

Selective Hydrolysis of α,β - and β,γ -Unsaturated Ketals: a Method for Deconjugation of β,β -Disubstituted α,β -Unsaturated Ketones

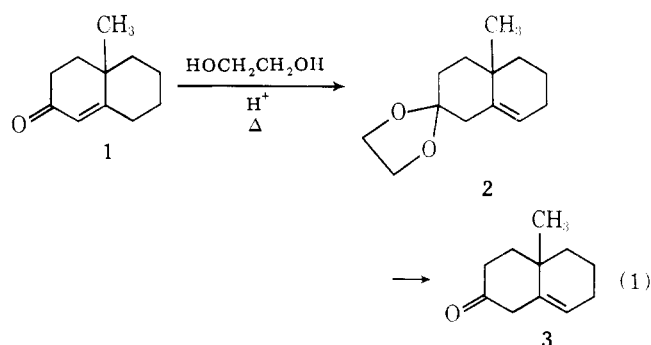
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As a starting material for a synthesis project we required substantial quantities of β,γ -unsaturated ketone **3**. Although the latter can be prepared in respectable yield by deconjugation of the readily accessible¹ octalone **1** using the method² developed by Ringold and Malhotra, this approach had its disadvantages. It not only required the use of a large excess of strong base (10 equiv of potassium *tert*-butoxide), but the desired β,γ -unsaturated ketone was reported by these same workers² to be contaminated with 20% of the conjugated enone (**1**). Although other investigators³ have studied methods for the deconjugation of α,β -unsaturated ketones, such routes invariably involve deprotonation of the starting material with strong bases, followed by acid treatment of the enolate anions formed, and lead to mixtures of both enones.

Since the ethylene ketal of 10-methyl-1(9)-octal-2-one (**1**) had been previously prepared⁴ and assigned structure **2**, we decided to investigate mild conditions for its hydrolysis to the desired β,γ -enone **3** (eq 1). Use of oxalic acid dihydrate (0.5 M solution) in 95% methanol at room temperature proved unsatisfactory, since under these conditions isomerization⁵ of enone **3** to conjugated octalone **1** appeared to occur faster



than the hydrolysis of ketal **2**. Use of 80% acetic acid at room temperature required 4 h to effect the hydrolysis of **2**, and the product was a 1:1 mixture of ketones **1** and **3** due to the apparent ease with which the latter compound isomerizes to the more stable enone **1**. However, only 5 min was required to effect the hydrolysis of ketal **2** in 80% acetic acid at 65 °C, and enone **3** could be isolated in 85% yield contaminated with a minor amount (12–15%) of the α,β isomer (**1**).

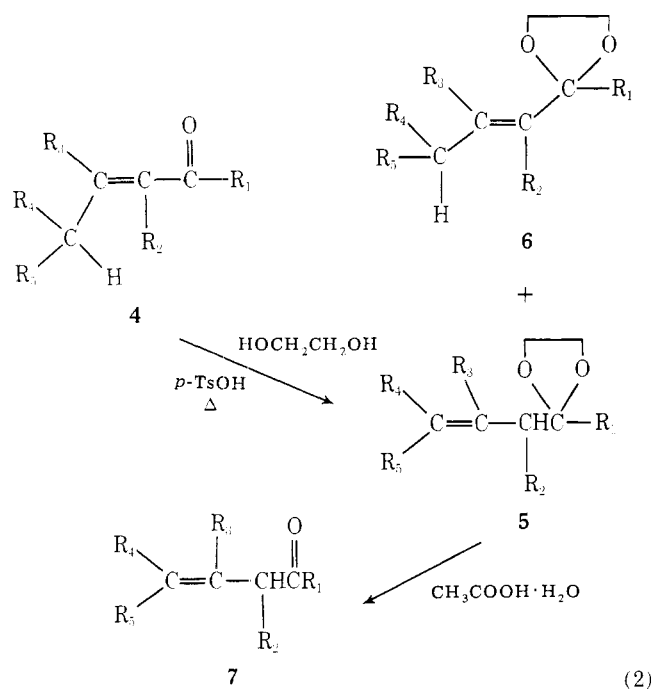
Since Santelli had reported⁶ that preparation of ethylene ketals of α,β -unsaturated ketones of general formula **4** in refluxing toluene using *p*-toluenesulfonic acid as the catalyst afforded the isomeric β,γ -unsaturated ketals (**5**) in yields as high as 90%, accompanied by the anticipated product (**6**), we decided to examine conditions for the hydrolysis of these ketals (**5**) as a possible route to the deconjugated enone **7** (eq 2).

