Acknowledgment. The author would like to thank Dr. W. J. Houlihan for his interest and support, Dr. Renate Coombs for supplying the mass spectral data, and Dr. S. Barcza and his staff for recording the spectra and for helpful discussion in evaluating the data.

Registry No.—**1a**, 57512-87-5; **1b**, 57512-88-6; **1c**, 57512-89-7; **1d**, 57512-90-0; **1e**, 57512-91-1; **1f**, 57512-92-2; **2**, 57512-93-3; **3**, 57512-94-4; indole, 120-72-9; 5-chloro-2-pentanone ethylene ketal, 5978-08-5; methyl indole-3-carboxylate, 942-24-5; 3-indoleacetic acid methyl ester, 1912-33-0; 3-methylindole, 83-34-1.

References and Notes

(1) For a comprehensive review see W. J. Houlihan, "The Chemistry of Heterocyclic Compounds, Indoles", Vol. 25, Parts I and II, Wiley, New York, N.Y., 1972.
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(3) The author is grateful to Dr. W. J. Houlihan for donating a sample of 2-*tert*-butylindole.
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Preparation and Reactions of β-Chloro-α,β-Unsaturated Ketones[1]

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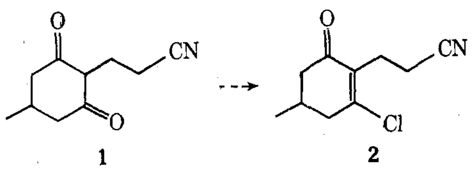
Received October 17, 1975

β-Chloro-α,β-unsaturated ketones are conveniently prepared by treating β-diketones or β-keto aldehydes with oxalyl chloride in an inert solvent such as benzene or chloroform. Symmetrical cyclic β-diketones and β-keto aldehydes afford a single β-chloroenone in good yield. Unsymmetrical cyclic β-diketones yield a mixture of isomeric β-chloroenones. Acyclic β-diketones yield a mixture of *E* and *Z* β-chloroenones. β-Keto esters do not afford β-chloro-α,β-unsaturated esters by this procedure; the only product produced is the enol chlorooxalate. The product β-chloroenones are smoothly dehalogenated by silver–zinc couple in methanol and readily couple with lithium dialkylcuprates. In contrast to β-alkoxy-α,β-unsaturated ketones, β-chloroenones do not undergo regiospecific base-catalyzed alkylation.

Preparation of β-Chloroenones. β-Chloro-α,β-unsaturated ketones have been prepared from β-diketones by reaction with phosphorus trichloride,[2–4] phosgene,[5] acetyl chloride,[6] thionyl chloride,[3] and phosphorus oxychloride.[2,7] Reported yields for this conversion are generally in the range 50–70%.[8]

In connection with a projected synthesis, we had occasion to prepare β-chloroenone **2** from cyanodione **1**. However, the presence of the nitrile function caused serious complications when we attempted to use standard methodology for this conversion. For example, treatment of **1** with acetyl chloride in chloroform[6] gives no β-chloroenone **2**. The only products obtained are acetate **3** (49–61%) and lactam **4** (29–39%).[9] Phosphorus trichloride does afford β-chloroenone **2** in 40–50% yield, but it is contaminated by substantial amounts of lactam **4**.



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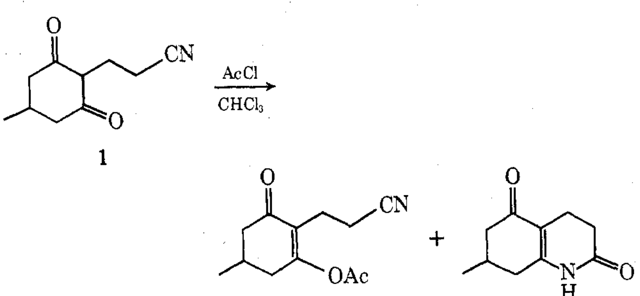
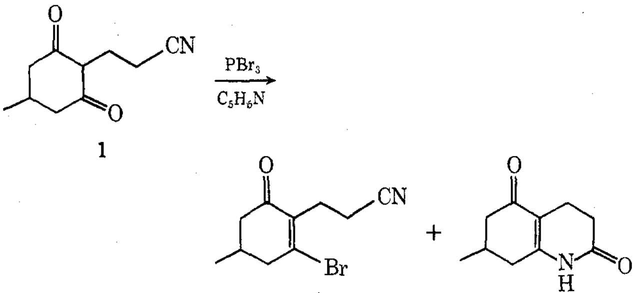


1 3 4

Similar difficulties were encountered when we attempted to transform dione **1** into β-bromoenone **5** using phosphorus tribromide in pyridine, a reagent often used to convert

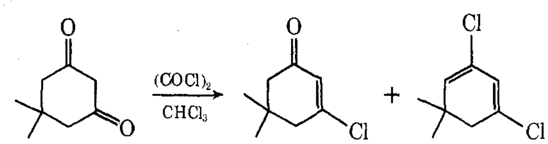


5 4

β-diketones into β-bromoenones.[2] In this case, β-bromoenone may be isolated in only 20% yield, and the major product appears to be lactam **4** (isolated in 20% yield).

These difficulties led us to explore alternate methods for accomplishing the conversion of β-diketones to β-haloenones. In this paper, we report a successful solution to this problem, using a method which appears to be generally applicable and which, in many cases, gives higher yields than do the standard methods.[2–6]

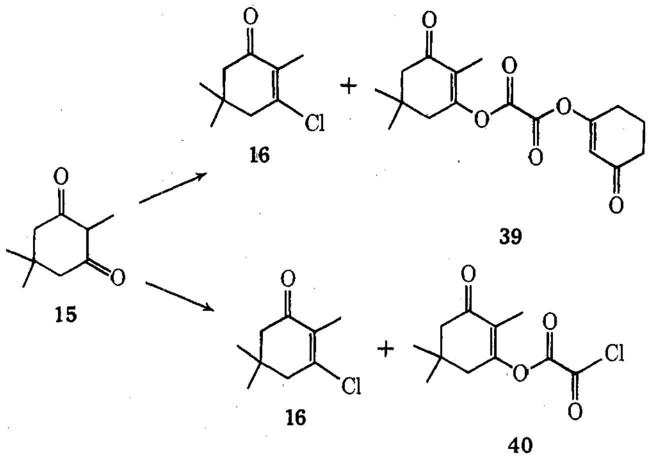
Dimedone (**6**) reacts with oxalyl chloride (2.5 equiv) in refluxing chloroform to afford β-chloroenone **7** in 91% yield. The only side-product is a small amount of dichlorodiene **8** (ca. 2%), and the amount of this material may be suppressed by minimizing the reaction time. Application of



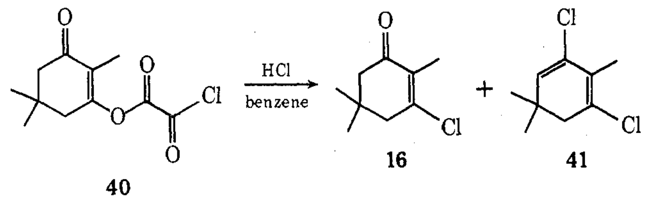
6 7 8

this method to dione 1 gave β-chloroenone in a distilled yield of 76%; none of the undesired lactam 4 was detected in the reaction product.

