The costs of the quantities of pyruvate kinase and acetate kinase required to achieve equal rates of ATP regeneration are comparable.[12]

The balance of these factors, in our experience, is that PEP^-K^+/pyruvate kinase is a more convenient and useful system for regeneration of ATP than $AcP^{2-}(NH_4^+)_2$/acetate kinase for syntheses generating products in quantities up to several moles. For larger preparations, AcP/acetate kinase may have economic advantages.

Experimental Section

All reagents and solvents (except for water, which was twice distilled) were obtained commercially and used without further purification.

Bromopyruvic Acid. Pyruvic acid (480 g of 95% pure material, 5.17 mol), 20 drops of concentrated H_2SO_4, and 450 mL of CH_2Cl_2 were added to a 3-L, three-necked flask equipped with an overhead stirrer, an addition funnel, and a reflux condenser connected to a bubbler. Bromine (265 mL, 5.17 mol) was added dropwise over a 3.5-h period to the stirred solution. A white precipitate formed when the addition of Br_2 was nearly complete. The suspension was stirred for an additional hour and diluted with 40 mL of cyclohexene and 200 mL of ligroin (bp 35–60 °C). The reaction mixture was cooled in an ice bath. The bromopyruvic acid was collected by filtration, washed with 300 mL of ligroin, and dried at 0.1 torr for 12 h. Its yield was 804 g [mp 64–67 °C (lit.[4] mp 70 °C), 97% pure,[13] 4.65 mol, 90% yield based on pyruvic acid].

Potassium Phosphoenolpyruvate (PEP^-K^+). Bromopyruvic acid was converted to the dimethyl ester of PEP, 1 (2-hydroxyacrylic acid dimethyl phosphate), in a 12-L, three-necked flask equipped with a reflux condenser connected to a bubbler, an addition funnel, and a magnetic stirrer. A solution of 752 g (4.37 mol) of bromopyruvic acid (97% pure, used without further purification) in 1.25 L of dry ether was added dropwise at a rate sufficient to maintain the ether at reflux (3.5 h) to a stirred solution of 557 mL (4.72 mol) of trimethyl phosphite in 3.85 L of dry ether. The reaction mixture was stirred for an additional hour at ambient temperature, and the ether was removed by rotary evaporation, yielding 1002 g of crude 1 as a brown viscous oil. This oil was dissolved in 1.67 L of water, and the solution was stirred at 20 °C for 15 h. The spontaneous hydrolysis reaction had proceeded to completion in this time and had produced 2.64 mol (60%) of PEP and 0.2 mol (5%) of pyruvate.[14] The solution was cooled in an ice bath, and 267 g of solid KOH (85% pure, 4.0 mol) was added (to produce a solution with pH 2.8) followed by 2.7 L of absolute ethanol. The white precipitate which formed was collected by filtration, washed with 800 mL of cold absolute ethanol, and dried at 0.1 torr, yielding 531 g of PEP^-K^+ (95% pure,[5,14,15] 2.45 mol, 50% yield based on crude pyruvic acid).

Glucose 6-Phosphate. The synthesis was carried out under argon in a 2-L, three-necked flask equipped with a pH electrode and a magnetic stirrer. A solution of 0.800 mol of glucose, 0.800 mol of PEP^-K^+, 35 mmol of $MgCl_2$, and 10 mmol of 2-mercaptoethanol in ca. 800 mL of doubly distilled water was adjusted to pH 7.6 with solid KOH, transferred to the reaction flask, and degassed with a stream of argon. ATP (1.20 mmol) and an aqueous suspension (0.78 L) of 1260 U of pyruvate kinase and 863 U of hexokinase (each separately immobilized in PAN gel[16]) were added. The reaction mixture (1.6 L) was stirred at 20 °C and maintained at pH 7.5–7.6 by occasional addition of a few drops of 12 M HCl. After 8.5 days the reaction mixture contained 0.77 mol of G-6-P (96%), 0.42 mol of pyruvate (53%), and no PEP.[14] The immobilized enzymes were separated by centrifugation, washed with 300 mL of doubly distilled H_2O, and again separated by centrifugation. The turnover numbers (and residual activities) of the components of this system were as follows: hexokinase, 2×10^7 (100%); pyruvate kinase, 4×10^7 (70%); ATP, 587 (not recovered). To the combined supernatant reaction mixture and wash solution was added 244 g of $BaCl_2 \cdot 2H_2O$ (1.00 mol), and the solution was adjusted to pH 7.0 with solid KOH and stored at 0 °C overnight. The white precipitate which formed was collected by filtration, washed in succession with 300 mL of cold H_2O, 400 mL of cold 50% aqueous ethanol, and 200 mL of cold 95% aqueous ethanol, and then dried at 0.1 torr. The yield of BaG-6-P·$7H_2O$ was 367 g (100% pure,[14,15] 0.704 mol, 88% yield).

