO_2H at room temperature and in water at pH 7.0 at 60 °C, and *o*-hydroxybenzonitrile, the only product in the former case and the major product in the latter case, was isolated from each reaction. Analysis of the ^1H NMR spectrum established that, within experimental error, the deuterium distribution in the product corresponded to that indicated by structure **8** in Scheme II (0.79 ^2H at C_4 and 0.21 ^2H at C_5 for the CF_3CO_2H-catalyzed reaction; 0.80 ^2H at C_4 and 0.20 ^2H at C_5 for the aqueous reaction). Consequently, aromatization of **6** (or 1) in each case occurs by initial cleavage of the C_1–O oxirane bond to afford **7** which subsequently gives *o*-hydroxybenzonitrile either by direct loss of H^+ or by NIH shift of hydrogen and enolization.[9] None of the product is formed by C_2–O cleavage to **9** and migration of the cyano group that would have produced product with deuterium distribution indicated by **10**.

The results described herein establish that oxirane cleavage of 1 to afford the cyclohexadienyl cation with positive charge distribution at the carbon atom α to the cyano group is favored to the total exclusion of oxirane cleavage to the cyclohexadienyl cation with positive charge distribution β to the cyano group. Since 1-(carbomethoxy)- and 1-formyl-benzene oxide aromatize predominantly by oxirane cleavage at C_2[2] and since, inductively, the electron-withdrawing character of the cyano group is greater than that of the carbomethoxy or formyl group, it appears that the mesomeric stabilization effect of the α-cyano group on the cationic intermediate, as discussed by Gassman and co-workers,[4,5] determines the reaction pathway for aromatization of 1.

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o-Hydroxybenzonitrile has been observed as a minor product in the metabolism of benzonitrile with liver microsomes.[10] Our results suggest that if the biological ortho hydroxylation of benzonitrile occurs via the arene 1,2-oxide (or 2,3-oxide) as in intermediate, then o-hydroxybenzonitrile is formed without migration of the cyano group. If cyano group migration does occur in the biological ortho hydroxylation of benzonitrile, it would suggest that the reaction occurs by addition of HO^+ (or HO·) to C_1 of the substrate rather than formation of an arene oxide intermediate.

Experimental Section

Melting points were determined by using a Thomas-Hoover Unimelt and are corrected. ^1H NMR spectra were obtained at 60 or 250 MHz with Varian T-60, Perkin-Elmer R24B, and Brüker FT spectrometers, respectively. Unless otherwise indicated, spectra were obtained at 60 MHz. Chemical shift values (δ) are reported in parts per million downfield from tetramethylsilane. Mass spectra were determined with a Varian MAT 44 instrument. Infrared spectra were obtained with a Perkin-Elmer Model 238 B spectrophotometer. Ultraviolet spectra were obtained with a Perkin-Elmer Model 552 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

1-Cyano-1,2-oxy-4-cyclohexene (3). A mixture of **2**[2] (24.6 g, 0.198 mol), hydroxylamine sulfate (16.4 g, 0.20 mol), $NaHCO_3$ (16.8 g, 0.20 mol), and 4 mL of water in 300 mL of ether was stirred vigorously at 10 °C for 1 h. The solution was decanted from insoluble salts and dried ($MgSO_4$). Concentration at 15 °C afforded the oxime as a colorless oil that was dissolved in 300 mL of CH_2Cl_2 and cooled to 5 °C. 1,1'-Carbonyldiimidazole (30 g) in 200 mL of CH_2Cl_2 was added dropwise with stirring. After addition was complete, the mixture was warmed to room temperature and stirred overnight at which time CO_2 was no longer evolved. The solution was washed with three 150-mL portions of water and dried ($MgSO_4$). The solvent was removed in vacuo to give a viscous oil that was purified by column chromatography (silica gel, 9:1 pentane–ether) and distillation to yield 5.2 g (22%) of **3**: bp 43 °C (0.13 mm); IR (neat) 2250, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (br s, 2 H), 3.67 (br s, 1 H), 2.9–2.5 (br d, 4 H). Anal. Calcd for C_7H_7NO: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.38; H, 5.92; N, 11.46.

1-Cyano-1,2-oxy-4,5-dibromocyclohexane (4). A solution of **3** (1.4 g, 11.5 mmol) in 50 mL of 1:1 CH_2Cl_2–$CHCl_3$ was cooled to −70 °C, and bromine (1.84 g, 11.5 mmol) in 40 mL of the same solvent was added dropwise over a period of 40 min. The solution was concentrated, and the residue was purified by column chromatography (silica gel, 9.1 pentane–ether) to give 3.1 g (96%) of **4** as colorless crystals: mp 74–75 °C; IR (KBr) 2240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 (m, 2 H), 3.72 (m, 1 H), 3.5–2.2 (m, 4 H). Anal. Calcd for $C_7H_7Br_2NO$: C, 29.92; H, 2.51; N, 4.99. Found: C, 30.12; H, 2.56; N, 4.99.