To test the generality of the procedure, we have carried out the reaction on a variety of other β-diketones and β-keto aldehydes. The results are summarized in Table I. Note that the procedure seems to be generally applicable for the conversion of cyclic β-diketones into β-chloroenones in good yield.[10] The sole cyclic β-diketone which has given us anomalous results is methyldimedone (**15**). Under our normal reaction conditions (2 equiv of oxalyl chloride, 180 min reflux, 5.7 mmol of **15** per ml of benzene), chloroenone **16** is produced in only 50% yield. The remainder of the product is the crystalline bisoxalate **39**. Under more dilute conditions (2 mmol of **15** per milliliter of benzene), β-chloroenone **16** is produced in 34% yield, accompanied by the crystalline chlorooxalate **40**. While one might reasonably



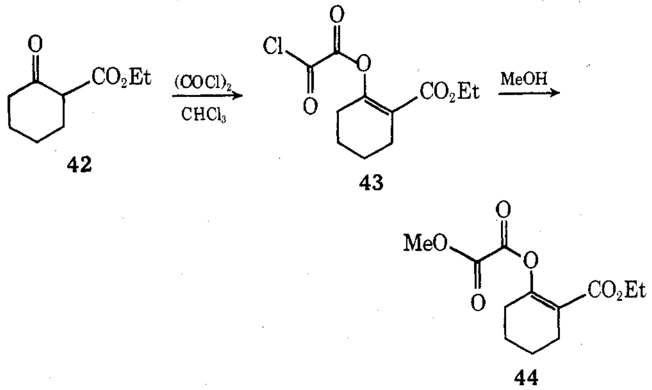
expect compounds **39** and/or **40** to be intermediates in the conversion of **15** into **16**, their isolation and stability in this case is somewhat surprising. We have not encountered analogous products with any of the other β-diketones we have studied. Decomposition of **40** can be effected with HCl in benzene, but under these conditions chloroenone **16** is substantially converted into dichlorodiene **41**.



The single acyclic β-diketone studied (**29**) afforded a 1:1 mixture of stereoisomeric β-chloroenones **30** and **31** in 50% yield. As a method for preparing **30** and **31**, this procedure is competitive with Julia's method in which 2-chloropropene is treated with acetyl chloride and $AlCl_3$ (57%).[11] The structures of isomers **30** and **31** are readily assigned on the basis of their ^1H NMR spectra (see Experimental Section). Unsymmetrical β-diketones such as **19** and **26** give good yields of β-chloroenones, but the reaction is not regioselective.

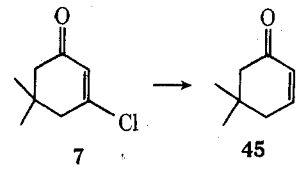
β-Keto aldehydes apparently react to yield a single β-chloroenone. The reaction is regiospecific *and* stereospecific. The chlorine appears to be cis to the carbonyl group in both examples we have studied (**32** → **33**, **34** → **35**). The stereostructure shown in Table I was assigned on the basis of ^1H NMR arguments.[12]

So far, we have been unsuccessful in transforming β-keto esters into β-chloro-α,β-unsaturated esters with oxalyl chloride. Ethyl 2-oxocyclohexanecarboxylate (**42**) yields only the high-boiling chlorooxalate **43**, which reacts with methanol to give the mixed oxalate diester **44**. Attempts to

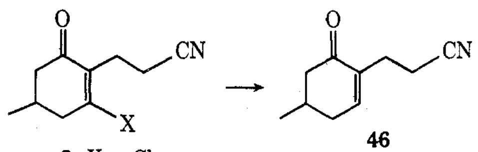


convert **43** into a vinyl chloride by reaction with anhydrous HCl in $CHCl_3$ were unsuccessful.

Reduction of β-Chloroenones. We have also studied the reduction of β-chloroenones to α,β-unsaturated ketones (e.g., **7** → **45**). Crossley and Renouf reported in 1907 that



such reductions may be accomplished by utilizing acid-washed zinc dust in methanol.[18] Frank and Hall reported in 1950 that acceptable yields in this reduction are obtained only when potassium iodide is also added to the reaction mixture.[3] Thus, these workers reduced **7** to **45** by using 5 equiv of zinc dust and 1 equiv of KI in methanol. Using these conditions, we found that chloroenone **2** and bromoenone **5** are slowly reduced to enone **46** in yields of 40–50%. Conia's zinc–silver couple[19] gave comparable re-



2, X = Cl
5, X = Br

sults—slow reduction, ca. 50% yield of **46**. In contrast, we found that a zinc–silver couple prepared from acid-washed zinc *dust* causes a rapid reduction of **5**, affording **46** in high yield (81% distilled).

In order to optimize the conditions for this reduction, a series of experiments were carried out on chloroenone **7**. Reaction aliquots were analyzed by GLC, using peak areas to monitor the percent reduction as a function of reaction time. It was first established that potassium iodide is not necessary for facile reduction; in fact, reduction is somewhat more rapid in its absence. Secondly, it was established that the manner in which the zinc dust is washed with dilute acid is essential to the formation of an active couple. Optimum results are obtained when the zinc is treated with 10% aqueous HCl with occasional shaking for 4–5 min. Finally, the amount of silver used in preparing the couple is important. The couple is prepared by adding the acid-washed zinc dust to a hot solution of silver acetate in acetic acid, and the most effective reagent is obtained when 30–40 mg of silver acetate per gram of zinc dust is used (see Table II).

