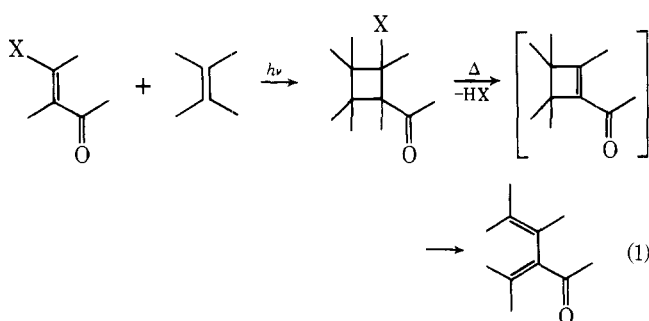


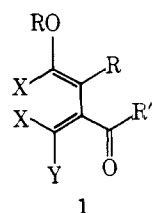
A New Route to Linear, Polycyclic, Substituted Aromatics: Diels–Alder Reactions of Bicyclic Dimethoxycyclobutenes

Summary: Photochemical cycloaddition of alkoxyolefins to enol acetates of β -diketones and β -chloroenones proceeds readily to afford the cyclobutane or derived cyclobutene. These substances, on thermolysis in the presence of a dienophile, readily eliminate the elements of mineral acid or acetic acid and/or undergo conrotatory opening to the butadiene followed by Diels–Alder reaction. This process provides a facile entry into certain polycyclic aromatic systems and highly substituted benzene derivatives.

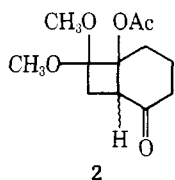
Sir: The use of photochemical cycloadditions to produce substituted cyclobutanes is well documented.^{1,2} We became interested in the utility of this process as a *general route* to substances which might serve as *stable, thermal precursors* of alkoxy-substituted butadienes by in situ conrotatory opening of a cyclobutene (eq 1).³ This route would provide



access to a variety of alkoxy dienes to which no routes presently exist and whose preparation would be extremely difficult by conventional methods. Of particular interest were the alkoxybutadienes (1), of which one precursor, 2, had previously

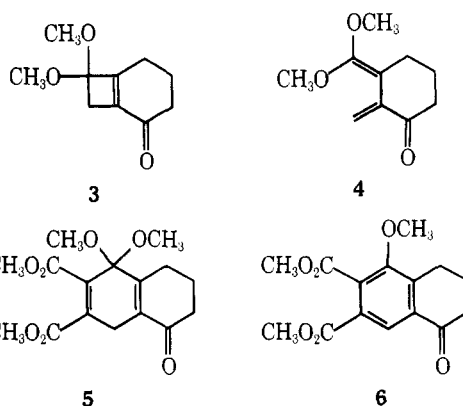


R = alkyl
X = H, OR
R' = alkyl, OR
Y = H, OR



been prepared by Cantrell.⁴ We initiated our investigation by preparing 2 and its elimination product 3.⁴ We found that irradiation of ketene dimethylacetal and 3-acetoxy-2-cyclohexen-1-one in ether⁵ produced a mixture of *trans* adduct 2 and cyclobutene 3. The latter substance apparently arises from extremely facile elimination of acetic acid from *cis*-2.⁶ Cyclobutene 3 is reasonably stable and can be handled easily. *trans*-2 resists elimination of acetic acid up to 180 °C and is recovered unchanged. However, equilibration of the crude mixture of 2 and 3 with alumina produces 3 in up to 60% overall yield from the initial photoreactants.^{7,8}

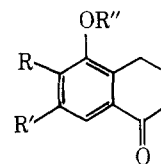
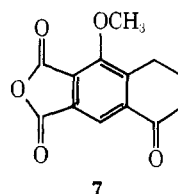
Reaction of 3 at temperatures from 150 to 170 °C in the presence of a dienophile readily generates the corresponding diene 4, which is efficiently trapped in situ. For example, with dimethylacetylene dicarboxylate, 3 affords 5 (mp 118.5–119.5 °C) and 6 in ~90% yield.⁹ Ketal 5 readily eliminates methanol on treatment with sodium methoxide or by silica gel chromatography, producing 6. Cyclobutene 3 also reacts readily with maleic anhydride and methyl propiolate, affording adducts 7 (~90%) and 8a only (64%) after oxidation and elimi-



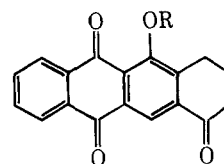
nation.⁹ This high reactivity and high regioselectivity is especially noteworthy and suggests that considerable regiochemical control can be exercised in the cycloaddition reactions of dienes like 4.

