Steroid Photochemistry. Facile [4 + 2] Adduct Formation in the Photocycloaddition of an Enedione to Olefins and Dienes[1]

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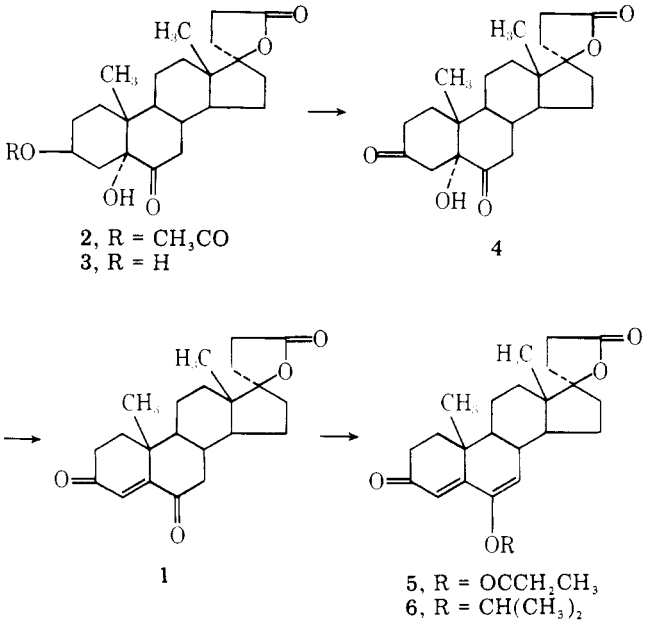
The photocycloaddition of a 4-ene-3,6-diketo steroid to the olefins cyclopentene and dihydropyran and to the dienes 2,3-dimethylbutadiene, 1,3-cyclohexadiene, and 4-methyl-1,3-pentadiene is described. The predominant reaction is a [4 + 2] cycloaddition involving the olefin and the 4-en-6-one of the steroid to form a dihydropyran. Initial bond formation occurs between C-4 of the steroid and the olefin or diene to form the most stable diradical. Accompanying the dihydropyran adducts are also varying amounts of the [2 + 2] adducts between the double bond of the steroid and the olefin or diene. These [2 + 2] adducts are also head-to-tail adducts. The photocycloaddition proceeds through the triplet excited state since it is quenched by 3,3,4,4-tetramethyl-1,2-diazetidine 1,2-dioxide. The formation of all of the photoproducts can be rationalized by initial formation of a diradical intermediate. Some of the dihydropyran [4 + 2] adducts are readily transformed into dienones by the action of base via an intermediate 6β-hydroperoxide. This hydroperoxide has been isolated from chromatography of the 2,3-dimethylbutadiene adduct, and both it and the precursor dihydropyran are converted into the 3-keto-4,6-diene. When these dienones are treated with methanolic hydrochloric acid, they are converted, in varying amounts, into the 5-methoxyenone.

The 4-ene-3,6-dione chromophore is one of the oldest known polyfunctional systems in steroids and formed a fascinating chapter in early steroid chemistry.[2] Despite its ready accessibility, very few investigations have been concerned with the photochemistry of this grouping, not only in steroids but also in simpler molecules. Hikino and Takeshita reported that cholest-4-ene-3,6-dione efficiently abstracted hydrogen from the solvent when irradiated to form cholestane-3,6-dione. Irradiation in cyclohexane additionally yielded 4ξ-cyclohexyl-5ξ-cholestane-3,6-dione.[3] The irradiation of 4-cyclopentene-1,3-dione in the presence of olefins has been reported to yield only oxetanes,[4] while 2-cyclooctene-1,4-dione underwent cis–trans isomerization and then subsequent thermal reactions.[5,6] The photocyclization and intramolecular hydrogen abstraction reactions of benzoquinone Diels–Alder adducts have been extensively studied by Scheffer and have led to the synthesis of a variety of unusual polycylcic systems.[7] We would like to report on our studies on the photocycloaddition of a steroidal enedione to various olefins and dienes, which lead to a facile dihydropyran synthesis via [4 + 2] cycloadditions. The results obtained herein also differ from the earlier Japanese work on the initial point of bond formation.[3] Perhaps the pertinent prior studies on enediones were reported by Barltrop and Giles, who studied the photocycloaddition of various tricyclic cyclohexene-1,4-diones to olefins and acetylenes.[8] Because of the geometry of the enedione studied, only cyclobutanes and cyclobutenes were obtained. Quenching experiments indicated that the reaction was proceeding through a moderately electrophilic low lying π,π^* triplet with an energy of approximately E_T = 58 kcal/mol.

The enedione **1** was formed from the 3-acetoxy-5-ene precursor via epoxidation, hydrolysis, and Jones oxidation to the ketol **2**. The ketol was saponified to the dihydroxy ketone **3**, which was oxidized to the hydroxydione **4**.[9] Elimination of water with alumina in refluxing toluene furnished the enedione **1** in 72% overall yield from **2**. It is known that a 6-ketone allows elimination of the 5α-hydroxyl group to the olefin without competing Westphalen backbone rearrangements.[10] The enedione **1** has a π,π^* absorption at 248 nm and a $n\pi^*$ band at 345 nm which tails out to 425 nm, giving **1** a faint yellow color. The selective enolization of the 6-ketone allowed the ready preparation of 6-hydroxy derivatives of the 3-keto-4,6-dienone.[11] Reaction of **1** with propionic anhydride in benzene, using acid catalysis, yielded the enol ester **5** in 89% yield. The UV spectrum of **5** (λ_{max} 283 nm) was very similar to the unsubstituted linear 3-keto-4,6-diene (282 nm),[12] but



had only half of its intensity. However, when the 2-propyl enol ether **6** was prepared from **1** in acidic 2-propanol, the UV spectrum of **6** was substantially different than that of **5**, having maxima at 250 and 307 nm with the latter being more intense. This characteristic UV spectrum was later very helpful in assigning the structures of the thermal conversion products of the primary [4 + 2] dihydropyran adducts.