Using a zinc–silver couple prepared from 30 mg of AgOAc per gram of Zn, the reduction of **7** to **45** is effective-

Table I
Preparation of β-Chloroenones

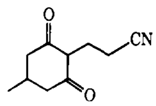
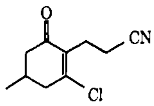
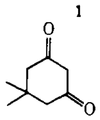
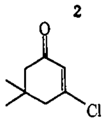
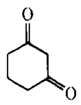
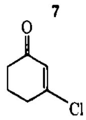
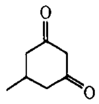
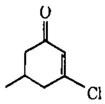
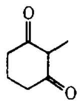
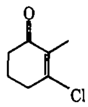
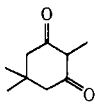
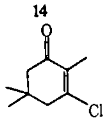
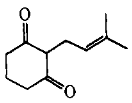
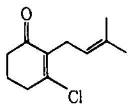
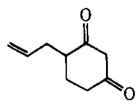
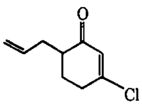
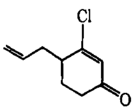
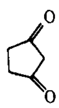
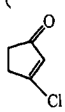
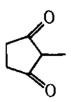
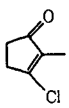
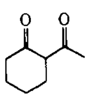
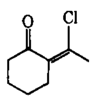
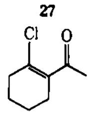
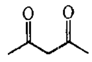
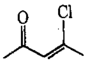
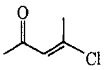
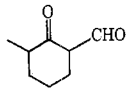
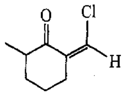
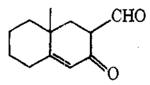
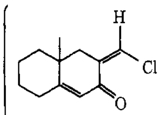
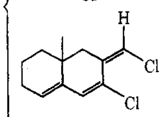
Starting β-dicarbonyl compd	Amount of $(COCl)_2$, equiv	Reaction time, min	Product	(% yield)[a]
 1	2.5[b]	60	 2	(76)
 6	2.0	20	 7	(91)
 9	2.5	13	 10	(78)
 11	2.5	120	 12	(92)
 13	2.5	60	 14	(87)
 15	2.0[b]	180	 16	(50)[c]
 17	2.0	15	 18	(62)
 19	2.0	15	 20	(51)
			 21	(22)
 22	2.0	15	 23	(78)
 24	2.0	15	 25	(73)
 26	2.0	15	 27	(51)
			 28	(27)

Table I
(Continued)

Starting β-dicarbonyl compd	Amount of $(COCl)_2$, equiv	Reaction time, min	Product	(% yield)[a]
 29	2.0	15	 30	(25)
			 31	(25)
 32	2.0	15	 33	(83)
 34	1.0	15	 35	(80)
			 36	(10)

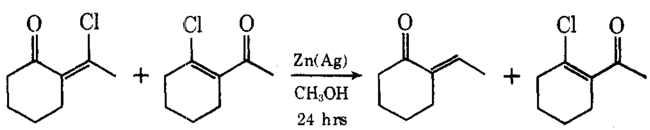
[a] Yields are distilled yields. [b] These reactions were carried out in benzene; all others were carried out in chloroform. [c] See text.

Table II
Reduction of β-Chloroenone 7

mg of AgOAc/g of Zn	% 45 in 5 min	mg of AgOAc/g of Zn	% 45 in 5 min
0	3	30	85
4	18	35	81
20	67	40	79
25	75		

ly quantitative in 15–20 min at room temperature. If acid-washed zinc dust is used, without being converted into the silver couple, the reduction requires more than 24 hr.

In order to explore the generality of the reduction procedure, a number of other β-chloroenones were reduced using the foregoing optimum conditions. Results are summarized in Table III. It is clear from Table III that this method of reductive removal of a halogen from a β-haloenone is widely applicable and constitutes a reliable synthetic method. Several generalizations may be made. β-Haloenones which have an alkyl group at the α position reduce much more slowly than those with hydrogen at this position. (**14** vs. **10**, **16** vs. **7**). β-Bromoenones reduce much more rapidly than β-chloroenones (**5** vs. **2**). In general, α-alkyl-β-chloroenones require on the order of 24 hr for complete reduction, while α-protio-β-chloroenones require only 15–60 min. One β-chloroenone, compound **28**, showed no signs of reducing at all, even after 24 hr. The reduction of this substance was actually carried out on a 2:1 mixture of **27** and **28**. After 24 hr, the reaction product consisted of a 2:1 mixture of **56** and **28**.

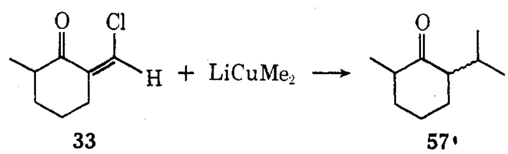


27 + **28** (2:1) → **56** + **28** (2:1)

Reduction of α-(chloromethylene)cyclohexanone (**33**) resulted in complete reduction to 2,6-dimethylcyclohexanone (**55**). Analysis by GLC showed that the product α-methylenecyclohexanone is reduced at a rate comparable to that for **33** itself.

It was found that dried zinc–silver couple is not nearly as effective as the freshly prepared couple. Furthermore, we noted that reduction of crude (undistilled) chloroenone results in substantial overreduction of the product enone, presumably owing to the acidity (HCl) of the undistilled chloroenone. We also investigated the Zn(Ag)–CH_3OH reduction of several other halides. o-Bromobenzoic acid, p-bromoethylbenzene, dichlorodiene **8**, and 1-chloro-4-methylcyclohexene were not reduced by the reagent in 24 hr.

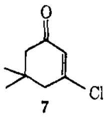
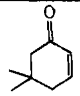
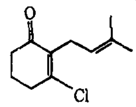
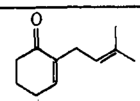
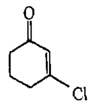
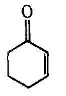
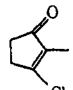
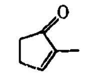
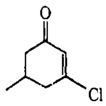
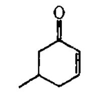
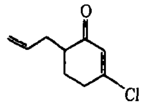
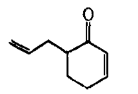
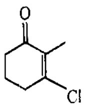
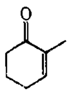
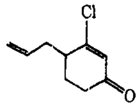
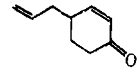
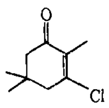
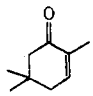
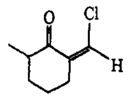
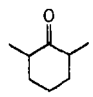
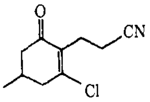
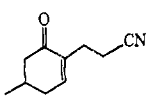
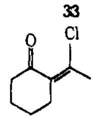
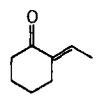
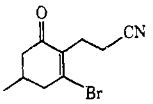
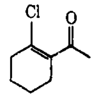
Reaction of β-Chloroenones with Organocuprates. Having a number of pure β-chloroenones in hand, we briefly investigated their reaction with lithium dimethylcuprate. Compound **33** reacts smoothly with 2 equiv of $LiCuMe_2$ to give 2-isopropyl-6-methylcyclohexanone (**57**) in 90% yield. Under the same conditions, the 2:1 mixture of **27**



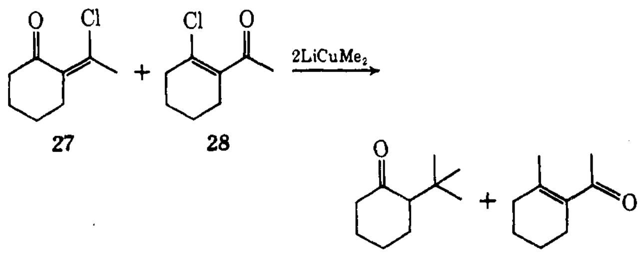
33 → **57**

and **28** affords a 2:1 mixture of 2-*tert*-butylcyclohexanone (**58**) and enone **59**.[20] A similar reaction with the α-(chloromethylene)octalone **35** resulted in exclusive alkylation of

