perature 135 °C) for 23 h. The reaction mixture was cooled to room temperature and chromatographed on silica gel. Elution with 2:1 hexanes–ether afforded 322 mg (97%) of crystalline olefinic alcohol **6**: mp 81.0–82.0 °C; R_f 0.42 (hexanes–ether, 1:2); IR (CCl_4) 3640, 3525, 3070, 2980, 2890, 1632, 1478, 1460, 1442, 1390, 1378, 1350, 1325, 1301, 1263, 1240, 1210, 1160, 1108, 1082, 1050, 1020, 950, 921, 898 cm^{-1}; NMR (CCl_4) δ 6.3–5.8 (m, 2 H, CH=CH), 4.21 (q, 1 H, J = 6 Hz, CHOH), 4.1–3.5 (m, 4 H), 2.66 (br s, 1 H), 2.3–1.9 (m, 2 H), 1.43 (d, 1 H, J = 12 Hz, C(3) endo proton), 1.38 (br s, 1 H, OH), 1.10 (s, 3 H), 1.98 (d, 3 H, J = 6 Hz); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.1256, found m/e 210.1260. Recrystallization from hexanes–ether provided analytically pure **6**, mp 82.5–83.5 °C. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.46; H, 8.72.

Preparation and Reduction of 7-Acetyl-7-methylspiro-[bicyclo[2.2.1]hept-5-en-2,2'-[1,3]dioxolane]. A solution of 10 g (34.6 mmol) of keto bromide **2** in 300 mL of xylene containing 52.6 g (0.35 mol) of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) was refluxed (bath temperature 160 °C). After 17 h, an additional 26.3 g (0.17 mol) of DBU was added, and heating was continued for 4 h. The reaction mixture was cooled to room temperature, diluted with 100 mL of benzene, washed with brine, and condensed under reduced pressure. Chromatography on 1.0 kg of silica gel using 2:1 hexanes–ether gave 6.84 g (95%) of 7-acetyl-7-methylspiro[bicyclo[2.2.1]hept-5-en-2,2'-[1,3]dioxolane]: R_f 0.57 (hexanes–ether, 1:1); IR (CCl_4) 3070, 2970, 2880, 1705, 1630, 1452, 1435, 1420, 1375, 1348, 1320, 1301, 1278, 1260, 1235, 1214, 1208, 1165, 1154, 1105, 1081, 1046, 1010, 973, 945, 915, 890, 870, 855 cm^{-1}; NMR (CCl_4) δ 6.3–5.8 (m, 2H, CH=CH), 4.0–3.6 (m, 4 H, OCH_2CH_2O), 2.82 (br s, 1 H), 2.65 (m, 1 H), 2.02 (dd, 1 H, J = 4, 13 Hz, C(3) exo proton), 1.91 (s, 3 H, CH_3CO), 1.52 (d, 1 H, J = 13 Hz, C(3) endo proton), 1.18 (s, 3 H); high-resolution mass spectrum calcd for $C_{12}H_{16}O_3$ m/e 208.1099, found m/e 208.1103. An analytical sample was prepared by distillation [61–70 °C (bath temperature; 2.5 mmHg)]. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.94; H, 7.73.