The photocycloaddition of **1** to cyclopentene was studied first because the symmetry of the olefin would facilitate the assignment of structure to the adducts and permit a general outline of the photoreactivity of the enedione. Irradiation of **1** in the presence of cyclopentene generated two photoproducts which were readily separated by column chromatography. The major adduct (**7**) was identified as a dihydropyran, the result of a [4 + 2] cycloaddition, on the basis of its spectral properties and its subsequent chemical transformations. Compound **7** possessed an unconjugated ketone (1725 cm^{-1}) and an enhanced double-bond absorption (1680 cm^{-1}), suggesting an enol ether. The NMR spectrum showed the hydrogen α to the ether at δ 3.83 and the tertiary axial 4β-hydrogen, which is α to the 3-ketone and 5 double bond, at δ 3.08. The double bond was fixed at the 5,6 position when the mass spectrum, in addition to possessing a parent peak at *m/e* 424, showed a reverse Diels–Alder reaction at *m/e* 218, the

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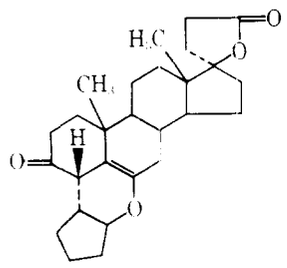

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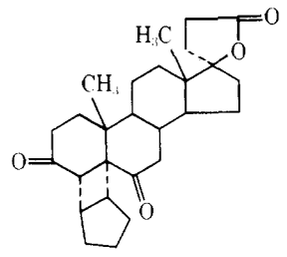

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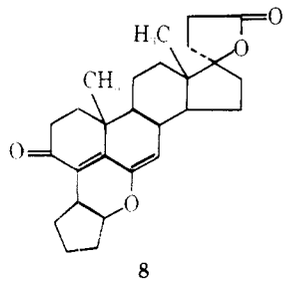

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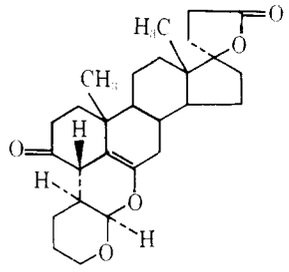
result of splitting the steroid skeleton between carbon atoms 7 and 8 and 9 and 10. Finally, the configuration of the newly formed carbon–carbon bond in **7** was shown to be α, with a 4β-hydrogen, by its positive ORD and CD spectra. We have assumed cis addition to cyclopentene by the excited steroid based on ample literature precedent[13] and subsequent results with dihydropyran and cyclohexadiene, where this could be demonstrated. Although the chromophore in compound **7** is a β,γ-enone, and as such is dissymmetric, there is some evidence that the ketone octant rule is applicable.[14] In this case, for 4α substitution the two groups would be expected to reinforce one another and yield a large chiroptical effect which, in fact, is what is observed. In the unlikely event that the substitution were 4β, this would force the A ring into a twist-boat conformation which would significantly lower the chiroptical effect and additionally also substantially deshield the 10-methyl group, neither of which is observed.

When conjugation of β,γ-enone to the α,β-enone was attempted with sodium methoxide, a new product (**8**) was isolated in 82% yield. The compound was shown to be the dienone **8** rather than the expected enone on the basis of its elemental analysis and physical properties. The IR spectrum showed the characteristic dienone absorptions at 1670, 1645, and 1600 cm^{-1}. The NMR spectrum of **8** was not particularly instructive, but did show the cyclopentane ether hydrogen at δ 4.12. The newly formed C-7 vinylic proton occurred as a doublet at δ 5.47 due to coupling with the axial 8β-hydrogen. The clinching evidence for the dienone structure for **8**, however, was when its UV spectrum (λ_{max} 266 and 311 nm) was found to be identical with the isopropyl enol ether **6** of the starting enedione **1**. The dienone **8** was detected in the mother liquors from the crystallization of **7**, but was not in the originl irradiation solution, indicating that it was formed during chromatography. The formation of the dienone occurred through the 6-hydroperoxide and will be discussed in light of the other experimental results.

The second photoproduct (**9**) was isolated in 30% yield and identified as the [2 + 2] adduct of cyclopentene and the C-4,5 double bond. The cyclobutane adduct could be recovered unchanged after refluxing in methanolic sodium methoxide, indicating a cis ring fusion. The ORD and CD spectra of **9** were complex. However, the CD spectra of 5α- and 5β-3,6-diones allow the unambiguous assignment of configuration,[15] and because of this **9** was assigned the 4α,5α-*cis*-cyclobutane structure. This particular configuration has been found in all of the steroidal enone cycloadditions studied.[16] A Dreiding model of **9** indicates that the equatorial 4β-hydrogen is coplanar with the 6-keto group and 2.55 Å removed. As a result, in its NMR spectrum this proton is strongly deshielded and occurs as a doublet at δ 3.17.

When the enedione **1** was irradiated in the presence of dihydropyran, only one [4 + 2] adduct was formed in 16% yield (36% based on recovered **1**). The adduct was isolated by chromatography and shown to have the structure **10** based on



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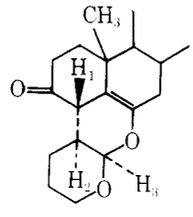
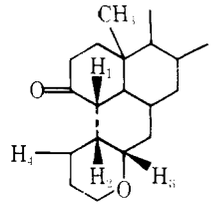
its spectral properties. The infrared spectrum indicated the presence of the unconjugated ketone and the enolic double bond. The ORD spectrum demonstrated that the stereochemistry at C-4 was α, the same as was found for its analogue **7**. The NMR spectrum allowed the assignment of stereochemistry in the pyran ring. Inspection of the two possible trans arrangements of the hydrogens on models indicated dihedral angles of 175–180°, which would lead to a large coupling constant. The two cis arrangements of the protons form a 60° dihedral angle, which indicates a coupling constant of 2.5 Hz.[17] The acetal proton in **10** occurs at δ 4.83 with a coupling constant equal to 2.5 Hz indicating a cis addition of the enedione to dihydropyran.

There was virtual coupling between the 4β-hydrogen and its vicinal proton. However differential Eu(fod)$_3$ shifts allowed the observation of the 4β-hydrogen as a doublet (J = 7.5 Hz). Within the constraint of the demonstrated cis addition of the enone to dihydropyran, both the cis and trans isomers (between H_1 and H_2) of the newly formed dihydropyran ring can exist in stable strain-free chair configurations. Measurement of the dihedral angles on Dreiding models indicated an angle of 65° between H_2 and H_3 for both the cis (B) and trans (A)



A ($\angle_{1,2}$ = 150°, $\angle_{2,3}$ = 65°)



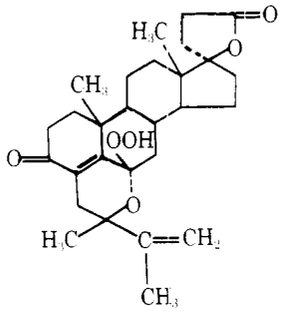
B ($\angle_{1,2}$ = 30°, $\angle_{2,3}$ = 65°)

isomers, which is in accord with the measured coupling constant (J = 2.5 Hz). Measurement of the dihedral angles between H_1 and H_2 in the trans (A) and cis (B) isomers yielded angles of 150 and 30°, respectively. Calculation of the expected coupling constant using the Karplus equation yielded J = 7–8 Hz for both angles. Therefore, there is no convenient NMR method of unequivocally demonstrating the stereochemical relationship between the 4β-proton (H_1) and its vicinal proton (H_2). We note, however, that in the all cis structure B the equatorial β-hydrogen labeled H_4 is coplanar with the 3-carbonyl group and only 1.8 Å removed from it. As a result we would have expected that this proton would be significantly shifted downfield and observable in the NMR spectrum. Compare the downfield shift observed for the 4β-hydrogen in the [2 + 2] adduct **9**, which is coplanar with the 6-carbonyl group and 2.55 Å distant. As a result, we tentatively favor structure A, where the stereochemistry is trans, over the

earlier favored all-cis arrangement.[1] This structure also has the advantage of permitting the formation of cis [2 + 2] adducts in the usual exo configuration,[13] utilizing a common intermediate, a diradical formed by initial coupling at C-4. Attempted conjugation in the same manner as **7** led to degradation of **10**, presumably due to the additional reactive center at the ketal hydrogen. The chromatography fractions presumably containing the cyclobutane adducts were shown to contain at least five closely moving compounds which were not separated on chromatography and, as a result, were not further investigated.