Table III
Reduction of β-Chloroenones

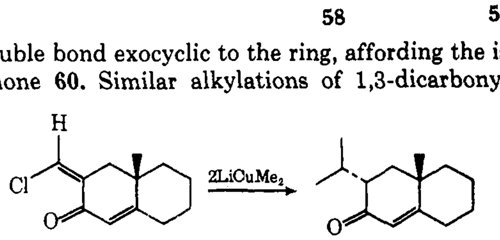
β-Chloroenone	Reaction time, min	Product	(% yield)[a]	β-Chloroenone	Reaction time, min	Product	(% yield)[a]
 7	20	 45	(81)	 18	1440	 51	(90)
 10	90[b]	 47	(75)	 25	1560	 52	(65)
 12	30	 48	(75)	 20	60	 53	(85)[d]
 14	2400	 49	(77)	 21	60	 54	(85)[d]
 16	2200	 50	(58)[c]	 33	60	 55	(80)
 2	1440	 46	(87, 81)	 27	1440	 56	*e*
 5	30			 28	1440		NR

[a] Isolated yield. [b] This reaction was carried out at 0° C. At room temperature, compound **10** reacts with methanol. [c] This reduction was incomplete after 37 hr; yield is by GLC. [d] Compounds **20** and **21** were reduced as a 70:30 mixture. The reduction products **53** and **54** were formed in 85% yield in a ratio of 70:30. [e] See text.



27 28 58 59

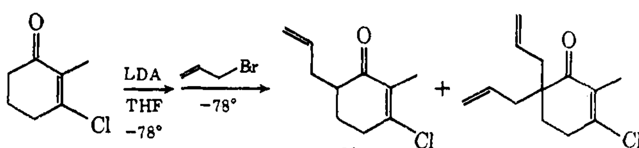
the double bond exocyclic to the ring, affording the isopropyl enone **60**. Similar alkylations of 1,3-dicarbonyl enol



35 60

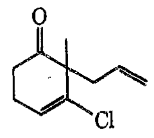
ethers,[22] enol sulfides,[22] and enol acetates[23] have been reported previously. However, alkoxyl (and presumably acyloxyl) groups cause the E_0 for an enone to be more negative,[21b] while halogens probably cause E_0 to be less negative.[24] Thus, in cases such as **35**, where there are two enone systems, greater selectivity is indicated.

Alkylation of β-Chloroenone Enolates. Finally, we have examined the kinetic alkylation of β-chloroenone **14**, in analogy to the kinetic alkylation of β-diketone enol ethers reported by Danheiser and Stork.[26] However, in the case of chloroenone **14**, we find proton transfer to compete very effectively with alkylation, even using allyl bromide as the electrophile. Thus, when **14** is converted into its kinetic enolate by lithium diisopropylamide (LDA) in THF, followed by alkylation with allyl bromide at −78°, a mixture of monoalkylated and dialkylated chloroenones (**61** and **62**) and recovered **14** is produced in a ratio of 30:25:45. Using inverse addition of preformed enolate to allyl bromide at −78° gave slightly more monoalkylation (**61**:**62**:**14** 48:22:



14 61 62

30), but the results were still not satisfactory. When the alkylation is carried out at 0°, with HMPT as cosolvent, either normal or inverse addition gave mixtures of mono- and dialkylated products, also containing the product of thermodynamically controlled enolization, **63**. The rapid proton transfer observed with β-chloroenones, in contrast to the exclusive monoalkylation observed with analogous enol ethers,[26] is probably due to the greater acidity of the chloroenones.



63

Experimental Section

All melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 spectrometer (in δ units with tetramethylsilane as internal reference). The infrared (ir) spectra were recorded on a Perkin-Elmer 137 infrared spectrophotometer. Mass spectra (MS) were obtained on a MS-12 mass spectrometer. Mass spectra are given as m/e with the relative intensity in parentheses. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif. Preparative and analytical gas–liquid chromatography (GLC) was carried out on an Aerograph Model A 90-P3 gas chromatograph using the following stainless steel (10 ft × 0.25 in.) columns: column A, 15% NPGS: column B, 5% SE-30; column C, 10% NPGS; column D, 10% FFAP.

3-Acetoxy-2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (3). Acetyl chloride (3.3 g, 42 mmol) was added to a suspension of dione 1[27] (5.0 g, 28 mmol) in chloroform (30 ml). The mixture was refluxed for 2 hr, evaporated, taken into ether, and filtered from a white solid. Evaporation of the ether filtrate gave 3.74 g (61%) of acetate 3 as a colorless oil: ir (film) 4.44, 5.67, 5.95, 8.40, 8.78, 9.52 μ; NMR (CCl_4) δ 1.08 (d, 3 H), 2.33 (s, 3 H), 2.00–2.60 (m, 9 H).

Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83. Found: C, 64.93; H, 6.97.

The white solid from above (1.44 g, 28.8%) was the known bicyclic lactam 4.[28] Recrystallization from chloroform–petroleum ether gave light yellow needles, mp 191–193° (lit.[28] mp 198–199°): ir (Nujol) 5.91, 6.11 μ; NMR (pyridine) δ 0.85 (d, 3 H), 2.00–2.70 (m, 9 H).

3-Bromo-2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (5). To a solution of diketone 1 (73.5 g, 410 mmol) in chloroform (700 ml) and lutidine (75 ml) was added phosphorus tribromide (62 ml, 660 mmol) and the resulting solution was refluxed for 3 hr. Water was slowly added to the cooled solution, the chloroform layer was separated, and the aqueous layer was washed with ether. The combined organic layers were washed with water, dried, and evaporated to a half-solid residue. Trituration with ether gave 14.6 g (20%) of crystalline lactam 4. The ether was evaporated and the residue distilled to give 19.4 g (20%) of bromoenone 5 (bath temperature 135°, 0.2 mm) as a colorless oil: ir (film) 4.50, 6.00, 6.19 μ; NMR (CCl_4) δ 1.05 (d, 3 H), 2.00–3.00 (m, 9 H).

Anal. Calcd for $C_{10}H_{12}ONBr$: C, 49.58; H, 4.96; N, 5.78; Br, 33.05. Found: C, 49.38; H, 4.93; N, 5.59, Br, 33.28.