As outlined in Table I, the ethylene ketals of mesityl oxide (**4a**),⁷ isophorone (**4b**),⁷ and 1-acetyl-2-methylcyclohexene

Table I. Preparation^a and Hydrolysis of Unsaturated Ketals

Registry no.	Ketone	% yield ^b of ketals 5 and 6	Hydrolysis ^c using oxalic acid dihydrate		Hydrolysis ^f of 5		
			Reaction time, min	% loss ^d of β,γ -unsaturated ketal 5	% yield ^e of β,γ -unsaturated ketal 5	β,γ -enone 7 ^g	% yield ^h of 7
141-79-7	 4a	50 ⁱ	20	<2	57	 7a	84
78-59-1	 4b	65 ^j	10	<5	64	 7b	98 ^k
	 4c	90	10	5–10	58	 7c	96

^a All reactions were run using the general procedure for ketal preparation listed in the Experimental Section. ^b The ratio of β,γ -unsaturated ketal **5** to the α,β isomer **6** was 75:25 for all three systems, as determined by NMR analysis. ^c All reactions were run at room temperature in 95% methanol, the solution being 0.17 M with respect to the ketal and 0.5 M with respect to oxalic acid. ^d Determined by NMR analysis. ^e This yield is based on the starting ketal mixture (**5** and **6**). Since the latter was a 3:1 mixture of **5**:**6**, the maximum yield of β,γ -unsaturated ketal **5** would be 75%. Ketal **5** was isolated from the crude hydrolysis product by chromatography on Florisil (elution with hexane–1% ether). The rest of the material, based on NMR analysis of the crude hydrolysis product, was mainly α,β -unsaturated ketone **4**, obtained from the α,β -unsaturated ketal (**6**) present in the starting ketal mixture. ^f The hydrolysis was effected using 4:1 (v/v) acetic acid:water at room temperature for 4 h. ^g β,γ -enone **7a** has previously been prepared; see ref 5. Ketone **7b** has been reported in several papers (ref 11 and 12), while deconjugated enone **7c** was reported by Dufort and LaFontaine (ref 8). ^h Based on starting β,γ -unsaturated ketal (**5**). NMR analysis indicated the product (**7**) to be >95% pure. No starting ketal (**5**) could be detected in the isolated product. Only in the case of enone **7b** could a minor amount (2–5%) of α,β isomer (**4b**) be detected by NMR analysis. ⁱ The moderate yield obtained can be ascribed to the difficulty in separating the volatile product mixture [bp 59–61 °C (60 mm)] from toluene. ^j The rest of the product consisted of starting material. The ketal mixture was purified via chromatography on Florisil (50 mL/g of product; elution with hexane–1% ether). ^k After a reaction time of 2.5 h, hydrolysis of ketal **5b** was approximately 95% complete, and no isophorone (**4b**) could be detected. After 4 h, no ketal (**5b**) was left, but the reaction product contained a minor (<5%) amount of isophorone (**4b**). ^l Prepared in 52% yield by Friedel–Crafts acylation of 1-methylcyclohexene with acetyl chloride using stannic chloride as the catalyst, followed by treatment of the crude adduct with *N,N*-dimethylaniline under reflux. VPC analysis (6 ft \times 1/8 in. SE-30 column, 150 °C) indicated the product [bp 60–70 °C (2.5 mm)] to be a 2:1 mixture of α,β - and β,γ -unsaturated ketones (retention times: 5.2 and 4.2 min, respectively). See ref 8 for further details.



(4c)⁸ were prepared and determined by NMR analysis to consist of approximately 75% of the isomerized⁹ ketals (5). Treatment of the mixture of isomeric ketals with oxalic acid dihydrate in 95% methanol at room temperature for a short time, as indicated by the data in this table, led to selective hydrolysis of the α,β -unsaturated ketal (6) with minimum loss (0–10%) of the isomeric ketal (5). After purification by chromatography¹⁰ the β,γ -unsaturated ketal (5) was able to be hydrolyzed to the corresponding deconjugated enone (7), without any concomitant isomerization,⁵ by the use of 80% acetic acid at room temperature. Perhaps most remarkable about the latter transformation (5 \rightarrow 7) was its successful application to the preparation of β,γ -enone **7b**¹¹ despite the report¹² that the latter converts slowly back to isophorone (4b) at room temperature and that this isomerization is accelerated slightly by a trace of acetic acid.