After the olefin cycloadditions had been studied, we next turned to the various types of dienes and have investigated the *s*-trans Diels–Alder diene 2,3-dimethylbutadiene,[18] the *cis*-diene 1,3-cyclohexadiene, and the non-Diels–Alder *s-trans*-diene 4-methyl-1,3-pentadiene.[19]

The addition of **1** to 2,3-dimethylbutadiene proceeded rapidly to generate one major and a number of minor adducts. Chromatography separated the major product which now, however, possessed a slightly different R_f value than the original adduct. Elemental analysis indicated that **11** was an adduct of **1**, diene, and oxygen. A hydroperoxide was indicated when **11** gave a positive starch–iodide test.[20] The infrared and



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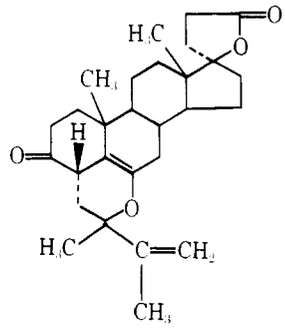

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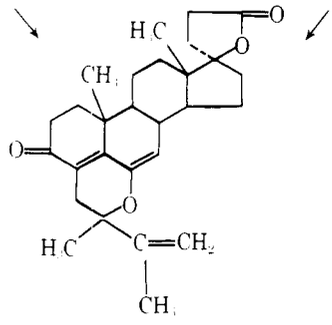

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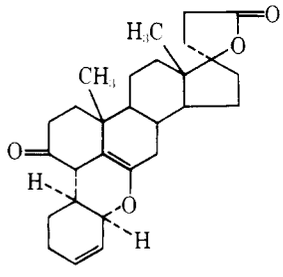
ultraviolet spectra indicated the presence of a 3-keto-4-ene grouping, permitting the assignment of the hydroperoxy group to C-6. The NMR spectrum allowed the structural assignment of the rest of the adduct. A 1,2 addition on the symmetrical diene was shown by the resonances for a tertiary methyl group and an isopropylene group. Based on these data, compound **11** was assigned the novel hydroperoxy hemiketal structure shown. The stereochemistry about the hemiketal was assigned based on the known axial attack by oxygen on steroidal allyl radicals.[21] It should also be emphasized that **11** possesses stereochemical integrity. Although four isomers are possible due to the hemiketal and to the methyl and isopropylene groups, only a single isomer was obtained.

In an identical experiment where the chromatography was conducted faster it was possible to isolate the primary photoproduct **12**. Again, it was found that only one of the two possible epimers was formed. When either the hydroperoxide **11** or the β,γ-enone **12** was stirred with sodium methoxide in methanol, both were converted into the dienone **13**. The dienone **13** was characterized by, among other things, its typical ultraviolet spectrum and the presence of the C-7 olefinic proton as a doublet due to coupling with the axial 8β-hydrogen.

The addition of the enedione **1** to 1,3-cyclohexadiene proceeded readily to generate a number of adducts which were partially separated by chromatography. The initial compound isolated (**14**) was the β,γ-enone, which was assigned the dihydropyran structure, the result of a [4 + 2] cycloaddition, rather than the equally plausible [4 + 4] adduct on the basis of its NMR spectrum. The hydrogen α to the ether oxygen in **14** appears as a triplet at δ 3.83, with a coupling constant of J



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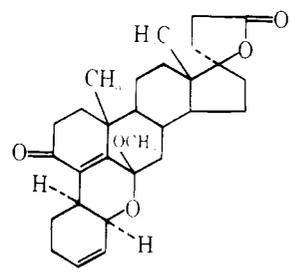

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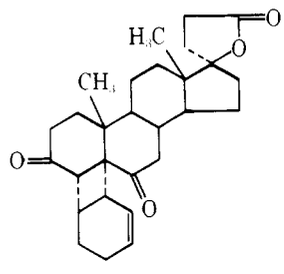

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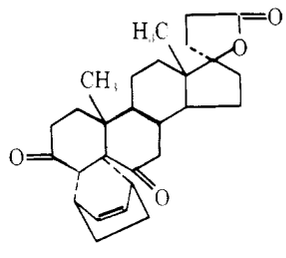

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= 3 Hz, due to coupling with the adjacent vinyl proton and the vicinal tertiary proton. In the [4 + 4] adduct, the α-ether hydrogen would be coupled to three vicinal protons and would appear as a more complex splitting pattern. Additionally, the small value for the coupling constant between the protons on the newly formed dihydropyran ring demonstrated a cis addition, which was also found in the addition of **1** to dihydropyran.[17]

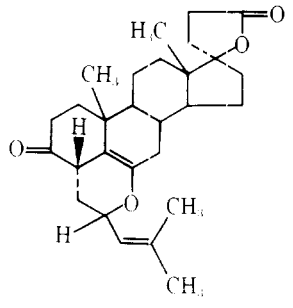
Closely following **14** was either the hydroperoxide or the dienone related to it. When crystallization was attempted from methanol–water, an emulsion formed. After a few drops of acetic acid were added to break the emulsion, a new product rapidly crystallized. The IR and UV spectra indicated the presence of an enone while the NMR spectrum demonstrated the presence of a methoxyl group. These data indicated that a derivative of **14** had been converted into the methoxyl ketal **15**, probably via the dienone. Treatment of the dimethylbutadienedienone **13** with methanol containing hydrochloric acid partially converted it into the ketal analogue of **15**. Reaction of the β,γ-enone **14** with sodium methoxide in methanol, followed by acidification, also formed the ketal **15**.