Registry No. 1, 4185-81-3; ATP, 56-65-5; ADP, 58-64-0; $PEP-K^+$, 4265-07-0; pyruvic acid, 127-17-3; bromopyruvic acid, 1113-59-3; glucose, 50-99-7; glucose 6-phosphate, 56-73-5; pyruvate kinase, 9001-59-6; hexokinase, 9001-51-8.

(12) Pyruvate kinase is less expensive and more stable than acetate kinase. The pronounced inhibition of pyruvate kinase by pyruvate (K_I = 1 mM, Reynard, A. M.; Hass, L. F.; Jacobsen, D. D.; Boyer, P. D. *J. Biol. Chem.* **1966**, *236*, 2277–2283) requires that a 10-fold larger number of units of this enzyme be used than that predicted on the basis of noninhibited assay to achieve satisfactory regeneration rates at high pyruvate concentrations.

(13) The purity of bromopyruvic acid (a substrate analogue of pyruvic acid for L-lactic dehydrogenase) was determined by enzymatic assay[14] and from its ^1H NMR spectrum.

(14) Assays of biological materials were performed following procedures in Bergmeyer, H. U. "Methods of Enzymatic Analysis"; Verlag Chemie Weinheim/Bergstr., Germany: 1974: PEP, pyruvic acid and bromopyruvic acid, p 1456; glucose 6-phosphate, p 1283; pyruvate kinase, p 774; hexokinase, p 473. Assays of immobilized enzymes were performed as described in ref 16.

(15) The ^{31}P NMR spectrum of PEP^-K^+ (0.5 M, H_2O) consisted of a single peak at −4.51 ppm (85% H_3PO_4 external reference); that of BaG-6-P (0.1 M HCl) was a single peak at 0.47 ppm. The ^1H NMR spectrum of PEP^-K^+ (in D_2O) consisted of a multiplet at 5.88 ppm (1 H) and a multiplet at 5.54 ppm (1 H) from an internal DSS reference.

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On the Oxidative Cleavage of 3,5-Di-*tert*-butyl-*o*-benzoquinone

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Model reactions[1-6] for the dioxygenase-catalyzed oxidative cleavage of catechols have been studied since the discovery of this class of enzymes.[7] In studies with 3,5-di-*tert*-butylcatechol (DBC) and 3,5-di-*tert*-butyl-*o*-benzoquinone (DBQ), 3,5-di-*tert*-5-(carboxyhydroxymethyl)-2-furanone, 1, has been isolated along with a host of other products.[1-5] 1 has been suggested to result from the oxidative cleavage of the C1–C6 bond of DBC followed by the oxidation of the product aldehyde and cyclization (Scheme I, mechanism A);[4] this would serve as a model for the reaction catalyzed by extradiol cleaving dioxygenases.[7] Using deuterium-labeled starting materials, we have demonstrated that 1 results not from the extradiol cleavage of DBC but from the initial epoxidation of DBQ followed by cleavage of the α-diketone C–C bond.