Our results demonstrate that preparation of ethylene ketals and their subsequent hydrolysis under the proper conditions offers an attractive method for deconjugation of α,β -unsaturated ketones of general structure 4. Since it avoids strongly basic reaction conditions, it complements the method of deconjugation² developed by Ringold and Malhotra. Furthermore, it offers the additional advantage of allowing the preparation of the *pure* β,γ -enone (7), uncontaminated by the isomeric compound (4) in most cases. If the α,β -unsaturated ketone (4) obtained by the selective hydrolysis of ketal 6 is recovered¹³ and converted back to the mixture of ketals (5 and 6), the overall process is quite efficient in terms of yield.

Experimental Section

General. The isolation of reaction products was accomplished by extracting thoroughly with the specified solvent. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated brine and were dried over anhydrous magnesium sulfate. The solvent was removed¹⁴ from the dried extracts by using a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian A-60 NMR spectrometer and infrared spectra were obtained using a Beckman Acculab 1 spectrophotometer. The microanalysis was performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

General Method for Ketal Preparation. A mixture containing 40 mmol of α,β -unsaturated ketone, 7.00 mL (125.5 mmol) of ethylene glycol, and 250 mg of *p*-toluenesulfonic acid monohydrate in 100 mL of toluene was heated at reflux for 16 h with continuous azeotropic removal of water and excess ethylene glycol by means of a Dean-Stark

Table II. ¹H NMR Spectral Data (CCl₄ vs. Me₄Si, δ in ppm)

Compd	Registry no.	¹ H Chemical Shifts
5a ^a	4362-28-1	1.24 (s, CH ₃), 1.80 (broad s, vinyl CH ₃), 2.29 (s, CH ₂), 3.85 (s, -OCH ₂ CH ₂ O-), 4.82 (m, C=CH ₂)
6a	4362-31-6	1.39 (s, CH ₃), 1.70 (broad s, vinyl CH ₃), 1.80 (broad s, vinyl CH ₃), 3.79 (s, -OCH ₂ CH ₂ O-), 5.23 (m, C=CH)
5b	65339-06-2	1.00 (s, 2CH ₃ 's), 1.52 (s, CH ₂), 1.65 (broad s, vinyl CH ₃), 2.05 (broad s, allylic CH ₂), 3.87 (s, -OCH ₂ CH ₂ O-), 5.12 (m, vinyl H)
6b	65339-07-3	0.96 (s, 2CH ₃ 's), 3.83 (s, -OCH ₂ CH ₂ O-), 5.23 (m, vinyl H)
5c ^b	17931-72-5	1.15 (s, CH ₃), 3.83 (s, -OCH ₂ CH ₂ O-), 5.51 (m, vinyl H)
6c	65339-08-1	1.33 (s, CH ₃)
7a	3744-02-3	1.76 (vinyl CH ₃), 2.07 (s, CH ₃), 3.04 (s, CH ₂), 4.85 (broad d, <i>J</i> = 5 Hz, CH ₂ =C)
7b	471-01-2	1.03 (s, 2CH ₃ 's), 1.72 (broad s, vinyl CH ₃), 2.23 (s, CH ₂), 2.65 (broad s, allylic CH ₂), 5.43 (m, vinyl H)
7c	15564-32-6	2.05 (s, C(O)CH ₃), 2.92 (m, CHC=O), 5.55 (m, vinyl H)

^a This compound has been reported previously in the literature. See ref 6. ^b See ref 8 for a previous synthesis of ketal 5c.

trap.¹⁵ The cooled mixture was washed with saturated aqueous sodium bicarbonate and saturated brine and was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure,¹⁴ followed by either distillation or (if contaminated by starting ketone) chromatography on Florisil (50 mL/g of the product; elution with hexane–1% ether), afforded the ketals in 50–90% yields.

Selective Hydrolysis of the Ethylene Ketal Mixture (5b and 6b) Derived from Isophorone (4b). A solution of 1.820 g (10 mmol) of ketal mixture **5b** and **6b** and 4.34 g (34.4 mmol) of oxalic acid dihydrate in 70 mL of 95% methanol was stirred at room temperature for 10 min. The reaction was then quenched by pouring the mixture into 200 mL of cold saturated aqueous sodium bicarbonate. Dilution of this mixture with 200 mL of saturated brine, followed by extraction with ether, afforded 1.545 g of ketal **5b** contaminated by isophorone (4b). Chromatography¹⁰ on Florisil (80 mL; elution with hexane–1% ether), followed by evaporative distillation, afforded 0.10 mmol of pure ketal **5b**: bp 40–50 °C (bath temperature, 0.10 mm); ν_{\max} (film) 1675 (C=C), 1375, 1350, 1310, 1280, 1255, 1220, 1180, 1145, 1090, 1040, 985, 945, 885, 870, 795 cm⁻¹; $\delta_{\text{Me}_4\text{Si}}$ (CCl₄) see Table II. Anal. Calcd for C₁₁H₁₈O₂: C, 72.49; H, 9.95. Found: C, 72.65; H, 9.92.