In this case, as opposed to dimethylbutadiene, it was possible to isolate the steroidal C-4 double bond adducts. The [2 + 2] adduct **16** was isolated in 29% yield, and its structural assignment as a cyclobutane rests primarily on its NMR spectrum. The 4β-hydrogen was shifted downfield, in a manner similar to **9**, due to the proximity of the 6-ketone and appeared as a doublet. However, underlying this signal was another broad signal which integrated for one proton. This signal was resolved upon running the spectrum in deuteriobenzene and appeared as a broad quartet at δ 2.89 while the 4β-hydrogen appeared as a doublet (J = 5 Hz) at δ 3.67. This quartet was assigned to the tertiary allylic cyclobutane proton

in 16 since we had previously shown that this type of proton appeared at low field.[12] The configuration of the adduct 16 was shown to be 4α,5α by its CD spectrum and the lack of epimerization by sodium methoxide in methanol.

Closely following 16 was a second adduct involving the double bond of the enedione, and it appears to be the [4 + 2] adduct 17. The NMR spectrum again showed a strongly deshielded 4β-hydrogen due to the proximity to the 6-ketone and a two-proton multiplet shifted slightly out of the methylene envelope which was assigned to the bridgehead protons in the bicyclic system. The CD spectra of compounds 16 and 17 also support the structural assignments. We have previously shown that the presence of a cyclobutane ring substantially flattens the A ring and causes the chiroptical effects to be substantially reduced.[16a] The CD spectrum of the [2 + 2] adduct 16 is approximately one-tenth the intensity of the [4 + 2] adduct 17.

The final diene studied was the *s-trans*-4-methyl-1,3-pentadiene, and the photocycloaddition with 1 again proceeded to yield a dihydropyran adduct (18) and a cyclobutane (19) each in 30% yield. The dihydropyran adduct 18 was assigned the structure indicated when its NMR spectrum indicated an olefinic proton at δ 5.28 and two vinyl methyl groups at δ 1.73 while the other spectral data were consistent with a β,γ-enone. The structure of the [2 + 2] adduct 19 was readily assigned when the NMR spectrum showed the 4β-hydrogen as a doublet of doublets at δ 3.72 and the allylic cylobutane proton as a hextet at δ 3.22 while two vinyl methyl groups resonated at δ 1.66. Investigated of the mother liquors from the crystallization of 19 indicated the probable presence of a small amount of its epimer.[12]



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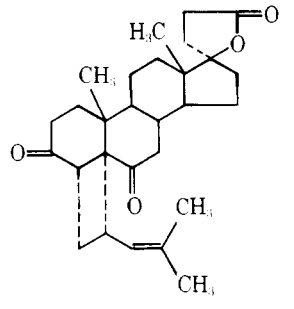

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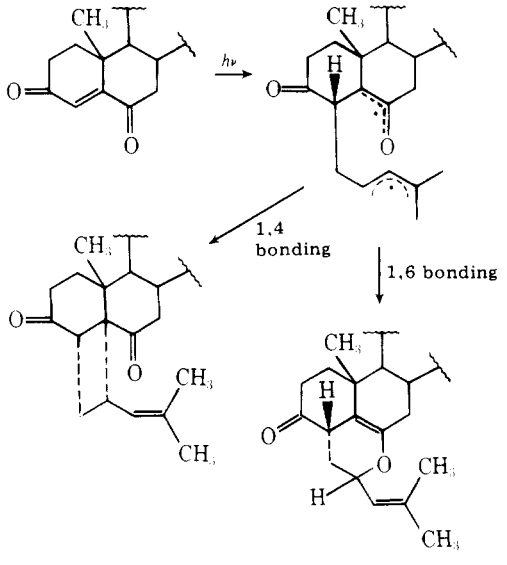
Quenching studies were conducted using Ullman's quencher, 3,3,4,4-tetramethyldiazetidine 1,2-dioxide, on the cycloaddition of 1 to cyclopentene.[22] While both the enedione 1 and the dihydropyran adduct 7 were stable to GLC conditions, unfortunately the cyclobutane adduct 9 was not. However, when the formation of the dihydropyran adduct 7 was measured in the absence and presence of the quencher, a significant reduction in the rate of formation of 7 was obtained with the quencher present. These results indicated that the cycloaddition reactions of the enedione were proceeding through its triplet state, as is common with most enone photocycloadditions.[23]

Discussion

Since the majority of enone cycloaddition reactions occur through their triplet excited states via the intermediacy of a biradical,[23] the majority of the chemistry of the dienone can be discussed in terms of this intermediate. The cycloadditions of 1, although somewhat more complex than the simpler steroidal enones,[16] also occur through its triplet state.

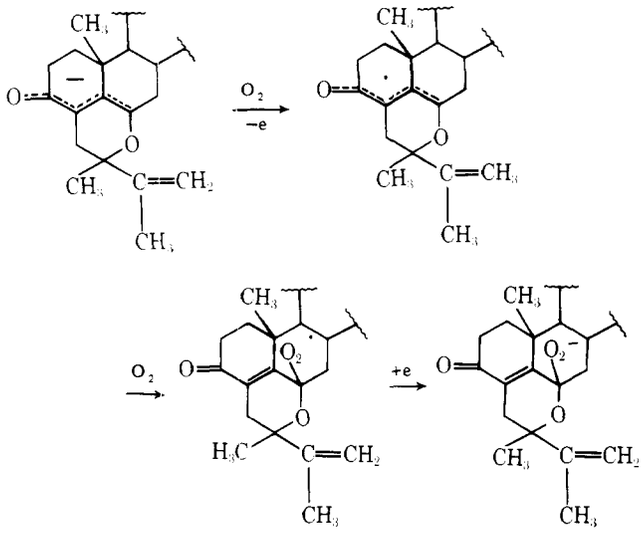
The reactive state is most probably a π,π* triplet since extending the conjugation strongly lowers the energy levels of the π,π* states while only slightly affecting the energies of the n,π* states.[24] Barltrop and Giles found phosphorescence from the 1,4-cyclohexenedione which they studied and determined that the lowest lying triplet state was π,π* and possessed an energy of 57.8 ± 1.2 kcal/mol.[8] This energy was in keeping with their finding that energy transfer to the dienes studied was competitive with cycloaddition. The energy level of the triplet state in the *trans,cis*-enedione 1 lies below ~55 kcal/mol because this enedione reacts readily with the dienes studied, whose triplet energies are equal to or greater than 59 kcal/mol.[25] The most stable conformation of a π,π* triplet state is not planar but involves twisting about the double bond to give, in the extreme, an orthogonal triplet with a minimum of overlap between the π orbitals.[26] Calculations have shown that in rigid enones the angle of twist needed to attain the energy minimum falls rapidly and is quite small in the steroidal enone testosterone.[26] Based on the chemical evidence now available for steroidal enones[16] and linear dienones,[27] and from the present study on enediones, in the π,π* triplet a stereospecific twisting occurs with the olefinic 4-hydrogen rotating into the β face of the A ring of the steroids. This then presents a more accessible π orbital (at C-4) on the α face of the steroid to the approaching addend. Bond formation can then occur between the C-4 atom of the olefin or diene to generate the more stable diradical. Ring closure can then occur to form either the cyclobutane or the dihydropyran by coupling between the allylic radical and either the carbon (1,4 bonding) or the oxygen (1,6 bonding) of the oxa-allylic radical, respectively. In this mechanism, all of the photoproducts can be derived through a common intermediate. Although the resultant β,γ-enones are reactive thermally, readily forming the novel hydroperoxide hemiketal, it is very surprising that they are also relatively stable to irradiation since these enones are known to be very reactive photochemically.[28] Although the excess diene used as the olefinic component in some of the cycloadditions could quench the triplet sensitized oxadi-π-methane reaction, no such possibility is present in the cycloadditions involving the simple olefins.[28] Apparently both the singlet and triplet reactions of these oxygen-substituted β,γ-enones are not competitive with the quantum yield for formation of the initial photoproducts. There are usually a variety of additional products formed in small amounts, but it is not known whether these are hydrogen abstraction products, reaction products of the β,γ-enones, or both.