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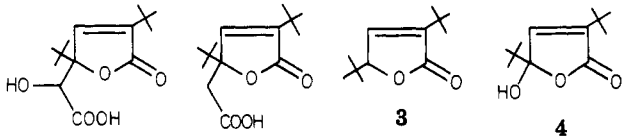
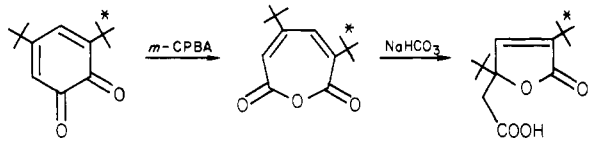


1 2 3 4

DBC with a deuterium-labeled 3-*tert*-butyl group (DBC*) was synthesized from 4-*tert*-butylcatechol and *tert*-butyl-d_6 alcohol. Oxidation of DBC* with Ag_2CO_3 afforded the labeled quinone (DBQ*), while treatment of DBQ* with an equivalent of Na/Hg yielded the labeled sodium salt of 3,5-di-*tert*-butyl-*o*-benzosemiquinone anion (NaDBSQ*). 1 was produced from these reagents under five sets of reaction conditions (Table I) and the position of the labeled *tert*-butyl group in the product was determined in three cases.

Three possible mechanisms were considered for the formation of 1 (Scheme I) and the fate of the labeled *tert*-butyl group allowed us to eliminate two of the mechanisms. Mechanism A[4] would result in the labeling of the 5-*tert*-butyl group of 1, while mechanism C would lead to the labeling of the 3-*tert*-butyl group. Mechanism B[3b,5] would have both *tert*-butyl groups labeled.

Examination of the *tert*-butyl region in the NMR spectra of a series of 3,5-di-*tert*-butyl-2-furanones (1–4) revealed the downfield *tert*-butyl resonance to be less sensitive to changes occurring at the C-5 position than the upfield *tert*-butyl resonance. The downfield resonance was thus assigned to the 3-*tert*-butyl group in all four furanones. To ascertain the NMR assignment, 2 with the 3-*tert*-butyl group deuterium labeled was synthesized from the hydrolysis of 3-labeled 3,5-di-*tert*-butylmuconic anhydride. The NMR spectrum of the product clearly showed the 3-*tert*-butyl group to be the more downfield of the two *tert*-butyl resonances observed.



DBQ 2

For our experiments, 1 was converted to 3,5-di-*tert*-butyl-2-furanone, 3, by alkaline treatment[1] and the position of the label in 3 was determined by NMR analysis. In all cases studied, only the 3-*tert*-butyl group of 3 was found to be deuterium labeled, thus eliminating A and B as possible mechanisms for ring cleavage.

Further investigations into the reaction of DBQ with peroxide provided further evidence that pathway C was indeed the mechanism for the formation of 1. Grinstead reported a 70% conversion of DBQ to 1 with a fivefold excess of peroxide.[1] When equimolar amounts of DBQ and peroxide were reacted under the experimental conditions, epoxide 7 was observed in addition to DBQ and 1 in agreement with the results of Grierer and Imsgard.[8] 7 results from the decomposition of hydroperoxide 6 derived from the 1,6 Michael addition of HO_2^- to DBQ.[9] That the 1,6 Michael addition occurs rather than an initial attack on the α-diketone is suggested by the absence of 2 in the product mixture. If the initial peroxide addition occurred at the α-diketone, the decomposition of the intermediate hydroperoxide would certainly have resulted in the formation of some quantity of 2. Ring cleavage of the epoxide is then effected by the action of a second peroxide on the α-diketone. That the epoxide moiety remains until final furanone formation is indicated by the NMR spectrum of 1, which exhibits only a singlet for the carboxyhydroxymethyl CH proton. That carbon as well as the C-5 on the furanone are chiral centers and thus should give rise to diastereomers. Though the diastereomers of 1 may coincidentally have the same chemical shifts, this is unlikely because of the observation of an AB quartet for the diastereotopic methylene protons in 2. The absence of diastereotopism in 1 thus suggests that only an enantiometric pair of diastereomers is formed in the ring cleavage reaction. This would result from stereoselective epoxide ring opening during the cyclization of the diacid to the furanone. Lastly, 7 has been shown to yield 1 under the reaction conditions.[8]

The observation of 3-labeled 1 in cases 2 and 5 suggests that DBQ and HO_2^- may be generated under the reaction conditions. A plausible mechanism is proposed in Scheme II. For the reaction of $DBSQ^-$ with O_2, hydroperoxide 8 is a necessary intermediate, since only 2 is formed under aprotic conditions (case 6). Under protic conditions (cases 2 and 3), 1 is also formed. This suggests that 8 decomposes under these conditions to generate DBQ and HO_2^-,[10] which recombine and yield 1 according to mechanism C. The instability of 8 under protic conditions would also explain the absence of 2 in cases 1 and 3. For cases 4 and 5, DBQ and HO_2^- can result from the disproportionation of $DBSQ^-$ and superoxide, $DBSQ^-$ resulting in case 4 from the deprotonation of DBC and subsequent oxidation and in case 5 from superoxide reduction of DBQ.