To a suspension of 1.37 g (36.1 mmol) of lithium aluminium hydride in 75 mL of anhydrous tetrahydrofuran cooled to 0 °C was added a solution of 5.0 g (24.0 mmol) of the above ketone in 25 mL of dry tetrahydrofuran. The reaction mixture was warmed to room temperature after the addition was complete. After 8 h, the reaction mixture was quenched at 0 °C with reagent grade ether and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo left 5.0 g (99%) of a crude mixture (1:1) of alcohols **6** [R_f 0.42 (hexanes–ether, 1:2)] and **7** (R_f 0.26). Chromatography on silica gel using 1:1 hexanes–ether provided in order of elution 2.38 g of crystalline **6** (mp 82.5–83.5 °C), identical in all respects with the sample of **6** prepared above, and 2.35 g of **7**: bp 84–90 °C (bath temperature; 0.45 mmHg); IR (CCl_4) 3640, 3525, 3070, 2980, 2880, 1635, 1475, 1445, 1390, 1376, 1345, 1324, 1301, 1240, 1210, 1151, 1110, 1080, 1048, 1018, 1008, 950, 920, 899 cm^{-1}; NMR (CCl_4) δ 6.1–5.9 (m, 2 H, CH=CH), 4.21 (q, 1 H, J = 6 Hz, CHOH), 4.1–3.5 (m, 4 H), 2.50 (m, 1 H), 2.21 (m, 1 H), 2.05 (dd, 1 H, J = 13, 4 Hz, C(3) exo proton), 1.42 (d, 1 H, J = 13 Hz, C(3) endo proton), 1.13 (s, 3 H), 0.96 (d, 3 H, J = 6 Hz); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.1256, found m/e 210.1250. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.67; H, 8.65.

Preparation of Aldehyde 3. A solution of 0.90 g (3.3 mmol) of 5-bromo-7-methylspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-methanol[5] in 10 mL of dry methylene chloride was added to 3.3 g (33 mmol) of chromium trioxide in 70 mL of dry methylene chloride containing 5.2 g (66 mmol) of pyridine. After 15 min at room temperature the reaction mixture was diluted with reagent grade ether and filtered through anhydrous magnesium sulfate. The filtrate was washed with dilute hydrochloric acid, sodium bicarbonate solution, and saturated sodium chloride solution and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave crude aldehyde which was chromatographed on 50 g of silica gel. Elution with 4:1 hexanes–ether provided 807 mg (88%) of pure aldehyde: IR ($CHCl_3$) 2955, 2920, 2870, 2800, 2700, 1710, 1445, 1430, 1385, 1370, 1340, 1305, 1280, 1255, 1240, 1220, 1168, 1155, 1141, 1100, 1075, 1050, 1010, 998, 985, 940, 918, 900, 885, 860, 825 cm^{-1}; NMR (CCl_4 90 MHz) δ 9.75 (s, 1 H, CHO), 3.6–4.1 (m, 5 H), 2.0–2.7 (m, 5 H), 1.60 (d, 1 H, J = 14 Hz), 1.22 (s, 3 H).

Reaction of Aldehyde 3 with Methyllithium. A solution of 359 mg (1.30 mmol) of aldehyde **3** in 7.0 mL of anhydrous ether cooled to −78 °C was treated with 2.33 mL (3.25 mmol) of a 1.4 M solution of methyllithium in ether. After 1.5 h at −78 °C, the reaction was quenched by the addition of an aqueous saturated solution of ammonium chloride and diluted with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification of the crude product on silica gel with 5:1 hexane–ether gave in order of elution 314 mg (83%) of pure alcohol **4** (mp 127–129 °C), identical in all respects (NMR, IR, melting point, mixture melting point, TLC) with a sample of **4** prepared above, and 37 mg (10%) of alcohol **5**: IR ($CHCl_3$) 3620, 3400, 2970, 2880, 1480, 1460, 1440, 1380, 1325, 1200, 1140, 1075, 1055, 1015, 1005, 970, 950, 930, 908, 885 cm^{-1}; NMR ($CDCl_3$) 4.80 (q, 1 H, J = 6 Hz), 3.7–4.2 (m, 5 H), 2.2–2.6 (m, 3 H), 2.0–2.2 (m, 2 H), 1.50 (d, 1 H, J = 14 Hz), 1.23 (d, 3 H, J = 6 Hz), 1.20 (s, 3 H).

Acknowledgment. This research was supported by a Public Health Research Grant from the National Institutes of Health and, in part, by a Grant from G. D. Searle and Co.

Registry No. 1, 75521-01-6; 2, 75521-02-7; 3, 75476-75-4; 4, 75476-76-5; 5, 75521-03-8; 6, 75521-04-9; 7, 75521-05-0; 7-acetyl-7-methylspiro[bicyclo[2.2.1]hept-5-en-2,2'-[1,3]dioxolane], 75476-77-6; 5-bromo-7-methylspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-7-methanol, 75521-06-1.