General Procedure for the Synthesis of Chloroenones. 3-Chloro-5,5-dimethylcyclohex-2-en-1-one (7). To a suspension of dimedone 6 (15.0 g, 107 mmol) in chloroform[29] (40 ml) was added slowly oxalyl chloride (27.2 g, 214 mmol). The addition was accompanied by vigorous evolution of gas. After stirring at room temperature for 10 min, the slurry was refluxed for 20 min to give a yellow solution which was evaporated and distilled to give 15.7 g (92%) of chloroenone 7 as a colorless liquid, bp 72° (5 mm) [lit.[3] bp 105° (20 mm)]: ir (film) 5.95, 6.17 μ; NMR (CCl_4) δ 1.10 (s, 6 H), 2.20 (s, 2 H), 2.78 (d, 2 H), 6.13 (t, 1 H); MS m/e (rel intensity) 160 (6), 158 (19), 104 (32), 102 (100), 79 (17), 77 (11), 67 (48).

Anal. Calcd for $C_8H_{11}OCl$: C, 60.56; H, 6.94; Cl, 22.37. Found: C, 60.36; H, 6.79; Cl, 22.38.

3-Chloro-2-(2-cyanoethyl)-5-methylcyclohex-2-en-1-one (2). Dione 1 (35.0 g, 196 mmol) in benzene (100 ml) was treated with oxalyl chloride (62.5 g, 493 mmol) according to the general procedure described above. After a 60-min reflux, the solvent was evaporated and the residue was distilled to give 29.1 g (75.5%) of chloroenone 2 as a colorless oil, bp 152° (3 mm): ir (film) 4.46, 5.95, 6.17 μ; NMR (CCl_4) δ 1.05 (d, 3 H), 2.00–3.00 (m, 9 H); MS m/e (rel intensity) 199 (8), 197 (27), 172 (16), 162 (100), 115 (74).

Anal. Calcd for $C_{10}H_{12}ONCl$: C, 60.90; H, 6.09; N, 7.11; Cl, 18.05. Found: C, 60.77; H, 6.19; N, 7.06; Cl, 18.02.

Other β-chloroenones prepared using this general procedure had the following physical properties.[30]

3-Chlorocyclohex-2-en-1-one (10): bp 63° (4 mm) [lit. bp 78° (14 mm),[31] 104° (24 mm[32])].

3-Chloro-5-methylcyclohex-2-en-1-one (12): bp 52° (1.2 mm).

3-Chloro-2-methylcyclohex-2-en-1-one (14): bp 46° (0.6 mm), 62° (2 mm) [lit.[33] bp 84° (7 mm)].

3-Chloro-2-(3-methyl-2-butenyl)cyclohex-2-en-1-one (18): bp 110° (2.5 mm).

3-Chloro-4-(2-propenyl)cyclohex-2-en-1-one (21), 3-chloro-6-(2-propenyl)cyclohex-2-en-1-one (20): bp 85° (2 mm).

3-Chlorocyclopent-2-en-1-one (23): bp 35° (0.7 mm).

3-Chloro-2-methylcyclopent-2-en-1-one (25): bp 43° (1.6 mm).

(Z)-2-Chloroethylidinecyclohexanone (27), 1-acetyl-2-chlorocyclohexene (28): bp 80° (2 mm).

Reaction of Methyl Dimedone (15) with Oxalyl Chloride. Oxalyl chloride (56.0 g, 460 mmol) was added slowly to methyl dimedone (15,[34] 35.0 g, 227 mmol) in benzene (40 ml) and the resulting solution was refluxed for 3 hr. The solvent was evaporated and the residue distilled to give 19.5 g (50%) of chloroenone 16 as a colorless oil, bp 78° (2 mm) [lit.[35] bp 78° (2 mm)]: ir (film) 5.95, 6.11, 7.50, 7.7 μ; NMR (CCl_4) δ 1.33 (s, 6 H), 1.90 (t, 3 H), 2.28 (s, 2 H), 2.65 (q, 2 H); MS m/e (rel intensity) 174 (7), 172 (24), 118 (32), 116 (100).

Anal. Calcd for $C_9H_{13}OCl$: C, 62.61; H, 7.53; Cl, 20.55. Found: C, 62.64; H, 7.58; Cl, 20.29.

The crystalline pot residue from the distillation (10.0 g) was recrystallized from ethyl acetate to give the bisoxalate 39, mp 159–161°: ir (Nujol) 5.62, 5.95, 6.80, 9.10 μ; NMR ($CDCl_3$) δ 1.16 (s, 12 H), 1.73 (t, 6 H), 2.38 (s, 4 H), 2.57 (q, 4 H).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.03; H, 7.27.

In a similar reaction of methyl dimedone (10.0 g, 65 mmol) and oxalyl chloride (20.6 g, 162 mmol) in benzene (30 ml), the higher boiling chlorooxalate 40 was obtained, bp 107° (1.2 mm): ir ($CHCl_3$) 5.37, 5.67, 5.95, 6.15 μ; NMR was identical with that of bisoxalate 39.

(Z)-3-Chloropent-3-en-2-one (30) and (E)-3-Chloropent-3-en-2-one (31). Acetylacetone (29, 5.0 g, 50 mmol) in chloroform (15 ml) was treated with oxalyl chloride (12.7 g, 100 mmol) and the resulting solution was refluxed for 15 min. Evaporation of solvents and distillation gave 2.95 g (50%) of chloroenones 30 and 31, bp 35° (6 mm) [lit.[11] bp 42° (11 mm)]. The two isomers were present in a 50:50 ratio by NMR analysis and were separated by preparative gas chromatography (column A, 140°). The E isomer 31 had retention time 2.2 min: NMR (CCl_4) δ 2.16 (s, 3 H), 2.33 (d, J = 1 Hz, 3 H), 6.43 (q, J = 1 Hz, 1 H). The Z isomer 30 had retention time 4.0 min: NMR (CCl_4) δ 2.08 (d, J = 1 Hz, 3 H), 2.30 (s, 3 H), 6.10 (q, J = 1 Hz, 1 H).

(Z)-2-Chloromethylene-6-methylcyclohexanone (33). A solution of 2-formyl-6-methylcyclohexanone (9.95 g, 71.7 mmol) in chloroform (40 ml) was treated with oxalyl chloride (13.6 g, 106 mmol) under the usual conditions to give 9.23 g (82.6%) of 33, bp 60° (1.5 mm). Gas chromatography (column B, 150°) showed one component at retention time 4.0 min: ir (film) 5.92, 6.23, 6.40, 6.90, 7.75 μ; NMR (CCl_4) δ 1.10 (d, 3 H), 1.40–2.80 (m, 7 H), 6.96 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_8H_{11}OCl$: C, 60.57; H, 6.94; Cl, 22.40. Found: C, 60.78; H, 6.90; Cl, 22.18.