In conclusion, our labeling study has ascertained the mechanism for the formation of furanone 1 in the oxidative cleavage DBQ with hydrogen peroxide. The oxidative cleavage of $DBSQ^-$ to form 1 is also suggested to occur via the reaction of DBQ and HO_2^-. We are continuing our studies on the formation of 2.

Experimental Section

DBC, DBQ, 4-*tert*-butylcatechol, and acetone-d_6 were obtained from Aldrich and the catechols sublimed before use. KO_2 was obtained from Alfa. Solvents were degassed, rigorously dried, and distilled under nitrogen. THF and toluene were dried by refluxing over potassium and benzophenone, acetonitrile was dried over P_2O_5, and methylene chloride was distilled over CaH_2. Reactions were performed in standard Schlenkware or in a drybox. Oxygen was passed through Aquasorb and molecular sieves before use.

NMR studies were obtained in $CDCl_3$ solution on either a Varian EM-390 or FT-80 spectrometer, mass spectra were run by the Cornell Mass Spectroscopy Facility, visible spectra were obtained on a Cary 219 spectrophotometer, and GC analyses were performed on a Perkin-Elmer Sigma 3 gas charomatograph using an OV-101 column at 150 °C.

3-*tert*-Butyl-d_n-5-*tert*-butylcatechol (DBC*). *tert*-Butyl-d_6 alcohol was prepared by reacting methyl Grignard with acetone-d_6 in diethyl ether under N_2 at 0 °C. Excess Grignard was quenched with water, xylenes added, and the mixture distilled to dryness. The distillate was dried by refluxing overnight over 4 g of CaH_2 under nitrogen. Fractional distillation yielded *t*-BuOH-d_6, pure by GC. 4-*tert*-Butylcatechol (2.0 g) was dissolved in 2.5 mL of *t*-BuOH-d_6, and the solution was cooled to 0 °C and concentrated H_2SO_4 (1 mL) added with vigorous stirring. After 15 min the solid was dissolved in diethyl ether and washed with water. The ether was dried with $MgSO_4$, the solvent removed under reduced pressure, and the pale-purple solid washed with cold heptane and then recrystallized again from *n*-heptane to yield DBC* as fine white crystals: NMR δ 1.26 (s, 9 H, 3-*t*-Bu) 1.41 (s, 4.3 H, 5-*t*-Bu), 4.87 (s, 1 H, OH), 5.42 (s, 1 H, OH), 6.75 (d, J = 2 Hz, 1 H), 6.90 (d, J = 2 Hz, 1 H). Mass spectral analysis of DBC* showed M^+