Treatment of 3 with 1,4-naphthoquinone followed by basic oxidation ($O_2/NaOCH_3$) affords tetracyclic ketone 9 (75%), thus providing a facile entry into these anthraquinone systems.⁹ This route should have great utility toward a highly convergent synthesis of the tetracyclic ring systems present in the clinically useful antitumor agents daunomycin and adriamycin.

We have extended this process to the photochemical cycloadditions of *cis*-1,2-dimethoxy- and diethoxyethylene to 3-acetoxy- and 3-chloro-2-cyclohexen-1-ones. Irradiation of enone (1 mol) and olefin (3 mol) in dry acetone through Pyrex (8–24 h) affords, after chromatography, the cyclobutane adducts 10–11 in extremely high yields (80–93%).¹⁰ This reaction proceeds much more efficiently in acetone than in other solvents investigated (ether, benzene). The halogen-containing adducts 11 proved to be quite sensitive, decomposing rapidly at room temperature. Both adducts 10 and 11 were obtained

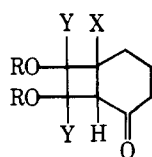


8a, R = CO_2CH_3 ; R' = H;
R'' = CH_3 , C_2H_5
b, R = H; R' = CO_2CH_3 ;
R'' = CH_3 , C_2H_5

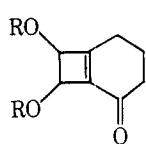


as mixtures of stereoisomers, and were utilized as such. The cycloaddition reactions of 1,2-dimethoxyethylene are unusually facile and clean, and proceed at stoichiometries much closer to the ideal (1:1) than comparable cycloadditions of simple olefins such as cyclohexene.¹¹ Furthermore, even the cycloaddition to 3-chlorocyclohex-2-en-1-one occurs cleanly, although chloroenones generally exhibit poor reactivity with ordinary olefins.¹² The cycloaddition process can be extended further to tetramethoxyethylene, affording 12 in low yield.¹³ Attempts to prepare and isolate the cyclobutene 13 resulting from base treatment of 11 produced mixtures containing 13, but were contaminated by substantial amounts of β,γ isomer 14 when amine bases were utilized (DBN, 0 °C). When nucleophilic bases were utilized with 10 and 11 ($NaOCH_3/$

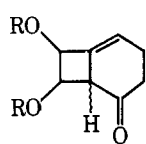
CH₃OH/room temperature), elimination–addition occurred, affording 15 cleanly.



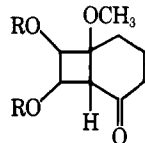
- 10a, X = OAc; R = CH₃; Y = H
 b, X = OAc; R = CH₂CH₃; Y = H
 11, X = Cl; R = CH₃, CH₂CH₃; Y = H
 12, X = OAc; R = CH₃; Y = OCH₃



13, R = CH₃,
CH₂CH₃

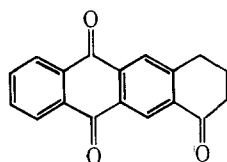


14, R = CH₃,
CH₂CH₃

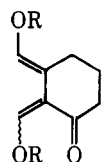


15, R = CH₃,
CH₂CH₃

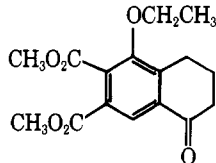
The reaction of a mixture containing 13 with 1,4-naphthoquinone at 137 °C (6 h) afforded the tetracyclic ketone 16 (mp 242–243 °C) in low yield, demonstrating the viability of the electrocyclic opening to generate 17 in situ. Since isolation and handling of 13 were precluded by its instability, we investigated direct generation of 17 from 10. Exposure of dimethylacetylene dicarboxylate (1 mol) to 10b (1 mol) in *o*-dichlorobenzene at 180 °C afforded ketone 18 in 50–60%



16



17, R = CH₃,
CH₂CH₃

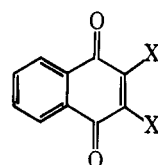


18

yield [bp 170 °C (0.3 mm) (Kugelrohr); NMR δ 1.43 (t, 3 H), 2.20 (m, 2 H), 2.80 (t, 2 H), 3.10 (t, 2 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 8.58 (s, 1 H)]. Reaction of 10a, under similar conditions, with maleic anhydride afforded 6 identical with that from 3 in good yield. Reaction of 10a with methyl propiolate (195 °C, sealed tube/3 h) afforded a mixture of regioisomers (3:2 *o/m*) 8a and 8b (66%). This result suggests that the 2-acyl group exerts little influence on the regiochemical outcome in the case where the normally dominant effects of the alkoxy groups cancel. This is in accord with the frontier orbital theory predictions.¹⁴