1-Cyanobenzene Oxide–Oxepin (1). To 1.7 g (6 mmol) of **4** in 30 mL of anhydrous ether at room temperature under N_2 was added dropwise 3 equiv of DBN. The mixture was stirred for 3 h. The ether solution was decanted from precipitated salts, washed with aqueous pH 7 phosphate buffer solution, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (silica gel, 10:1 pentane–ether) to give 300 mg (42%) of **4** as yellow crystals that were recrystallized from pentane: mp 36–37 °C; IR (KBr) 2210 (sh 2250), 1628, 1610, 1585, 1555 cm^{-1}; UV_{max} (CH_3OH) 204 (ϵ 10950), 307 nm (1680); ^1H NMR (250 MHz, $CDCl_3$) δ[11] 6.49 (dd, 1 H, H_4), 6.36 (d, 1 H, H_6), 6.26 (dd, 1 H, H_5), 5.99 (d, 1 H, H_2), 5.76 (t, 1 H, H_3) ($J_{2,3}$ = 5.3, $J_{3,4}$ = 6.0, $J_{4,5}$ = 10.6, $J_{5,6}$ = 5.7 Hz); mass spectrum (70 eV), m/e (relative intensity) 119 (45, M^+), 103 (6), 93 (18), 91 (57), 82 (100), 81 (45), 80 (95), 79 (51), 68 (23), 65 (42), 64 (86), 63 (44), 39 (79). Anal. Calcd for C_7H_5NO: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.43; H, 4.18; N, 11.62.

Crystalline arene oxide **1** sublimes at room temperature and should be kept in a closed container.

Deuterium-Labeled Arene Oxide 6. The synthetic sequence for preparation of **1** from **2** was used to convert **5**[2] (80% ^2H at C_4, 20% ^2H at C_5) to **6**; ^1H NMR (250 MHz, $CDCl_3$) δ 6.49 (0.20 H, H_4), 6.36 (1 H, H_6), 6.26 (0.8 H, H_5), 5.99 (1 H, H_2), 5.76 (1 H, H_3).

Aromatization of 1 and 6. Arene oxide **1** was aromatized in pure $CF_3CO_2{}^2H$ and in 1:1 tetrahydrofuran–water at pH 1.1 and 7.0. The results are summarized in the discussion. o-Hydroxybenzonitrile was characterized by TLC and 250-MHz ^1H NMR comparison with an authentic sample. For o-hydroxybenzonitrile: ^1H NMR (250 MHz, acetone-d_6) δ 7.58 (H_6), 7.50 (H_4), 7.09 (H_3), 6.99 (H_5) ($J_{3,4}$ = 8.5, $J_{4,5}$ = 7.4, $J_{5,6}$ = 7.7, $J_{3,5}$ = 1.1, $J_{4,6}$ = 1.6 Hz).

Arene oxide **6** was dissolved in CF_3CO_2H and kept at room temperature for 3 h, at which time the yellow oxepin color had disappeared. The solution was diluted with ether, extracted with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to give **8**; ^1H NMR (250 MHz, acetone-d_6) δ 7.58 (1 H, H_6), 7.50 (0.21 H, H_4), 7.09 (1 H, H_3), 6.99 (0.79 H, H_5).

A mixture of **6** and water (pH 7, phosphate buffer) was heated at 60 °C for 12 h. The solution was extracted with ether, dried ($MgSO_4$), and concentrated. Preparative TLC (silica gel, 1:1 ether–pentane) of the residue gave **8**; ^1H NMR (250 MHz, acetone-d_6) δ 7.58 (1 H, H_6), 7.50 (0.20 H, H_4), 7.09 (1 H, H_3), 6.99 (0.80 H, H_5).

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Registry No. 1, 73654-30-5; 2, 75961-78-3; 3, 75961-79-4; 4, 75961-80-7.

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Confirmation of the Structure of the Guanine–Methylmalondialdehyde Reaction Product by Unequivocal Synthesis

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The ability of several mono-[1-3] and dicarbonyl[4-7] aldehydes to form stable, covalent adducts with guanine derivatives (1) has prompted investigation into their use as potential DNA[8,9] and RNA[4,8] modifying agents. Malondialdehyde (**2**, R^2 = H), a naturally occurring β-dialdehyde,[10-13] has been reported to react with DNA both in vitro and in vivo[14] with a corresponding loss of DNA template activity.[15]

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