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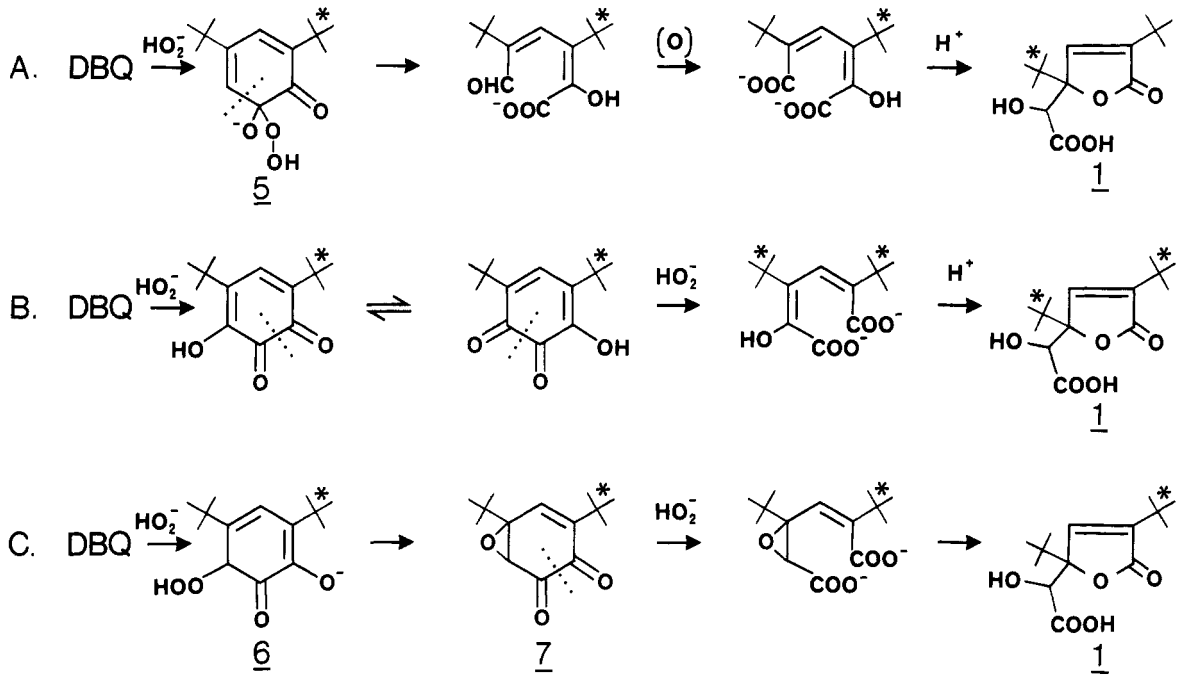
Scheme I



Scheme II

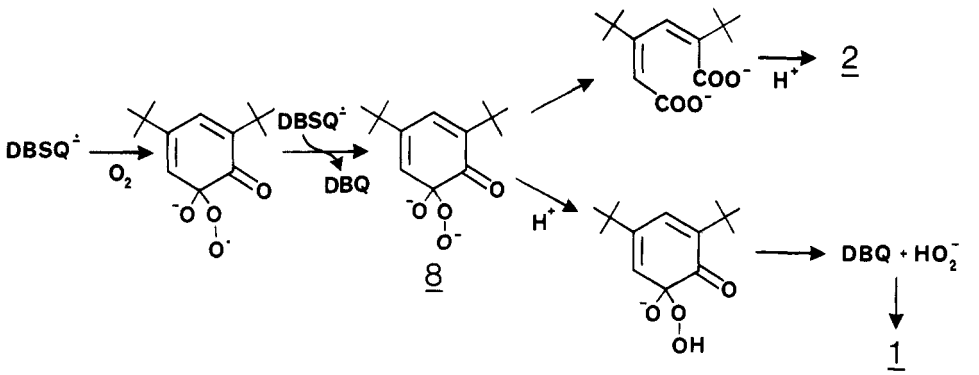


Table I. Yields of 1 and 2 from Oxidative Cleavage Reactions

	reaction	time, h	solvent	% yield 1	% yield 2
1.	DBQ (0.1 M) + $1H_2O_2$	0.5	MeOH/H_2O (7:3)	17[a]	0
2.	$DBSQ^-$ (0.011 M) + O_2	5.5	THF/toluene/*t*-BuOH (10:10:3)	5.4	4.4
3.	$DBSQ^-$ (0.026 M) + O_2	0.5	THF/H_2O (10:1)	8.0	0
4.	DBC (0.092 M) + $2KO_2$(s)	3	THF	1.1	6.5
5.	DBQ (0.11 M) + $2KO_2$(s)	3	THF	1.5	5.6
6.	$DBSQ^-$ (0.011 M) + O_2	56	THF	0	11.4

[a] Includes methyl ester.

peaks at *m/e* 222–230, indicating deuterium scrambling within one *tert*-butyl group with d_5 and d_6 isomers predominating.

3-*tert*-Butyl-d_n-5-*tert*-butyl-*o*-benzoquinone. DBC* was dissolved in diethyl ether and treated with Ag_2CO_3/Celite reagent for 1 h. The green solution was then dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give solid red DBQ*: NMR δ 1.22 (s, 9 H, 5-*t*-Bu), 1.25 (s, 4.3 H, 3 *t*-Bu), 6.19 (d, J = 2 Hz, 1 H), 6.92 (d, J = 2 Hz, 1 H).