It is also interesting to compare the results obtained in this study with the reported photoreduction of enediones.[3] All of the results obtained from the photocycloadditions of 1 are consistent only with initial bonding between C-4 and an olefin or diene, while the radical abstraction from cyclohexane has been reported to yield the 4-cyclohexyl-3,6-dione. If the structure of this compound is correct, then this implies that

the C-5 atom is abstracting the hydrogen from cyclohexane to form a C-4 radical, which is the direct opposite of what would be expected based on the structures of the photoproducts in our study.

The conversion of β,γ-enones into γ-hydroperoxy-α,β-enones is well known in steroid chemistry,[21] and the conversion of dihydropyran photoadducts into dienones is readily understandable in terms of these intermediates. Thus, the enolate derived from the [4 + 2] adduct **12** reacts with oxygen



to form the delocalized radical, which in turn adds oxygen to form the hydroperoxy radical at the 6β position. The conjugation of the double bond with the carbonyl group is undoubtedly the reason for the formation of the carbon–oxygen bond of the hydroperoxide at C-6. The hydroperoxy radical is then reduced by additional enolate anion to the hydroperoxide anion; thus, propagating the chain reaction.[29] Elimination of the tertiary hydroperoxide group by base either intramolecularly or intermolecularly then forms the dienone. The formation of the dienone **13** from both the hydroperoxide **11** and the β,γ-ketone **12** strongly supports the above mechanism.

Experimental Section

General. Melting points were taken in open capillary tubes on a Thomas-Hoover Uni-Melt capillary apparatus and are uncorrected. IR spectra were recorded in KBr pellets unless otherwise noted, and UV spectra were run in methanol and are not reported if only n → π^* absorption was observed. A Varian Associates A-60, T-60, or HA-100 spectrometer was used to record spectra. All spectra were run in deuteriochloroform using tetramethylsilane as an internal standard, unless otherwise noted, and are reported as chemical shift (δ) followed by a first-order analysis of the splitting pattern, the coupling constant in hertz when appropriate, and then the integrated signal intensity. ORD and CD spectra were obtained on methanol solutions in a Jasco ORD/UV-5 spectrometer, and mass spectra were run on a MS-30 mass spectrometer under the direction of Dr. Jeremy Hribar. Elemental analyses were conducted by the Searle Laboratories Microanalytical Service, Mr. E. Zielinski, Director.

17β-Hydroxy-3,6-dioxoandrost-4-ene-17α-propionic Acid γ-Lactone (1). A solution of 50 g (0.12 mol) of **2** (3β,5α,17β-trihydroxy-6-oxoandrostane-17α-propionic acid γ-lactone 3β-acetate)[30] was stirred magnetically and 30 g of sodium methoxide was added. After 4 h, a thick slurry had formed which was diluted to 2 L with distilled water, and 100 mL of concentrated hydrochloric acid was added. The precipitated dihydroxy ketone was filtered and washed with distilled water until neutral. After being dried the dihydroxy ketone was partially dissolved in 2 L of analytical reagent acetone and oxidized with 35 mL (140 equiv) of Jones reagent at 0 °C. TLC indicated incomplete oxidation, and an additional 10 mL (40 equiv) of Jones reagent was added. After a further 15 min, excess oxidant was quenched with excess 2-propanol, and 0.5 L of distilled water was added. After the acetone was removed on a rotary evaporator, the 5α-hydroxy-3,6-dione was filtered and washed with water until both the steroid and filtrate were colorless. The material was dried at 45 °C in a vacuum overnight to yield 37.3 g of 5α,17β-dihydroxy-3,6-dioxoandrostane-17α-propionic acid γ-lactone.[30] The hydroxydione was dissolved in 750 mL of toluene in a 2-L three-neck flask equipped with a mechanical stirrer. After the addition of 100 g of Woelm alumina, the rapidly stirred solution was brought to reflux. After 1 h, TLC indicated complete consumption of starting material and the reaction mixture was filtered hot. The alumina was extracted with 750 mL of chloroform in portions. The combined organics were evaporated, and the residue was crystallized from ether to yield 28.15 g (0.086 mol, 72%) of **1** as light yellow crystals: mp 221–223 °C; IR ν 1780 (γ-lactone), 1690, 1605 (enedione) cm^{-1}; UV 220 nm (end, ϵ 13 000), 231 (min, 10 750), 248 (12 250), in benzene **1** shows a n → π^* absorption at 345 nm (ϵ 120) which tails to 425 nm; NMR δ 6.21 (s, 1 H, C-4 H), 1.21 (s, 3 H, C-19 H), 1.02 (s, 3 H, C-18 H); MS *m/e* (%) 356 (parent, 27).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.08; H, 7.91.

Selective Formation of the 6-Enol Propionate 5 of Enedione 1. A solution of 1.00 g (2.81 mmol) of **1** in 25 mL of dry benzene was stirred with 4 mL of propionic anhydride and 0.25 g of *p*-toluenesulfonic acid monohydrate. After 24 h, the majority of the starting material had been converted into a single product as shown by TLC on silica (development with ethyl acetate and visualization using phosphomolybdic acid in ethanol spray). A further 24 h was required to complete the reaction, at which time 4 mL of pyridine and 10 mL of methanol were added to destroy excess anhydride and neutralize the acids. The solvents were removed on a rotary evaporator, and the residue was dissolved in ethanol and slowly diluted with water to yield 1.03 g (2.5 mmol, 89%) of **5**: melting point softens 195 °C, melts 210–211 °C; IR ν 1775 (γ-lactone), 1760 (enol propionate), 1680, 1650 sh, 1615 (dienone) cm^{-1}; UV 283 nm (ϵ 15 000); NMR δ 5.80 (s, 2 H), 1.28 (s, 3 H, C-19 H), 1.03 (s, 3 H, C-18 H).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.81; H, 7.99.