A New Synthesis of α-Keto Esters and Acids

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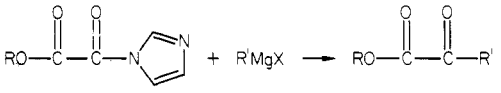
Received June 11, 1980

α-Keto acids have been studied extensively because of their widespread distribution in living organisms. However, general methods for synthesis of α-keto acids and α-keto esters are few,[1] and these often involve several nonconvergent steps. We wished to develop a reagent for direct, one-step formation of α-keto esters with a variety of substituents. Futhermore, we wanted to obtain the *tert*-butyl esters so that acid-catalyzed cleavage could readily give the keto acids.[2] The imidazolides **1** and **2**



1, R = Et
2, R = *t*-Bu

appeared promising for this purpose because of the high reactivity of acylimidazolides[3] toward Grignard reagents to yield ketones without significant further reaction to give tertiary alcohols.

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Table I. Products of Grignard Reactions with Imidazolides 1 and 2

imidazolide, $C_3H_3N_2COCOOR$ R =	Grignard, RMgX	product,[a] R'COCOOR	bp, °C (mmHg)	% yield
1, Et	PhMgBr	3, $PhCOCO_2Et$[b]	88 (0.5)	72
1, Et	p-$CH_3O(C_6H_4)MgBr$	4, p-$CH_3O(C_6H_4)COCO_2Et$[c]	133 (0.8)	57
1, Et	p-$Cl(C_6H_4)MgBr$	5, p-$Cl(C_6H_4)COCO_2Et$[d]	110 (0.7)	72
1, Et	p-$CH_3(C_6H_4)MgBr$	6, p-$CH_3(C_6H_4)COCO_2Et$[a,e]	112 (0.6)	55
1, Et	EtMgBr	7, $CH_3CH_2COCO_2Et$[f]	65 (21)	26
2, t-Bu	PhMgBr	8, $PhCOCO_2C(CH_3)_3$[g]	83 (0.6)	77
2, t-Bu	p-$CH_3O(C_6H_4)MgBr$	9, p-$CH_3O(C_6H_4)COCO_2C(CH_3)_3$[a]	130 (0.5)	55
2, t-Bu	p-$Cl(C_6H_4)MgBr$	10, p-$Cl(C_6H_4)COCO_2C(CH_3)_3$[a]	96 (0.3)	67
2, t-Bu	p-$CH_3(C_6H_4)MgBr$	11, p-$CH_3(C_6H_4)COCO_2C(CH_3)_3$[a]	119 (1.0)	54
2, t-Bu	i-BuMgCl	12, $(CH_3)_2CHCH_2COCO_2C(CH_3)_3$[a]	95 (20)	22
2, t-Bu	t-BuMgCl	13, $(CH_3)_3CCOCO_2C(CH_3)_3$[a]	68 (20)	22

[a] Satisfactory spectral and analytical data (±0.3% for C and H) were obtained for new compound. [b] Reference 5. [c] Reference 6. [d] Reference 7. [e] In a second experiment, Grignard addition to the imidazolide was at −20 °C instead of −50 °C. The yield of 6 decreased to 41% and 8% of the tertiary carbinol was isolated. [f] Reference 8. [g] Reference 9.

Table II. α-Keto Acids from Their *tert*-Butyl Esters

starting ester	product, R'COCOOH	mp, °C	isolated yield, %
8	14, $PhCOCO_2H$[a]	61-64	57
9	15, p-$CH_3O(C_6H_4)COCO_2H$[b]	83-86	61
10	16, p-$Cl(C_6H_4)COCO_2H$[c]	89-91	67
11	17, p-$CH_3(C_6H_4)COCO_2H$[d]	91-93	54
12	18, $(CH_3)_2CHCH_2COCO_2H$[e]	[f]	54
13	19, $(CH_3)_3CCOCO_2H$[g]	[f]	56

[a] Reference 11. [b] Reference 1c. Upon addition of 9, or the corresponding ethyl ester 4, the solution became intensely purple. This may be explained by formation of the quinoid enol cation of the esters or resulting acids. [c] Reference 1a. This material crystallized as the hemihydrate, mp 61-63 °C, and was dried over P_2O_5. [d] Reference 1c. [e] Reference 12. [f] Purified by bulb-to-bulb vacuum distillation. [g] Reference 13.