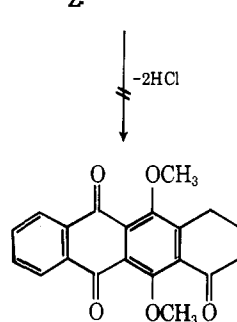
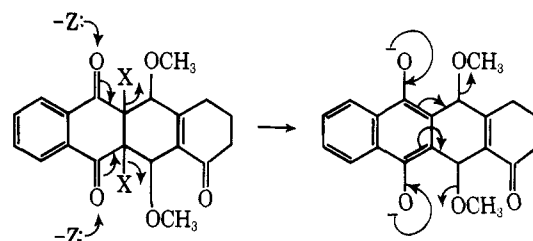
The diene precursor 10 is, however, useful in the construction of polycyclic systems. Treatment of 10 (1 mol) in *o*-dichlorobenzene (180 °C; ~3 h) with 1,4-naphthoquinone (1 mol) provides 16 in ~60% yield. This yield could conceivably be improved by increasing the amount of quinone-trapping agent. Furthermore, we had interest in the production of bismethoxylated derivatives such as 19. Such systems are present as indicated previously in the adriamycin/daunomycin class of antitumor agents. To accomplish this, the α positions of the dienophile were substituted with leaving groups (20–21). The reactivity of the dichloro derivative 20 was considerably diminished, and the only isolable crystalline product on reaction with 10a was ketone 16 (~20%). An unprecedented oxidation–reduction had occurred, resulting in the apparent loss of 2 mol of MeOCl. A rationale for this result is given in eq 2.

To induce the elimination of HCl from the initial Diels–Alder adduct, an inorganic base (1 mol of Li₂CO₃)¹⁶ was introduced. This modification permitted the elimination of one but not both moles of HCl (the second Cl being lost as

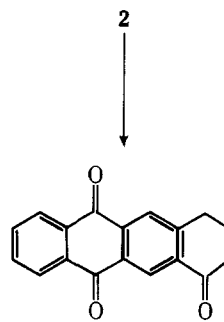


20, X = Cl

21, X = CN



19

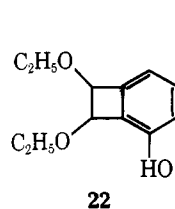


16

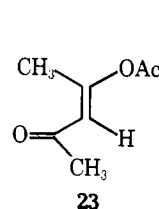
Z: = hydroquinone
derived from dienophile

MeOCl), providing 9 in ~40–50% yield.¹⁷ Other experimental modifications have thus far been unsuccessful in promoting the elimination of a second mole of HCl to produce 19. The substitution of CN for Cl in the dienophile, e.g., 21, in an effort to enhance its reactivity, surprisingly led to oxidation of the diene precursor 10b to 22 and the quantitative production of the hydroquinone derived from 21.¹⁸ This occurs in spite of the apparently low reactivity of 21 in previous dehydrogenation studies.¹⁹

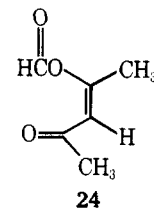
Preliminary attempts to extend this process to acyclic enol acetates such as 23 have been unsuccessful.²⁰ In these cases, energy depleting *cis*–*trans* isomerization may be preventing cycloaddition. Conceivably, proper choice of the protecting group, such as formate 24, may restrict rotation, and allow the



22



23



24

desired process to occur. We are presently investigating this as well as substituent effects on the photoreaction with substituted enol acetates and β -chloroenones, and applications of this chemistry to the total synthesis of polycyclic anthraquinone natural products.

Acknowledgment. We wish to thank the National Institutes of Health (National Cancer Institute) for the award of a research grant (CA-15061) in support of this research and for a Career Development Award to one of us (R.K.B.) (CA-00273).

Supplementary Material Available: Experimental Section of this paper (5 pages). Ordering information is given on any current masthead page.