Selective Formation of the 6-Isopropyl Enol Ether 6 of Enedione 1. A suspension of 500 mg (1.40 mmol) of **1** in 50 mL of 2-propanol containing 0.25 g of *p*-toluenesulfonic acid monohydrate (PTSA) was stirred magnetically. After 2 h, a second portion of 1 g of PTSA was added and stirring was continued for a further 22 h. After the addition of 2 mL of pyridine, the reaction mixture was diluted with water and the majority of the alcohol was removed on a rotary evaporator. The white crystalline precipitate was filtered, washed with distilled water, and dried to 0.55 g (1.38 mmol, 99%) of **6**: mp 188–190 °C; IR ν 1775 (γ-lactone), 1670, 1630, 1595 (dienone) cm^{-1}; UV 250 nm (ϵ 8000), 307 (13 500); NMR δ 6.33 (s, 1 H, C-4 H), 5.23 (d, $J \cong 2$ Hz, 1 H, C-7 H), 1.27 (d, $J \cong 6$ Hz, 6 H, isopropyl methyl groups), 1.17 (s, 3 H, C-19 H), 1.07 (s, 3 H, C-18 H).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.61. Found: C, 75.25; H, 8.81.

Photocycloaddition of Enedione 1 to Cyclopentene. The enedione **1** (4.00 g, 11.2 mmol) was dissolved in 165 mL of toluene by gentle warming, and the solution was placed in a 200-mL Pyrex irradiation vessel. After the addition of 35 mL of cyclopentene, the solution was irradiated under argon with a Hanovia 450-W medium-pressure mercury arc. After 3 h, TLC indicated the consumption of starting material and the presence of two photoproducts. The solvents were removed under reduced pressure on a rotary evaporator, and acetone was added. Immediately crystallization occurred and filtration yielded 1.551 g of the faster moving photoproduct **7**. The residue, after evaporation of the mother liquor, was chromatographed on 500 g of CC-7 silica, using ethyl acetate–petroleum ether combination as eluants. Elution with a 1:4 ratio of solvent gave an additional 475 mg of **7**: total 2.026 g (4.78 mmol, 43%); mp 217–219 °C; IR ν 1785 (γ-lactone), 1725 (C-3 cyclohexanone), 1685 (enol double bond) cm^{-1}; NMR δ 3.83 (broad s, 1 H), 3.08 (broad s, 1 H), 1.23 (s, 3 H, C-19 H), 0.98 (s, 3 H, C-18 H); $[\alpha]^{25}_D$ −95.5 ± 3° (*c* 0.112, $CHCl_3$); ORD $[\phi]_{317}$ +6160°, $[\phi]_{306}$ 0°, $[\phi]_{255}$ −12 970°; *a* = +191; CD $[\theta]_{302}$ +14 860°; MS *m/e* (%) 424 (parent, 64), 409 (–C-19 methyl, 100), 381 (–C_3H_7, 56), 367 (–15 and –42, 36) 218 (reverse Diels–Alder reaction between B,C rings, 28).

Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.56. Found: C, 76.46; H, 8.80.

TLC examination of the mother liquor after crystallization of **7** showed the presence of the dienone **8** and another faster moving spot, indicating that thermal reactions had occurred during column chromatography.

Elution with a 1:7 solvent combination yielded 755 mg of a solid, which TLC indicated was at least six closely moving compounds. As

a result this fraction was not further investigated.

Elution with a 1:1 solvent combination furnished 1.421 g (3.35 mmol, 30%) of the cis-4α.5α [2 + 2] adduct **9**: melting point turns brown at 250 °C, melts 272–274 °C; IR ν 1780 (γ-lactone), 1715 (C-3,6 dione) cm^{-1}; NMR δ 3.17 (d, J = 6 Hz, 1 H), 0.95 (s, 3 H, C-18 H), 0.69 (s, 3 H, C-19 H); $[\alpha]^{22}_D$ 0.0° (c 0.107, ($CHCl_3$)); ORD $[\phi]_{325}$ +680°, $[\phi]_{319}$ 0°, $[\phi]_{315}$ −380°, $[\phi]_{313}$ 0°, $[\phi]_{309}$ +550°, $[\phi]_{305}$ +340°, $[\phi]_{299}^{sh}$ +2270°, $[\phi]_{289}$ +3140°; CD $[\theta]_{338}$ −170°, $[\theta]_{324}$ +300°, $[\theta]_{321}$ 0°, $[\theta]_{316}$ −1020°, $[\theta]_{312}$ −765°, $[\theta]_{306}$ −1995°, $[\theta]_{299}$ −900°, $[\theta]_{295}$ 0°, $[\theta]_{281}$ +600°, $[\theta]_{263}$ +3050°; MS m/e (%) 424 (parent, 10), 409 (−CH_3, 19), 396 (−C_2H_4, 19), 381 (−CH_3 and −C_2H_4, 17), 358 (−cyclopentadiene, 100), 357 (−cyclopentadiene H, 62).

Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.07; H, 8.61.

Elution with ethyl acetate returned 393 mg (10%) of starting enedione **1**.

Attempted Epimerization of the [2 + 2] Adduct 9. A solution of 319 mg of **9** in 50 mL of 2% sodium methoxide in methanol was stirred magnetically and refluxed under argon for 17.5 h. After acidification with dilute hydrochloric acid and dilution with distilled water, the methanol was removed on a rotary evaporator and the resultant solid was filtered. Drying returned 282 mg of starting material.

Preparation of Dienone 8 from the [4 + 2] Adduct 7. To a solution of 346 mg (0.82 mmol) of **7** in 100 mL of methanol was added 1 g of sodium methoxide, and the mixture was protected from moisture with a calcium chloride drying tube and stirred overnight. After the addition of 5 mL of concentrated hydrochloric acid and 5 mL of distilled water, the majority of the methanol was removed using a rotary evaporator. Further dilution with water caused the dienone **8** to crystallize. Filtration and drying yielded 284 mg (0.67 mmol, 82%) of **8**: mp 140–145 °C; IR ν 1780 (γ-lactone), 1670, 1645, 1600 (dienone) cm^{-1}; UV 311 nm (ε 12 250), 266 (5000); NMR δ 5.47 (d, $J \cong 2.5$ Hz, 1 H, C-7 H), 4.12 (m, 1 H), 1.14 (s, 3 H, C-19 H), 1.04 (s, 3 H, C-18 H); $[\alpha]^{25}_D$ −58° (c 0.103, $CHCl_3$).

Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.63; H, 8.05.