(Z)-2-Chloromethylene-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (35). Oxalyl chloride (2.41 g, 19 mmol) was slowly added to a cooled (10–15°) solution of formyl ketone 34 (3.58 g, 18.6 mmol) in chloroform (50 ml). After the addition was complete, the solution was stirred at room temperature for 15 min and then refluxed for 15 min. Evaporation and distillation gave 3.0 g of yellow oil, bp 125° (1.5 mm). NMR analysis showed a 9:1 mixture of chloroenone 35 and dichlorotriene 36, which were separated by preparative gas chromatography (column C, 200°). Compound 36 had retention time 2.5 min: ir (film) 6.12, 6.20, 6.40, 9.80 μ; NMR (CCl_4) δ 1.00 (s, 3 H), 2.83 (d, 1 H), 5.53 (t, 1 H), 6.10 (s, 1 H), 6.56 (d, J = 2 Hz, 1 H); MS m/e (rel intensity) 232 (6), 230 (35), 228 (54), 195 (34), 193 (100), 165 (24), 157 (39).

Compound 35 had retention time 3.7 min: ir (film) 6.01, 6.20, 6.30, 7.65, 8.00 μ; NMR (CCl_4) δ 1.16 (s, 3 H), 2.93 (d, 1 H), 5.70 (t, 1 H), 7.05 (d, J = 2 Hz, 1 H); MS m/e (rel intensity) 212 (34), 210 (100), 195 (48), 175 (68), 105 (70).

Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.13. Found: C, 68.16; H, 7.23.

Under the usual conditions for formation of the β-chloroenone (2.0 equiv of $COCl_2$), compound 34 gave only dichlorotrienone 36 in good yield.

Reaction of Ethyl Cyclohexanone-2-carboxylate (42) with Oxalyl Chloride. To a solution of ethyl cyclohexanone-2-carboxylate (5.0 g, 29 mmol) in benzene (20 ml) was added oxalyl chloride

(7.9 g, 62 mmol). After 3.5 hr reflux, the mixture was evaporated and distilled to give 5.3 g of chlorooxalate **43** as a thick oil, bp 130° (1.5 mm): ir (film) 5.43, 5.56, 5.71, 5.80, 8.10 μ; NMR was virtually superimposable with that of the starting material.

When this material was refluxed in methanol, a colorless oil was obtained which was readily identifiable as the methyl oxalate **44:** ir (film) 5.68, 5.71 μ; NMR (CCl_4) δ 3.72 (s, 3 H).

General Procedure for the Reduction of β-Chloroenones. 5,5-Dimethylclohex-2-en-1-one (45). Aqueous 10% hydrochloric acid (10 ml) was added to zinc dust (Mallinckrodt analytical, 2.1 g, 31.5 mmol) and the resulting suspension was shaken periodically. After several minutes, the supernatant liquid was decanted and the zinc was washed with acetone (2 × 10 ml) and ether (10 ml). A suspension of silver acetate (60–70 mg) in boiling acetic acid (10 ml) was added. After the mixture was stirred for 1 min, the supernatant was decanted and the black zinc–silver couple was washed with acetic acid (5 ml), ether (4 × 10 ml), and methanol (10 ml). To the moist couple was added a solution of chloroenone **7** (1.0 g, 6.3 mmol) in methanol (3 ml). The reduction was exothermic, and GLC analysis (column A, 150°) showed it to be complete after stirring vigorously at room temperature for 10–20 min. The zinc was filtered off and washed with methanol. The filtrate was evaporated and the residue was partitioned between ether and 10% hydrochloric acid. The ether layer from five similar runs was dried and evaporated to yield 3.2 g (81%) of enone **45** as a colorless oil, bp 36° (1 mm): ir (film) 5.95 μ; NMR (CCl_4) δ 1.10 (s, 6 H), 2.30 (m, 4 H), 5.93 (m, 1 H), 6.80 (m, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74; Found: C, 77.04; H, 10.09.

2-(2-Cyanoethyl)-5-methylcyclohex-2-en-1-one (46). Reduction of chloroenone **2** (27.6 g, 140 mmol) with the zinc–silver couple (63.0 g, 978 mmol) in methanol (120 ml) for 26 hr as above gave 19.5 g (86.5%) of enone **46** after distillation, bp 92° (0.3 mm): ir (film) 4.44, 5.97 μ; NMR (CCl_4) δ 1.10 (d, 3 H), 2.00–2.50 (m, 5 H), 2.46 (s, 4 H), 6.85 (d, 1 H).

Anal. Calcd for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.28; H, 8.13; N, 8.40.

2,6-Dimethylcyclohexanone (55). To the zinc–silver couple (5.2 g, 80 mmol) was added chloroenone **33** (2.5 g, 15.8 mmol) in methanol (10 ml). An exothermic reaction ensued which required mediation with an ice bath. GLC analysis (column B, 150°) showed the reaction to be complete in less than 5 min. The usual work-up gave 1.50 g (80%) of colorless oil which was identical (ir, NMR, GLC) with an authentic sample of 2,6-dimethylcyclohexanone.

Reduction of Chloroenones 27 and 28. A 2:1 mixture of chloroenones **27** and **28** (1.0 g, 6.4 mmol) in methanol (2 ml) was treated with the zinc–silver couple (1.25 g, 19 mmol) at room temperature for 20 hr. Work-up afforded 0.75 g of light red oil. GLC analysis (column B, 130°) showed two peaks at retention times of 4.8 and 6.6 min, in a 2:1 ratio. Both peaks were collected by preparative GLC and the major peak was (*E*)-2-ethylidinecyclohexanone (**56**): ir (CCl_4) 5.91, 6.19 μ; NMR (CCl_4) δ 1.68 (doublet of triplets, *J* = 7, 1 Hz, 3 H), 2.00–2.60 (m, 4 H), 6.55 (quartet of triplets, *J* = 7, 2 Hz, 1 H).[36]

The minor peak was chloroenone **28:** ir (CCl_4) 5.90, 6.20 μ; NMR (CCl_4) δ 1.53–1.90 (m, 4 H), 2.37 (s, 3 H), 2.00–2.60 (m, 4 H); MS *m/e* (rel intensity) 160 (8), 158 (24), 145 (22), 143 (69, loss of methyl, ^{35}Cl isomer).

Spectral[30] and physical properties of other enones prepared by this general method were in complete accord with the assigned structures. Furthermore, the synthetic samples of enones **45, 47, 48, 50,** and **54**[26] were identical with authentic samples of these materials.

Reaction of β-Chloroenones with Lithium Dimethylcopper. 2-Isopropyl-6-methylcyclohexanone (57). A solution of chloroenone **33** (5.0 g, 31.8 mmol) in ether was added to a −30° solution of lithium dimethylcopper (65 mmol) in ether (100 ml). The mixture was allowed to warm to room temperature, then was poured into aqueous ammonium hydroxide solution. Ether extraction gave 4.47 g (91.4%) of **57** as a light yellow oil: ir (film) 5.84, 6.89, 7.70 μ; NMR (CCl_4) δ 0.80–1.07 (overlapping methyl and isopropyl doublets from two isomers, 9 H), 1.07–2.40 (m, 9 H); MS *m/e* (rel intensity 154 (22).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.02; H, 11.93.