NaDBSQ. DBQ (1.16 g, 5.3 mmol) in THF was treated under N_2 with sodium amalgam. The solution was separated from excess amalgam and transferred to a new vessel containing 1 equiv of DBQ (1.16 g, 5.3 mmol) and the solution instantaneously turned blue. The solution was filtered and the solvent removed under vacuum to yield a dark-blue solid. The visible spectra, in *t*-BuOH, gave the expected absorbance [λ_{max} 730 nm (ϵ 680 M^{-1} cm^{-1})].[10]

3,5-Di-*tert*-butyl-5-(carboxyhydroxymethyl)-2-furanone (1). The method of Grinstead[1] was used in the oxidation of DBQ in buffered (0.05 M HCO_3^-/CO_3^{2-}) 70% aqueous methanol with a fivefold excess of hydrogen peroxide. Extraction for the organic acid and removal of solvent yielded 1: NMR δ 1.05 (s, 9 H, 5-*t*-Bu) 1.20 (s, 9 H, 3-*t*-Bu), 4.65 (s, 1 H, CHOH), 7.09 (s, 1 H, olefinic).

3,5-Di-*tert*-butyl-5-(carboxymethyl)-2-furanone (2). 8 was hydrolyzed by refluxing in 25 mL of 10% $NaHCO_3$ overnight. The solution of the hydrolysis product was washed with diethyl ether, acidified, and extracted into diethyl ether. Removal of solvent gave white solid, 2, which was recrystallized from isooctane/benzene: NMR δ 0.97 (s, 9 H, 5-*t*-Bu), 1.21 (s, 9 H, 3-*t*-Bu), 2.94, 2.76 (AB q, J_{AB} = 14 Hz, 2 H, CH_2), 6.92 (s, 1 H, olefinic).

3,5-Di-*tert*-butyl-2-furanone (3). 1 was dissolved in 2 N NaOH and stirred at 50 °C for 1 h. The white precipitate was extracted with diethyl ether and dried with $MgSO_4$, the solvent removed, and 3 purified by sublimation. 3: NMR δ .95 (s, 9 H, 5-*t*-Bu), 1.25 (s, 9 H, 3-*t*-Bu), 4.49 (d, J = 2 Hz, 1 H), 6.92 (d, J = 2 Hz, 1 H, olefinic).

5-Hydroxy-3,5-di-*tert*-butyl-2-furanone (4). White crystals of 4 were prepared by the method of Nishinaga:[3a] NMR δ 1.03 (s, 9 H, 5-*t*-Bu), 1.25 (s, 9 H, 3-*t*-Bu), 2.84 (1 H, OH), 6.78 (s, 1 H, olefinic).

4,5-Epoxy-6-oxo-2,4-di-*tert*-butylcyclohex-2-enone (7). The method of Grierer and Imsgard[8] was used to produce yellow-orange needles of 7 after recrystallization from petroleum ether: NMR δ 1.09 (s, 9 H, 4-*t*-Bu), 1.20 (s, 9 H, 2-*t*-Bu), 3.83 (s, 1 H), 7.09 (s, 1 H, olefinic).

3,5-Di-*tert*-butyl-1-oxacyclohepta-3,5-diene-2,7-dione (9). The method described by Demmin and Rogić[11] was used to prepare 9. Recrystallization from *n*-pentane yielded colorless cubes. 9: NMR δ 1.13 (s, 9 H), 1.24 (s, 9 H), 6.12 (d, J = 2 Hz, 1 H), 6.44 (d, J = 2 Hz, 1 H).

General Procedure for Oxidations. DBC, DBQ, or DBSQ were accurately weighted into a Schlenk tube and dissolved in the appropriate solvent. The solution was either transferred via syringe to solid KO_2 or oxygen was slowly flowed over the vigorously stirred solution. Solutions to be quenched were degassed with three freeze–pump–thaw cycles, and 5% HCl was added, which destroyed any blue color which remained in solution. The solution was exposed to air, and 5% $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with diethyl ether (3 × 10 mL). The combined layers were again extracted with 5% $NaHCO_3$ and the aqueous layers combined. The GC was calibrated with fresh solutions of DBQ and DBC, and the product peak areas were determined by weighing. The aqueous layer was acidified with 25 mL of 5% HCl, extracted with diethyl ether (3 × 10 mL), and dried over $MgSO_4$. If an NMR spectrum of the acidic products was to be recorded, an internal standard of *p*-dimethoxybenzene was added, the solvents were removed, and the spectra were recorded in $CDCl_3$. For GC analysis the acids were methylated with diazomethane, with excess diazomethane destroyed by acetic acid. Yields reported (Table I) are based on original reactant amounts.