2,2-Ethylendioxy-10-methyl-8-octalin (2). In order to ensure the absence of any α,β -unsaturated ketal, the ethylene ketal (1.074 g, 5.17 mmol) prepared from 864 mg of octalone **1**¹ using the general procedure cited above was added to 60 mL of 95% methanol containing 3.829 g (30.4 mmol) of oxalic acid dihydrate. After stirring this mixture for 10 min at room temperature, the product (975 mg) was isolated in the same manner as described for ketal **5b**. Chromatography of this material on 50 mL of Florisil (elution with hexane–1% ether) yielded 660 mg (61%) of pure ketal **2**, the spectral properties of which were identical to those previously reported⁴ for this same compound.

General Procedure for the Hydrolysis of β,γ -Unsaturated Ketals (5). A solution of 1 mmol of ketal **5** in 4.0 mL of acetic acid and 1.0 mL of water was stirred at room temperature for 4 h. The mixture was then poured cautiously into 75 mL of cold aqueous sodium bicarbonate. After dilution of the mixture with 50 mL of saturated brine, the product was isolated by extraction with ether.

10-Methyl- Δ^5 -octalin-3-one (3). Ketal **2** (218 mg, 1.05 mmol) was added to a mixture of 4.0 mL of glacial acetic acid and 1.0 mL of water in a flask maintained at 65 °C (bath temperature). After stirring this solution at 65 °C for 5 min, the reaction was quenched by pouring the mixture into 75 mL of ice-cold saturated aqueous sodium bicarbonate. Extraction with ether in the usual manner afforded 163 mg (95%) of

enone **3** contaminated by approximately 12–15% of the α,β -isomeric ketone (**1**) as determined by NMR analysis. Octalone **1** was characterized by an absorption band at δ 5.65 (vinyl H), whereas the corresponding signal for the β,γ -enone **3** occurred at δ 5.41 (m, 1 vinyl H).

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Registry No.—**1**, 826-56-2; **2**, 3287-60-3; **3**, 22789-80-6; α,β -unsaturated **4c**, 2047-97-4; 1-methylcyclohexene, 591-49-1; acetyl chloride, 75-36-5.

References and Notes

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- (4) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966).
- (5) For a discussion of the mechanism of the acid-catalyzed isomerization of β,γ -unsaturated ketones to the corresponding α,β -enone, see D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 394, 397 (1972).
- (6) M. Santelli, *C. R. Hebd. Seances Acad. Sci.*, **261**, 3150 (1965).
- (7) Available from Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.
- (8) Preparation of ketone **4c** has been reported several times in the Chemical literature. See N. Dufort and J. LaFontaine, *Can. J. Chem.*, **46**, 1065 (1968), and references therein.
- (9) Isomerization of the double bond occurs subsequent to ethylene ketal formation. This was demonstrated by isolation of the reaction products (**5a** and **6a**) obtained from mesityl oxide (**4a**) after 3.5 h and discovering it to be a 40:60 mixture of α,β -unsaturated ketal (**6a**) and the isomeric ketal (**5a**).
- (10) On a large scale, fractional distillation would be more convenient to separate β,γ -unsaturated ketal **5** from enone **4**.
- (11) For previous syntheses of enone **7b**, see J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971), and references therein.
- (12) M. S. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).
- (13) No attempt was made to recover α,β -unsaturated ketone **4** after selective hydrolysis of ketal **6** in the presence of β,γ -unsaturated ketal **5**. However, NMR analysis of the crude hydrolysis product, prior to chromatography on Florisil, indicated the expected mixture of ketal **5** and enone **4**, accompanied by minor (1–9%) amounts of the corresponding β,γ -enone **7**.
- (14) Due to their volatility, ketals **5a** and **6a**, as well as enone **7a**, were recovered from the extracts by fractional distillation of the solvent at atmospheric pressure.
- (15) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Synth.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere.