2-*tert*-Butylcyclohexanone (58) and 1-Acetyl-2-methylcyclohexene (59). An ether solution of chloroenones **27** and **28** (1.6 g, 10 mmol) was added to a −50° solution of lithium dimethylcopper (25 mmol) in ether (25 ml). The mixture was allowed to warm to room temperature and was poured into 10% aqueous hydrochloric acid and extracted with ether to give 1.7 g of yellow oil. GLC analysis (column B, 150°) showed two peaks at retention times 5.8 and 7.0 min, in a 65:35 ratio. Both components were collected and the major peak was 2-*tert*-butylcyclohexanone (**58**): ir (film) 5.83, 7.40, 7.65 μ; NMR (CCl_4) δ 0.96 (s, 9 H), 1.40–2.40 (m, 9 H).

The minor peak was the enone **59:** ir (film) 5.93, 6.20, 7.40 μ; NMR (CCl_4) δ 1.40–1.80 (m, 4 H), 1.82 (t, *J* = 1 Hz, 3 H), 2.10 (s, 3 H), 1.90–2.40 (m, 4 H).

3α-Isopropyl-4aβ-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (60). Reaction of choroenone **35** (2.2 g, 10.5 mmol) with lithium dimethylcopper (22 mmol), followed by aqueous ammonium hydroxide work-up, gave 1.9 g (88%) of the isopropyl enone **60** as a colorless oil. GLC analysis (column C, 200°) showed a single peak at retention time 6.1 min: ir (film) 6.00, 6.16 μ; NMR (CCl_4) δ 0.80 (d, *J* = 7 Hz, 3 H, nonequivalent isopropyl methyl), 0.93 (d, *J* = 7 Hz, 3 H), 1.25 (s, 3 H), 5.56 (s, 1 H).

Anal. Calcd for $C_{14}H_{22}O$: 206.1670. Found: 206.1675.

This material was unchanged upon prolonged treatment with sodium methoxide in methanol or *p*-toluenesulfonic acid in benzene.

3-Chloro-2-methyl-6-(2-propenyl)cyclohex-2-en-1-one (61) and 3-Chloro-2-methyl-6,6-di(2-propenyl)cyclohex-2-en-1-one (62). To a −78° solution of lithium diisopropylamide (16 mmol) in THF (3 ml) was added a solution of chloroenone **14** (2.0 g, 15.8 mmol) in THF (4 ml) dropwise over a 20-min period. After 10 min at −78°, the solution was treated with allyl bromide (2.1 g, 17.2 mmol) and allowed to warm to room temperature overnight. After dilution with ether, the solution was washed with water, 5% hydrochloric acid, and brine, dried, and evaporated to 2.62 g of reddish oil. GLC analysis (column D, 170°) showed three peaks at retention times 2, 3.7, and 6.2 min, in a ratio of about 45:30:25, respectively. Collection of individual peaks showed the first to be starting material **14:** MS *m/e* (rel intensity) 146 (13), 144 (41), 118 (32), 116 (100), 88 (66), 53 (64).

The second peak was the monoallylated chloroenone **61:** ir (film) 3.14 5.97, 6.11, 10.92 μ; NMR (CCl_4) δ 1.90 (t, *J* = 1 Hz, 3 H), 1.80–2.90 (m, 7 H), 4.80–6.00 (complex ABX, 3 H); MS *m/e* (rel intensity) 186 (12), 184 (39), 149 (19), 118 (33), 116 (100), 81 (50), 53 (68).

The third peak was the diallylated enone **62:** ir (film) 3.14, 5.97, 6.11, 10.93 μ; NMR (CCl_4) δ 1.90 (t, *J* = 1 Hz, 3 H), 1.80–2.90 (m, 8 H), 4.80–6.00 (complex ABX, 6 H); MS *m/e* (rel intensity) 226 (2), 224 (7), 183 (36), 155 (32), 118 (28), 116 (80), 93 (16), 91 (49), 42 (100).

Acknowledgments. We gratefully acknowledge Mr. Lee Kozar for his technical assistance in some aspects of this work, and the National Science Foundation for generous financial support under Grant GP-31321X.

Supplementary Material Available. NMR and infrared spectra for all new compounds (48 pages). Ordering information is given on any current masthead page.

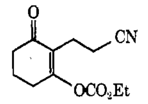
Registry No.—**1**, 2172-73-8; **2**, 42747-36-4; **3**, 57428-51-0; **4**, 17812-55-4; **5**, 42747-37-5; **6**, 126-81-8; **7**, 17530-69-7; **9**, 504-02-9; **10**, 5682-75-7; **11**, 4341-24-6; **12**, 42747-34-2; **13**, 1193-55-1; **14**, 35155-66-9; **15**, 1125-11-7; **16**, 39776-34-6; **17**, 56946-66-8; **18**, 57428-52-1; **19**, 57428-53-2; **20**, 57428-54-3; **21**, 57428-55-4; **22**, 3859-41-4; **23**, 53102-14-0; **24**, 765-69-5; **25**, 35173-23-0; **26**, 874-23-7; **27**, 57428-56-5; **28**, 16111-92-5; **29**, 123-54-6; **30**, 49784-64-7; **31**, 49784-51-2; **32**, 1194-91-8; **33**, 57428-57-6; **34**, 57428-58-7; **35**, 57428-59-8; **36**, 57428-60-1; **39**, 57428-61-2; **40**, 51238-70-1; **42**, 1655-07-8; **43** (R = Me), 57428-62-3; **43** (R = Et), 57428-63-4; **44** (R = Me), 57428-64-5; **44** (R = Et), 57428-65-6; **45**, 4694-17-1; **46**, 42747-40-0; **47**, 930-68-7; **48**, 7214-50-8; **49**, 1121-18-2; **50**, 42747-41-1; **51**, 57428-66-7; **52**, 1120-73-6; **53**, 57428-67-8; **54**, 4166-61-4; **55**, 2816-57-1; **56**, 7417-55-2; **57**, 17781-07-6; **58**, 1728-46-7; **59**, 2047-97-4; **60**, 57428-68-9; **61**, 57428-69-0; **62**, 57428-70-3; acetyl chloride, 75-36-5; phosphorus tribromide, 7789-60-8; oxalyl chloride, 79-37-8.

References and Notes

(1) Portions of this work have appeared in preliminary form: R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **38**, 3658 (1973); *Synthesis*, 47 (1974).
(2) A Crossley and H. LeSeur, *J. Chem. Soc.*, **83**, 110 (1903).
(3) R. L. Frank and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **72**, 1645 (1950).
(4) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).
(5) M. Shemyakin et al., *Zh. Obshch. Khim.*, **30**, 542 (1960).
(6) W. Hückel and K. Thiele, *Chem. Ber.*, **94**, 96 (1961).
(7) W. Pfelderer and K. Schundehütte, *Justus Liebigs Ann. Chem.*, **613**, 158 (1958).