Results and Discussion

Ethyl α-oxo-1*H*-imidazole-1-acetate, **1**, was prepared in 90% yield according to the procedure of Staab[3a] by addition of ethyl oxalyl chloride to 2 molar equiv of imidazole in tetrahydrofuran (THF). Similarly, *tert*-butyl α-oxo-1*H*-imidazole-1-acetate, **2** was prepared in 92% yield by addition of *tert*-butyl oxalyl chloride (generated in situ) to imidazole. The desired product **2** was accompanied by approximately 6% di-*tert*-butyl oxalate.[4] The results from the reaction of Grignard reagents with **1** and **2** are shown in Table I. These data show that the yields with aromatic Grignard reagents were good while those for alkyl Grignard reagents were low. The reasons for the low yields are not clear, although in the case of 12, aldol-type side products were also obtained[10] and it may be that this was general for the more basic alkyl-type Grignard reagents.

Cleavage of the *tert*-butyl esters in trifluoroacetic acid at 0 °C gave the corresponding carboxylic acids in fair yields as seen in Table II.[14] Therefore these results offer a general, simple method for making a wide spectrum of α-keto esters and acids, especially those where the substituent is furnished by an aromatic Grignard reagent.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Melting points were determined on an aluminum block (Meltemp apparatus) and were uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian T-60 instrument; chemical shifts are given in δ values (parts per million) downfield from tetramethylsilane; multiplicities are given as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, with relative areas as 1 H, 2 H, 3 H, etc. Infrared spectra were obtained on a Perkin-Elmer 237B instrument. Mass spectra were obtained on a Mat-44 instrument at 70 eV. Analyses were performed by Mr. Erich Meier at Stanford University Chemistry Department.

Ethyl α-Oxo-1*H*-imidazole-1-acetate (1). Ethyl oxalyl chloride (20.0 mL, 0.179 mol, Aldrich) in THF (80 mL) was added to stirred solution of imidazole (24.3 g, 0.35 mol) in THF (500 mL) at 0 °C under N_2 over a 1-h period. After an additional 1 h of being stirred at 0 °C, the mixture was filtered and the precipitate was washed with anhydrous THF (100 mL). The THF was removed from the filtrate and washings under vacuum, and the residue was distilled to furnish 27.2 g (90%) of **1**: bp 100 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 1.45 (t, 3 H), 4.45 (q, 2 H), 7.05 (s, 1 H), 7.60 (s, 1H), 8.40 (s, 1 H); IR (neat 1730 (ester), 1770 (amide) cm^{-1}; mass spectrum, *m/e* 168 (M^+). This material underwent slow discoloration at room temperature and was stored at 5 °C.

Anal. Calcd for $C_7H_8N_2O_3$: C, 49.96; H, 4.79; N, 16.72. Found: C, 49.87; H, 4.94; N, 16.59.

***tert*-Butyl α-Oxo-1*H*-imidazole-1-acetate (2).** *tert*-Butyl alcohol (10.8 mL, 115 mmol) was added in one batch to a stirred solution of freshly distilled oxalyl chloride (10.0 mL, 115 mmol) in THF (200 mL) at 0 °C under N_2. After 1 h, a solution of imidazole (23.5 g, 345 mmol) in THF (100 mL) was added over 30 min. After an additional 15 min, the stirred reaction mixture was filtered, and the imidazole hydrochloride precipitate was washed with THF (100 mL). The THF was then removed under reduced pressure from the filtrate and washings. The residual oil, 21.8 g, was found by ^1H NMR analysis to be 94% **2** (92% yield) containing 6% di-*tert*-butyl oxalate. This material was used without further purification in the subsequent Grignard reactions. Attempts at distillation (0.3 mmHg) immediately after preparation resulted in decomposition, but after storage at 5 °C for several days followed by filtration, it was distilled normally, giving **2**, bp