References and Notes

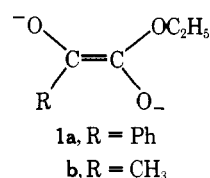
- (1) (a) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964), and references cited therein; (b) J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *ibid.*, **95**, 532 (1973); G. Buchi, J. A. Carlson, J. E. Powell, Jr., and L. F. Tietze, *ibid.*, **95**, 540 (1973); (c) R. S. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4645 (1966); (d) J. F. Bagli and T. Bogri, *ibid.*, 349 (1970).
- (2) (a) P. DeMayo, *Acc. Chem. Res.*, **4**, 41 (1971); (b) P. G. Sammes, *Q. Rev., Chem. Soc.*, **24**, 37 (1970); (c) P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968), cf. also ref 20.
- (3) (a) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965); (b) W. Oppolzer, *ibid.*, **93**, 3833, 3834 (1971); W. Oppolzer and K. Keller, *ibid.*, **93**, 3836 (1971); (c) B. J. Arnold and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1034 (1972); (d) M. E. Jung, *ibid.*, 956 (1974). (e) R. K. Hill and R. G. Carlson, *J. Org. Chem.*, **30**, 2414 (1965).
- (4) T. S. Cantrell, W. S. Heller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969).
- (5) The reactants were irradiated in anhydrous ether at room temperature with a medium-pressure lamp (Hanovia 450 W) through a corex sleeve. Typical irradiation times were 8–24 h. The enol acetate was purified by distillation to remove traces of acid, and all apparatus was washed with methanolic KOH, rinsed with methanol (anhydrous), and dried thoroughly.
- (6) Cantrell (cf. ref 4) reports only the formation of *trans*-**2** in ~45% yield. This substance was isolated from the crude product mixture by preparative VPC. This procedure undoubtedly led to loss of any *cis* adduct **2** via loss of acetic acid to **3**, opening to **4**, and decomposition. At no time did we isolate or characterize the *cis* adduct, although we cannot exclude its presence in the crude mixture and transformation to **3** during workup.
- (7) Alumina is known to catalyze the epimerization of trans-fused bicyclo[4.2.0]octan-2-one systems to the thermodynamically more stable *cis* system (cf. ref 1a). In this case elimination of acetic acid occurred simultaneously.
- (8) All new substances described have satisfactory spectral data [NMR, UV, and mass spectra (low resolution)] and analytical data or high resolution data. All yields refer to isolated and purified materials.
- (9) Spectral data. **5**: NMR δ 2–2.7 (m, 6H), 3.18 (s, 6H), 3.28 [s (br), 2H], 3.83 (s, 6H). **7**: NMR δ 2.30 (m, 2H), 2.90 (t, 2H), 3.30 (t, 2H), 3.98 (s, 3H), 8.18 (s, 1H). **8a**: NMR δ 2.16 (dt, 2H), 2.65 (t, 2H), 3.03 (t, 2H), 3.87 (s, 3H), 3.97 (s, 3H), 7.70 (dd, J_{ortho} = 8.0 Hz, 2H). **9**: NMR δ 2.23 (dt, 2H), 2.78 (t, 2H), 3.18 (t, 2H), 4.0 (s, 3H), 7.71 (dd, J_{ortho} = 6.0, J_{meta} = 3.0 Hz, 2H), 8.22 (dd, J_{ortho} = 6.0, J_{meta} = 3.0 Hz, 2H). **16**: NMR δ 2.26 (pentuplet, 2H), 2.83 (t, 2H), 3.23 (t, 2H), 8.30 (s, 1H), 9.03 (s, 1H). **7** was characterized by conversion to diester **6**.
- (10) The production of these photoadducts is particularly facile. An unusually low stoichiometric ratio of olefin to enone can be maintained, and high yields are still obtained. No evidence of significant amounts of oxetane formation by reaction with the solvent is seen; however, the yields are reduced markedly if corex-filtered UV is utilized as in the production of adducts **2**. Spectral data for **10b** [bp 113–120 °C (0.3 mm)]: NMR δ 1.25 (m, 6H), 2.00, 2.05 (s, 3H), 3.60 (m, 4H). **11b** NMR: δ 1.20 (m, 6H), 2.70 (d, 1H), 4.0 (d, 1H).
- (11) H. Hikino and P. DeMayo, *J. Am. Chem. Soc.*, **86**, 3582 (1964).
- (12) S. Arthur, Ph. D. Dissertation, University of California, Berkeley, Calif., 1976; cf. also ref 4 and T. Cantrell, *Tetrahedron*, **27**, 1227 (1970).
- (13) The structure of the photoproduct (*hv*/corex/ether) is supported by IR, NMR, and mass spectra (low resolution). Apparently, elimination is not unidirectional (both methanol and acetic acid are lost), and under the usual reaction conditions no Diels–Alder adducts are obtained.
- (14) (a) I. Fleming, F. L. Gianni, and T. Mah, *Tetrahedron Lett.*, 881 (1976); (b) K. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).
- (15) For example, daunomycin, adriamycin, the rhodomycins; cf. I. A. Scott and T. Devon, "Handbook of Naturally Occurring Compounds", Vol. 1, Academic Press, New York, N.Y., 1975.
- (16) If excess base is utilized, the yields are lowered. A variety of amine bases were investigated and all proved unsatisfactory due to incompatibility with the haloquinone at elevated temperatures.
- (17) This result may be due to the stereochemical orientation of the leaving groups and hydrogens in the intermediate Diels–Alder adduct. If the structure of the photoadducts have the alkoxy groups *cis*, the diene must be *cis,trans* and the resulting adduct has only 1 mol of HCl *trans* deposited and readily eliminated. This result could also arise by sequential loss of Cl₂ and methanol.
- (18) The structure of **22** is inferred from the quantitative production of the hydroquinone. Presently, we are attempting to trap the *o*-quinodimethane derived from **22**, which undoubtedly results from thermal opening of **22** under the reaction conditions.
- (19) G. A. Reynolds and J. A. VanAllen, *J. Org. Chem.*, **29**, 3591 (1964).
- (20) S. W. Baldwin, R. E. Gawley, R. J. Doll, and K. H. Leung, *J. Org. Chem.*, **40**, 1865 (1975).
- (21) Fellow of the Alfred P. Sloan Foundation (1976–1978).