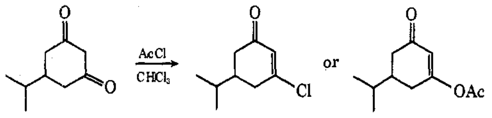
(8) It has recently been found that β-diketones react with triphenylphosphine dihalides to product β-halo-α,-β-unsaturated ketones. With chlorides and bromides, yields are excellent (90–97%). With iodides, the yields are lower, but respectable (71–83%): E. Piers and I. Nagakura, *Synth. Commun.*, **5**, 193 (1975).

(9) We also found that dione **1** reacts with ethyl chloroformate in chloroform to give the mixed carbonate i in 91% yield. These results lead us



i

to suspect that the reported conversion of dione ii into β-chloroenone iii[6] may be in error. Since no characterization of the alleged iii was reported, the reaction product may well be acetate iv.

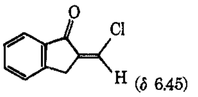


ii iii iv

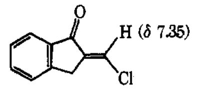
(10) The reaction may also be carried out on the sodium salt of the β-diketone. Thus, the sodium salts of **1** and **11** reacted with oxalyl chloride in benzene to give **2** and **12**, in isolated yields of 46 and 56%, respectively. We have also briefly explored the analogous use of oxalyl bromide for the formation of β-bromoenones. Dione **6** reacts rapidly, giving the corresponding β-bromoenone in good yield. However, dione **1** was simply polymerized by treatment with oxalyl bromide.

(11) M. Julia, *Ann. Chim. (Paris)*, **5**, 595 (1950).

(12) Although several cyclic α-(chloromethylene) ketones have been reported,[13] no stereostructural assignments have been made except in the case of isomers v and vi,[14] and then on the basis of comparative chemical shifts. The general principle used in assigning structures to v



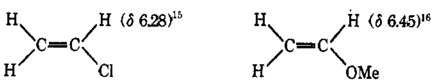
v



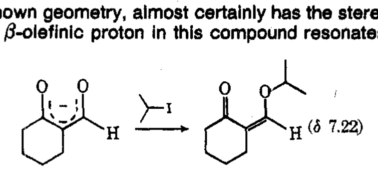
vi

and vi is the empirical observation that olefinic β protons cis to the carbonyl group in enones resonate downfield from their trans counterparts.[14] However, in our case, only one isomer is in hand, and such comparative arguments may not be made.

Our assignment is based on the following argument: Protons α to the heteroatom in vinyl chloride and methyl vinyl ether resonate at δ 6.28 and δ 6.45, respectively. The enol ether vii, prepared by alkylation of an

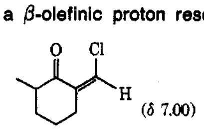


enolate of known geometry, almost certainly has the stereostructure indicated. The β-olefinic proton in this compound resonates at δ 7.22.[17]



vii

Compound **33** shows a β-olefinic proton resonance at δ 7.00 ppm.



33

Thus, it would appear that vii and **33** both have the same relative stereostructure, since the $\Delta\delta$ of 0.22 ppm observed is about the same as the $\Delta\delta$ of 0.17 ppm observed with vinyl chloride and methyl vinyl ether (vide supra). The cis and trans β-olefinic protons in α-methylenecyclohexanone resonate at δ 5.72 and 5.04, respectively. Thus, for vii and **33** to differ in stereostructure, their β-olefinic proton resonances should differ by about 1 ppm.

(13) (a) J. Wolinsky, D. Chan, and R. Novak, *Chem. Ind. (London)*, 720 (1965); (b) A. E. Pohland and W. R. Benson, *Chem. Rev.*, **66**, 161 (1966).

(14) L. M. Jackman and S. Sternhall, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Elmsford, N.Y., 1969, p 223.

(15) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

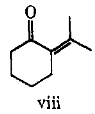
(16) J. E. Sohn, unpublished spectrum.

(17) P. M. Wege, unpublished spectrum.

(18) A. Crossley and N. Renouf, *J. Chem. Soc.*, **91**, 63 (1907).

(19) J. M. Denis, C. Girard, and J. M. Conia, *Synthesis*, **5**, 549 (1972).

(20) Note that there is a large difference in reactivity between the presumed intermediate in the formation of **58** (enone viii) and enone **59**. By



viii

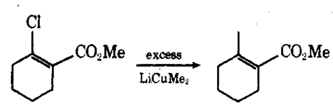
House's empirical rules for estimating standard reduction potentials for α,β-unsaturated carbonyl compounds, both viii and **59** should have E_0 vs. SCE of -2.3 V,[21] just on the borderline for reaction with lithium dimethylcuprate. However, these two enones may well differ in conformation, with **59** being *s*-trans and viii *s*-cis. This might well result in a less negative E_0 for viii, relative to **59**.

(21) (a) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972); (b) H. O. House, L. E. Huber, and M. J. Umen, *ibid.*, **94**, 8471 (1972).

(22) G. H. Posner and D. J. Brunelle, *J. Chem. Soc., Chem. Commun.*, 907 (1973).

(23) C. P. Casey, D. F. Marten, and R. A. Boggs, *Tetrahedron Lett.*, 2071 (1973).

(24) That halogens add a positive increment to the E_0 of an unsaturated carbonyl system is suggested by the rapid and quantitative conversion of chloro ester ix to unsaturated ester x.[25] By House's rules, compound ix



ix x

should have $E_0 = -2.4$ V $\pm$ the effect of the halogen. Since E_0 for $LiCuMe_2$ is estimated to be ca. -2.3 V, the β halogen probably contributes $\geq +0.1$ V to E_0 for the system. Note that x, with a predicted E_0 of -2.5 V, does not react even though excess $LiCuMe_2$ is employed.

(25) C. H. Heathcock and J. Leong, unpublished results.

(26) R. L. Danheiser and G. Stork, *J. Org. Chem.*, **38**, 1775 (1973).

(27) C. A. Grob and H. R. Kiefer, *Helv. Chim. Acta*, **48**, 799 (1965).

(28) This lactam has been prepared in high yield by reaction of **1** with HCl: H. Dugas, M. E. Hazenberg, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4931 (1967).

(29) Commercial chloroform was freed from ethanol by washing with dilute acid followed by drying over magnesium sulfate and distillation.

(30) See paragraph at end of paper regarding supplementary material.

(31) L. Bateman and F. W. Shipley, *J. Chem. Soc.*, 1996 (1955).

(32) A. Crossley and P. Haas, *J. Chem. Soc.*, **83**, 494 (1903).

(33) S. I. Zav'yalov and G. V. Kondrat'eva, *Zh. Obshch. Khim.*, **39**, 3975 (1961).

(34) R. D. Clark, J. E. Ellis, and C. H. Heathcock, *Synth. Commun.*, **3**, 347 (1973).

(35) F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).

(36) For NMR spectra of (*E*)-2-alkylidinecyclohexanones, see G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975), and references cited therein.