(4) This high selectivity has been reported before in the synthesis of ethyl *tert*-butyl oxalate; cf: Crandall, J. K.; Sojka, S. A.; Komin, J. B. *J. Org. Chem.* **1974**, *39*, 2172.

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(10) In the reaction of benzylmagnesium chloride with **2**, only aldol type prodcts were obtained.

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(14) It is reported that α-keto acids can be obtained by basic hydrolysis of their ethyl esters; cf.: Oehme, G.; Fischer G.; Schellenberger, A. *Chem. Ber.* **1967**, *100*, 425. It is also reported that *N*-*tert*-butyl α-keto amides were hydrolyzed to the corresponding α-keto acids in 48–88% yields by boiling in a 1:1 mixture of concentrated hydrochloric acid–acetic acid for 24 h.[11] In the absence of acid-sensitive groups, the same hydrolysis treatment should work equally well on the α-keto esters described in Table I.

113 °C (1.2 mmHg). This material was stable for several weeks when stored in the dark at 5 °C, but it slowly decomposed on standing at room temperature: ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 9 H), 7.05 (s, 1 H), 7.60 (s, 1 H), 8.45 (s, 1 H); IR (neat) 1735 (ester), 1765 (amide) cm^{-1}; mass spectrum, *m/e* 196 (M^+).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.06; 6.16; N, 14.33. Found: C, 54.77; H, 6.14; N, 14.06.

Preparation of Grignard Reagents. The Grignard reagents were prepared from freshly distilled halide (26.4 mmol) in THF (30 mL) with magnesium (642 mg) below 40 °C. An aliquot was titrated with 0.1 N HCl to determine the molarity.

Grignard Reactions with Imidazolides 1 and 2. The procedures were identical with reagents 1 and 2. The imidazolide (24.0 mmol) was dissolved in THF (75 mL) under nitrogen and cooled to −50 °C in a dry ice/acetone bath. The Grignard solution, (1.0 equiv in 50 mL of THF) was added by dropping funnel over 1 h with stirring. The solution was allowed to come to room temperature over 3 h and poured into ice–water (200 mL). The solution was extracted with ether (a few drops of acetic acid was added if necessary to break up emulsions) and the ether extracts were washed with brine and dried ($MgSO_4$ or K_2CO_3). Removal of solvents under reduced pressure and distillation afforded the α-keto esters.[15] The data on compounds **3–13** are listed in Table I.

Cleavage of *tert*-Butyl Esters to Acids.[14] The procedure for all examples was as follows. The *tert*-butyl ester (500 mg) was added to CF_3CO_2H (5 mL) and stirred in an ice bath. After approximately 60 min, TLC monitoring showed the reaction to be complete and the CF_3CO_2H was removed under reduced pressure. The residue was either recrystallized from benzene/petroleum ether (bp 60–110 °C) (for compounds **14–17**) or purified by bulb-to-bulb distillation (for compounds **18** and **19**).

Acknowledgment. We gratefully acknowledge financial support by the National Institutes of Health, NS 14345, and the Hertz Foundation for a fellowship.

Registry No. 1, 75716-82-4; 2, 75716-83-5; 3, 1603-79-8; 4, 40140-16-7; 5, 34966-48-8; 6, 5524-56-1; 7, 15933-07-0; 8, 7332-98-1; 9, 75716-84-6; 10, 75716-85-7; 11, 75716-86-8; 12, 75716-87-9; 13, 75716-88-0; 14, 611-73-4; 15, 7099-91-4; 16, 7099-88-9; 17, 7163-50-0; 18, 816-66-0; 19, 815-17-8; PhBr, 108-86-1; *p*-$CH_3O(C_6H_4)$Br, 104-92-7; *p*-Cl(C_6H_4)Br, 106-39-8; *p*-$CH_3(C_6H_4)$Br, 106-38-7; EtBr, 74-96-4; *i*-BuCl, 513-36-0; *t*-BuCl, 507-20-0; ethyl oxalyl chloride, 4755-77-5; imidazole, 288-32-4; *tert*-butyl alcohol, 75-65-0; oxalyl chloride, 79-37-8.