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Alkoxy Enediolates

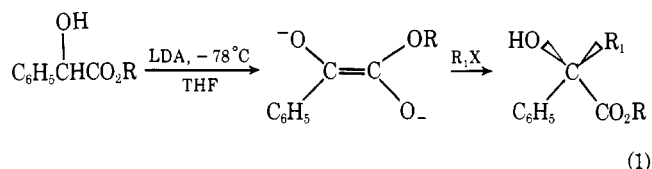
Summary: Multiple deprotonations of α -hydroxy esters by lithium diisopropylamide lead directly to alkoxy enediolates, which are useful as synthetic intermediates in electrophilic substitution reactions with primary and secondary alkyl halides and sulfonates to form disubstituted α -hydroxy esters, and with carbonyl compounds and ethylene oxide to form substituted glyceric acids and a substituted α -hydroxy- δ -butyrolactone, respectively.

Sir: In this communication we describe procedures for the preparation, characterization, and use of dianions derived from α -hydroxy esters by reaction with lithium diisopropylamide (LDA) in THF. The alkoxy enediolates (**1**)² prepared in this fashion can be used in reactions with a variety of alkylation reagents to form more complex α -hydroxy esters. Preliminary results indicate that carbonyl compounds and epoxides also react as electrophiles with the alkoxy enediolates. Oxidative decarboxylation of the product α -hydroxy acids derived from these esters by hydrolysis leads to carbonyl compounds and makes intermediates like **1** acyl anion



equivalents.^{3–6} While geminal enediolates from carboxylic acids⁷ and vicinal enediolates from α -hydroxy ketones⁸ have previously been prepared by deprotonation with LDA, alkoxy enediolates have not been prepared before. Enediolates are also postulated to be intermediates in the acyloin condensation.⁹

Alkoxy enediolates are synthetically useful in alkylation reactions such as eq 1, leading to disubstituted α -hydroxy



esters. These reactions are characterized by high isolated yields of products and can be utilized in a variety of systems as is shown by representative data in Table I. We find that primary alkyl iodides, bromides, tosylates, and mesylates work about equally well as alkylating agents in these reactions, but a less reactive primary alkyl chloride is unsatisfactory. Extension of these reactions to secondary systems shows that even cyclohexyl iodide, which is prone to elimination reactions, reacts with enediolate **1a** to give a 66% yield of ethyl cyclohexylhydroxyphenylacetate. Preliminary work indicates that these reactions are tolerant of some functional groups in the alkylating agent. For example, we have successfully used both allyl bromide and ethyl bromoacetate as reagents in reactions with **1a**. Halides known to be unreactive in S_N2 reactions (e.g., tertiary and aryl halides) do not react with alkoxy enediolates.

Although most of our initial work has concerned reactions of enediolate **1a**, we have also examined enediolates in which the phenyl group of **1a** has been replaced by either a methyl or a hydrogen. While enediolates derived from ethyl lactate and iodides, similar reactions with ethyl glycolate (**1**, R = H) fail. In both of these cases, elimination of HX from the alkyl halide to form alkene or possibly decomposition of the alkoxy enediolate is a limitation of these reactions. Addition of