Photolysis of *o*-Phenylene Oxalate. A High-Yield Photodecarbonylation Reaction

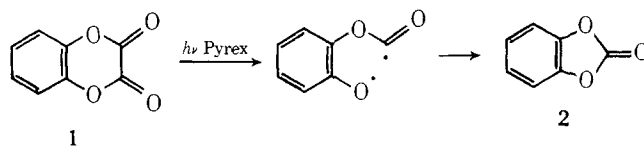
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The photolysis of aryl esters in solution generally results in their rearrangement to isomeric phenolic ketones via the photo-Fries pathway.² Acyclic aryl oxalates, in particular, have been observed to undergo the photo-Fries rearrangement, with the simultaneous formation of phenols.^{3,4} The photochemistry of cyclic oxalate esters, however, has not been studied thoroughly. We therefore have investigated the photolysis of *o*-phenylene oxalate (**1**).

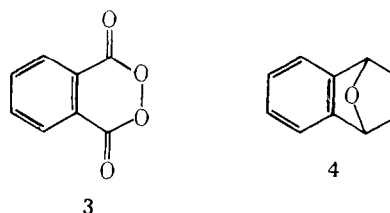
In contrast to the photolysis of aryl esters in general and acyclic oxalate esters in particular, the photolysis of **1** induced the formation of no photo-Fries products. Instead, nearly quantitative decarbonylation resulted. Irradiation of deaerated hexane solutions of **1** afforded *o*-phenylene oxalate (**2**)



as the exclusive observed product (by NMR, VPC), identified by comparison of physical and spectral properties with an authentic sample.⁵ The chemical yield of **2** was 94% (by VPC) and was found to be independent of the presence of either oxygen or acrylonitrile.

The primary photochemical reaction is evidently an α cleavage of either the acyl–oxygen bond, as is postulated for other aryl esters,² or the acyl–acyl bond, as is common in α -dicarbonyl compounds.⁶ In any event, decarbonylation of the biradical intermediate, followed by reclosure, results in the observed carbonate **2**. The formation of the typical photo-Fries product is probably precluded due to geometrical constraints.

Interestingly, *o*-phenylene oxalate, unlike its structural isomer phthaloyl peroxide (**3**), does not photodecarbonylate to benzyne.⁷ Thus, photolysis of **1** in the presence of furan did not lead to a detectable amount of the known benzyne adduct **4**.



As is often the case, the mass spectrum of **1**, which has been reported previously,⁸ parallels the photochemical results. Thus, expulsion of CO is the important initial process for **1** as well as other cyclic oxalates, while no loss of CO₂ from the molecular ion was observed.

In summary, our findings demonstrate that the photolysis of *o*-phenylene oxalate is qualitatively different from that of other aryl esters, in that α cleavage, followed by decarbonylation, is the exclusive reactive pathway.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237-B instrument. NMR spectra were obtained with a Varian EM-390 spectrometer. Gas chromatography analyses were performed using a Varian Aerograph Series 2700 flame ionization instrument. Mallinckrodt spectrograde hexane was used as received.

***o*-Phenylene Oxalate (1).** In a modification of the procedure of Gosh,⁹ this compound was prepared by the dropwise addition of oxalyl chloride (1.7 mL, 20 mmol) in 5 mL of dry ether to 2.0 g (18 mmol) of catechol and 5.1 mL (36 mmol) of triethylamine in 40 mL of ether. After being stirred vigorously for 3 h, the mixture was filtered and the residue was thoroughly ether extracted. Concentration in vacuo of the combined organic materials afforded crude product, which was sublimed (90–95 °C (0.5 mm)) to give *o*-phenylene oxalate (2.4 g 79%), mp 185.5–186.5 °C (lit.⁸ mp 185 °C), after recrystallization from benzene under nitrogen. The previously unreported spectral data were: IR (CHCl₃) 3010, 1805, 1790, 1495, 1740, and 1285 cm⁻¹; NMR (acetone-*d*₆) δ 7.28 (pseudo-s); UV (hexane) λ_{\max} (ϵ) 277 broad (3060), 320 tail (990).

Photolysis of *o*-Phenylene Oxalate (1). Preparative runs were performed using an immersion well apparatus with a 450 W medium pressure Hg arc and a Pyrex filter sleeve. The solution was purged with dry nitrogen for 1 h prior to and then throughout the photolysis. In a typical run, **1** (90 mg, 0.54 mmol in 400 mL of hexane) was irradiated for 4 h. The course of the reaction was monitored conveniently by UV spectroscopy. Removal of solvent afforded 54 mg of *o*-phenylene carbonate (**2**).⁴

Chemical yield and quenching runs were performed using a merry-go-round apparatus with irradiation of ca. 5-mL samples in capped test tubes. Solutions were purged with nitrogen, if appropriate,