Acknowledgment. This work was supported by the National Institutes of Health (GM-25422). We thank Professor Barry Carpenter for valuable discussions.

Registry No. 1, 53846-98-3; 2, 22802-86-4; 3, 53904-87-3; 4, 3807-35-0; 7, 82337-97-1; DBQ*, 82323-89-5; DBC*, 82323-90-8; NaDBSQ, 82323-91-9; 3,5-di-*tert*-butyl-1-oxacyclohepta-3,5-diene-2,7-dione, 24289-60-9; *tert*-butanol-d_6, 53853-65-9; acetone-d_6, 666-52-4; 4-*tert*-butylcatechol, 98-29-3.

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Condensation of Monosubstituted Isopropylidene Malonates with Mannich Bases

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In recent years there have been a variety of studies concerned with the chemistry of Meldrum's acid[1] (the cyclic isopropylidene ester of malonic acid). We have been particularly interested in preparative applications, where this reagent or its derivatives can be employed with advantage over acyclic malonic esters. One type of application would make use of the high acidity ($pK_a \approx 5$) of the cyclic malonates such that basic substrates could be activated toward reaction by protonation or N-acylation with concomitant formation of appreciable amounts of the enolate anion. We previously described[2] some reactions that could be explained on such a basis.

Table I. Condensation Products of Mannich Bases and Isopropylidene Malonates

compd[a]	mp, °C	recryst solvent	yield, %
1a	71–72	ether/hexane	74
1b	90–91	ether/hexane	93
1c	96–97	ether/hexane	86
2a	205–207	acetone/hexane	70
2b	205–206	acetone/hexane	66
2c	159–160	acetone/hexane	92
3a	178–179	acetone/hexane	87
3b	158–159	acetone/hexane	80
3c	157–158	acetone/hexane	66
3d	170–171	acetone/hexane	85
3e	214–215	acetone/hexane	84
3f	144–145	acetone/hexane	83
4a	102–103[b]	ether/hexane	74
4b	100–101	ether/hexane	89
4c	169–170	ether/hexane	71

[a] All compounds, except 4a which has been previously reported, were analyzed and gave satisfactory results (±0.4%) for C, H, and N where present. [b] Lit.[19] mp 105–106 °C.

We report that Mannich bases derived from acetone, ferrocene, β-naphthol, and indole readily condense with monosubstituted derivatives of Meldrum's acid in the presence of acetic anhydride. The alkylation of acyclic malonates by Mannich bases has been extensively investigated as part of a synthetic route to various substituted carboxylic acids. These reactions have usually been conducted by treating the sodium salt of the malonate with either the Mannich base or its generally more reactive quaternary salt.[3] There are a few reports of the alkylation by Mannich bases of barbituric acids,[4] 1,3-cyclohexanediones,[5] and 4-hydroxycoumarins,[6] in which the enol was heated with Mannich base, sometimes with an added base as a catalyst. When we tried heating monosubstituted Meldrum's acid derivatives with Mannich bases in neutral solvents such as benzene, 1,2-dimethoxyethane, or methanol, the reactions proceeded sluggishly, and often only moderate yields were obtained. Only upon addition of acetic anhydride did the reaction proceed readily. See Table I.

4-(Diethylamino)-2-butanone was the least reactive of the Mannich bases when subjected to reaction with the cyclic malonates in an acetic anhydride/1,2-dimethoxyethane mixture. Examination of the reaction mixture by TLC indicated that 2 days at room temperature were required for complete reaction although good product yields could also be obtained by warming at 55 °C overnight. The mechanism of these reactions may involve the generation of methyl vinyl ketone and subsequent alkylation through conjugate addition. An elimination–addition mechanism seems to be a commonly suggested pathway for alkylations by Mannich bases,[3] and it has been previously reported that isopropylidene malonates will readily undergo conjugate addition to α,β-unsaturated carbonyl compounds.[7] The conditions employed in our procedure are apparently

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