(15) Yields were not improved by use of ether as the reaction solvent, by quenching with aqueous ammonium chloride, with pH 7.0 buffer or with aqueous acetic acid at low temperature.

Mechanistic Studies on the Addition of Cysteine to 3,4-Dihydroxyphenylalanine

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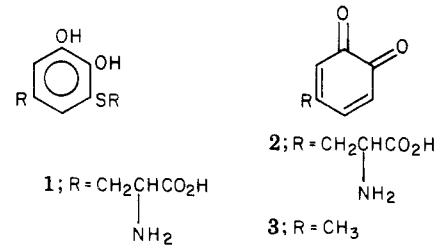
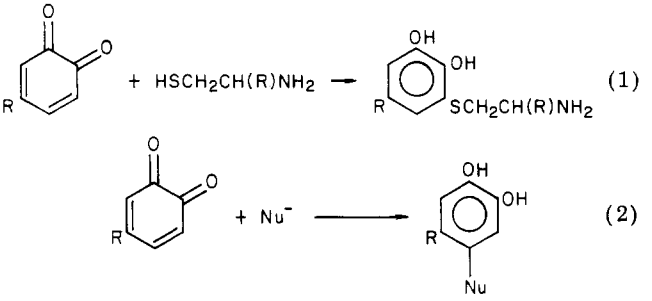
Received July 10, 1980

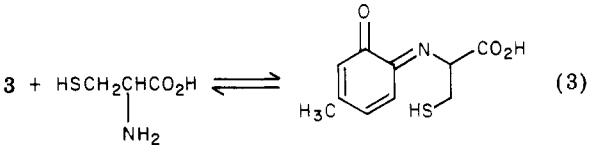
Urine levels of 5-(*S*-cysteinyl)dopa, **1**, are indicative of melanocyte activity,[2] and, as such, have been used for early detection of metastasizing melanoma.[3,4] Cysteinyldopas (the 2-*S*-, 5-*S*-, and 2,5-*S*,*S*-di isomers) are important biosynthetic intermediates of the red-brown polymeric pheomelanin pigments found throughout nature.[5] However, cysteinyldopas are by no means confined to phenomelanocytes; indeed, they are now known to be found in all tyrosinase-containing melanocytes[6] and have been proposed to be detoxification products of dopaquinone,[7] **2**. Herein we communicate preliminary work on the in vitro mechanism of cysteinyldopa formation.



Previous workers have speculated that addition of β-aminoethanethiols to *o*-benzoquinones occurred in a 1,6-fashion as depicted in eq 1.[8] However, no mention was made of the strong literature precendence favoring a general 1,4-addition of nucleophiles as depicted in eq 2.[9] Since the structure of **1** has been confirmed by independent synthesis,[10] a viable explanation for this abnormal addition is needed.



Initially we felt that a rapid preequilibrium, such as depicted in eq 3, might serve to position the incoming



nucleophile so as to favor attack at the 6 position. If this reasoning was correct, substitution of *N*-acetylcysteine for cysteine would dramatically alter the course and products of the reaction. In order to simplify both the isolation and analysis of the products, we decided to use 4-methyl-*o*-quinone, **3**, in place of **2**.

Various molar ratios of *N*-acetylcysteine, **4**, and preformed **3** were mixed together in the absence of oxygen. Inverse and simultaneous addition of the two was also tried. However, after workup of the reaction mixture, no trace of addition of **4** to the quinone could be detected. The same result was obtained if the quinone was prepared

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