Photocycloaddition of Enedione 1 to Dihydropyran. The enedione **1** (4.00 g, 11.2 mmol) was dissolved by heating in 165 mL of toluene, and then 30 mL of dihydropyran was added. The solution was placed in a Pyrex irradiation vessel and irradiated with a 450-W mercury arc while passing a stream of argon through the solution. After 3.75 h, the irradiation was stopped, the solvent removed, and the residue chromatographed on 600 g of CC-7 silica. Elution with ethyl acetate–petroleum ether (3:7) gave 777 mg (1.8 mmol, 16%) of the [4 + 2] adduct **10**: mp 248–252 °C (ether–petroleum ether); IR ν 1775 (γ-lactone), 1725 (cyclohexanone), 1690 (enol double bond) cm^{-1}; NMR δ 4.83 (d, J = 2.5 Hz, 1 H), 3.50–4.17 (m, 2 H), 1.25 (s, 3 H, C-19 H), 0.98 (s, 3 H, C-18 H); NMR (C_6D_6) δ 5.12 (d, J = 2.5 Hz, 1 H), 3.33–4.17 (m, 2 H), 2.83 (m, 1 H), 2.55 (m, 1 H), 0.92 (s, 3 H), 0.83 (s, 3 H); $[\alpha]^{25}_D$ −65.3° (c 0.101, $CHCl_3$); ORD $[\phi]_{317}$ +6080°, $[\phi]_{306}$ 0°, $[\phi]_{277}$ −28 817°; a = +352.

Anal. Calcd for $C_{27}H_{36}O_5$: C, 73.60; H, 8.24. Found: C, 73.73; H, 8.25.

Elution with ethyl acetate–petroleum ether returned 2.211 g (55%) of starting enedione **1**, and continued elution yielded fractions which contained 1.06 g and at least five closely moving compounds which were not separated and further investigated.

Reaction of **10** with oxygen in the presence of base gave a large number of compounds which were not further investigated.

Photocycloaddition of 1 to 2,3-Dimethylbutadiene. A solution of 4.00 g (11.2 mmol) of the enedione **1** in 160 mL of benzene and 30 mL of redistilled 2,3-dimethylbutadiene was irradiated under argon in a Pyrex vessel with a 450-W medium-pressure mercury arc. After 2.75 h, the reaction was complete, the solvent was evaporated, and the residue was chromatographed on 500 g of CC-7 silica. Elution with 1:1 ethyl acetate–cyclohexane yielded 2.032 g (4.32 mmol, 39%) of **11**. A further 0.77 g was eluted which consisted of additional amounts of **11** and two other compounds which were subsequently identified as the dienone **13** and the enone **12**. Compound **11**: 145–146 °C (ether–petroleum ether); IR ν 3435 (−O_2–H), 1790 (γ-lactone), 1675, 1630 (enone) cm^{-1}; UV 247 nm (ε 10 000); NMR δ 8.20 (s, 1 H, hydroperoxide H, exchanges with D_2O), 4.93 (s, 1 H, vinyl H), 4.83 (m, 1 H, vinyl H), 1.78 (s, 3 H, vinyl methyl), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.00 (s, 3 H, C-18 H).

Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.46; H, 8.08.

There was a strong positive hydroperoxide test with the immediate liberation of iodine when **13** was reacted with aqueous potassium iodide in acetic acid.

An identical experiment where the chromatography was conducted faster allowed the isolation of the two other components noted above. Crystallization of the initial fractions gave the hydroperoxide **11** (1.00 g, 2.13 mmol, 19%). Intermediate mixed fractions were followed by reasonably pure fractions containing **12** which was purified by trituration with ether to yield 182 mg (0.42 mmol, 4%) of the enone **12**: mp 244–246 °C; IR ν 1790 (γ-lactone), 1710 (cyclohexanone), 1650 (enol double bond) cm^{-1}; NMR δ 4.87 (broad s, 2 H, vinyl H), 3.62 (broad s, 1 H, C-4β H), 3.13 (d, J = 13 Hz, 1 H), 1.63 (s, 3 H, vinyl methyl), 1.23 (s, 3 H), 0.95 (s, 3 H, C-18 H), 0.63 (s, 3 H, C-19 H); $[\alpha]^{25}_D$ −27.0° (c 0.100, $CHCl_3$); ORD $[\phi]_{327}$ +615°, $[\phi]_{320}$ 0°, $[\phi]_{312}^{sh}$ −1840°, $[\phi]_{303}$ −3224°, $[\phi]_{296}^{sh}$ −2325°, $[\phi]_{282}$ 0°, $[\phi]_{267}$ +1162°; a = +38; CD $[\theta]_{317}$ +2325°, $[\theta]_{308}^{sh}$ +1360°.

Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.36; H, 8.76.

The residues from the above crystallizations were dissolved in 150 mL of methanol, and 0.5 g of sodium methoxide was added to yield 1.25 g (2.87 mmol, 26%) of dienone **13**, for an overall yield of 48% for the [4 + 2] adducts.

A small amount, 300 mg (7.5%), of starting enedione **1** was recovered. The most polar fractions, which weighed 815 mg and which probably contained the [2 + 2] and possibly the [4 + 2] adducts of the C-4 double bond, were found to contain six compounds by TLC and a large amount of degradation material as judged by streaking on the TLC plates. As a result, these were not further investigated.

Basic Elimination of Hydrogen Peroxide from Hydroperoxide 11. To a solution of 286 mg (0.60 mmol) of **11** in 100 mL of methanol was added 1 g of sodium methoxide. After stirring magnetically overnight, 5 mL of concentrated hydrochloric acid in 15 mL of distilled water was added and the methanol was removed on a rotary evaporator. The result white solid was filtered, washed until neutral with distilled water, and dried to yield 203 mg (0.47 mmol, 78%) of the dienone **13**: mp 130–135 °C; IR ν 1785 (γ-lactone), 1675, 1635, 1610 (dienone) cm^{-1}; UV 263 nm (ε 6000), 317 (13 000); NMR δ 5.50 (d, $J \cong 2$ Hz, 1 H, C-7 H), 4.97 (broad s, 1 H), 4.87 (q, 1 H), 1.78 (s, 3 H, vinyl methyl), 1.25 (s, 3 H), 1.18 (s, 3 H), 1.05 (s, 3 H, C-18 H).

Anal. Calcd for $C_{28}H_{36}O_4 \cdot 0.5H_2O$: C, 75.47; H, 8.37. Found: C, 75.21; H, 8.27.

Photocycloaddition of 1 to 1,3-Cyclohexadiene. Argon was bubbled through a solution of the enedione **1** (4.00 g, 11.2 mmol) in 170 mL of toluene and 25 mL of 1,3-cyclohexadiene for 1.5 h prior to the start of the irradiation and during it. TLC examination of the reaction solution prior to irradiation demonstrated the absence of any ground state Diels–Alder reactions. Irradiation for 2 h with a 450-W medium-pressure mercury lamp (Pyrex filter) consumed the starting material and generated a series of photoproducts. After removal of solvent, the residue was chromatographed on 500 g of CC-7 silica. Elution with ethyl acetate–petroleum ether (1:1) gave 517 mg (1.19 mmol, 11%) of the [4 + 2] dihydropyran adduct **14**: mp 188–190 °C (methanol–water); IR ν 1775 (γ-lactone), 1720 (cyclohexanone), 1700, 1690 (double bonds) cm^{-1}; NMR δ 5.83–6.00 (m, 2 H), 3.83 (broad, t, J = 3 Hz, 1 H), 1.26 (s, 3 H, C-19 H), 0.98 (s, 3 H, C-18 H).

Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.11; H, 8.52.

The primary adduct **14** was closely followed by a derived product, either the hydroperoxide or the dienone. When crystallization was attempted from methanol–water, an opaque emulsion was formed. When a few drops of acetic acid were added to facilitate crystallization, 578 mg (1.24 mmol, 11%) of the enone **15** crystallized: mp 160–164 °C; IR ν 1780 (γ-lactone), 1680, 1620 (enone) cm^{-1}; UV 246 nm (ε 9000); NMR δ 5.58–6.25 (m, 2 H), 4.14 (t, J = 4.5 Hz, 1 H), 3.23 (s, 3 H), 1.28 (s, 3 H), 1.02 (s, 3 H); $[\alpha]^{25}_{589}$ +30.6 ± 3.1° (c 0.093, $CHCl_3$), $[\alpha]^{25}_{365}$ −292.9 ± 3.1°.

Anal. Calcd for $C_{29}H_{38}O_5$: C, 74.65; H, 8.21. Found: C, 74.20; H, 8.28.

Elution with ethyl acetate–petroleum ether (6:4) yielded 1.408 g (3.23 mmol, 29%) of the adduct **16**: mp 244–252 °C (ethyl acetate–petroleum ether); IR ν 1780 (γ-lactone), 1708 (cyclohexanones) cm^{-1}; NMR δ 5.58–6.17 (m, 2 H), 3.39 (d, J = 5 Hz, 1 H), 3.25 (m, 1 H, overlaps δ 3.39 signal), 0.96 (s, 3 H, C-18 H), 0.68 (s, 3 H, C-19 H); NMR (C_6D_6) δ 5.42–6.08 (m, 2 H), 3.67 (d, J = 5 Hz, 1 H), 2.89 (broad q, $J \cong 9.5, 6$ Hz, 1 H), 0.71 (s, 3 H), 0.43 (s, 3 H); $[\alpha]^{25}_{589}$ = +53.5 ± 3.5° (c 0.086, $CHCl_3$); $[\alpha]^{25}_{365}$ +233.7 ± 3.5°; CD $[\theta]_{318}$ +611°, $[\theta]_{314}$ 0°, $[\theta]_{310}$ −262°, $[\theta]_{306}$ −131°, $[\theta]_{301}$ −1135°, $[\theta]_{295}$ −393°, $[\theta]_{292}$ −524°, $[\theta]_{288}$ 0°, $[\theta]_{272}$ +700°.

Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.10; H, 8.49.

Closely following **16** was the other double-bond adduct **17** (570 mg, 1.31 mmol, 12%): mp 235–236 °C (methanol–water); IR ν 1780 (γ-lactone), 1705, 1690 (cyclohexanones) cm^{-1}; NMR δ 5.67–6.42 (m, 2

H), 3.42 (m, 1 H), 2.83 (m, 2 H), 0.98 (s, 3 H); CD $[\theta]_{319}$ +4850°C, $[\theta]_{310}^{sh}$ +3150°, $[\theta]_{305}$ 0°, $[\theta]_{298}^{sh}$ −3925°, $[\theta]_{284}$ −6775°, $[\theta]_{245}$ 0°; MS *m/e* (%) 436 (parent, 3.3), 80 (100, see structure i).

i

Anal. Calcd for $C_{28}H_{36}O_4 \cdot H_2O$: C, 73.50; H, 8.41. Found: C, 73.90; H, 8.43.

Treatment of **14** with methanolic sodium methoxide furnished **15** in low yield after acidification with hydrochloric acid, and TLC indicated the presence of several other compounds.

Photocycloaddition of Enedione 1 to 4-Methyl-1,3-pentadiene. A solution of 6.0 g (16.8 mmol) of **1** in 160 mL of ethyl acetate and 34 mL of freshly distilled 4-methyl-1,3-pentadiene was irradiated in a Pyrex vessel under argon with a 450-W mercury arc for 3 h. The solvent was removed on a rotary evaporator and the residue subjected to low-pressure liquid chromatography on silica. Elution with ethyl acetate–benzene (1:2) gave 2.194 g (5.01 mmol, 30%) of [4 + 2] dihydropyran adduct **18**: mp 168–171 °C (ether–petroleum ether); IR ν 1775 (γ-lactone), 1720 (cyclohexanone), 1680 (enol double bond) cm^{-1}; NMR δ 5.28 (m, 1 H), 4.13 (broad t, 1 H), 1.73 (broad s, 6 H, vinyl methyl groups), 1.27 (s, 3 H, C-19 H), 0.98 (s, 3 H, C-18 H); $[\alpha]^{25}_{589}$ −67.0 ± 9° (*c* 0.100, $CHCl_3$), $[\alpha]^{25}_{436}$ −99.0°; ORD $[\phi]_{318}$ +5000°, $[\phi]_{306}$ 0°, $[\phi]_{275}$ −14 360°; *a* = +194; CD $[\theta]_{302}$ +12 400°.

Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.76; H, 8.51.

Continued elution yielded 2.218 g (5.06 mmol, 30%) of the [2 + 2] adduct **19**: mp 225–233 °C (ether–petroleum ether); IR ν 1775 (γ-lactone), 1700 (cyclohexanones) cm^{-1}; NMR δ 4.92 (d, with secondary splitting, $J \cong 7.5$ Hz, 1 H), 3.72 (dd, $J = 10, 2$ Hz, 1 H), 3.22 (m, 1 H), 1.66 (s, 3 H, vinyl methyl group), 1.57 (s, 3 H, vinyl methyl group), 0.97 (s, 3 H, C-18 H), 0.68 (s, 3 H, C-19 H); CD $[\theta]_{319}$ +400°, $[\theta]_{316}$ 0°, $[\theta]_{308}^{sh}$ −1850°, $[\theta]_{298}^{sh}$ −5000°, $[\theta]_{291}$ −5825°, $[\theta]_{260}$ −1225°.

Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 77.02; H, 8.85.

The NMR spectrum of the residue after evaporation of the mother liquors from **19** showed that in addition to more **19**, a second isomer, probably the vinylcyclobutane epimer, was present.

Attempted conversion of **18** into a dienone with sodium methoxide in methanol gave a large number of products and was not further investigated.

Quenching Experiments. Quenching experiments were carried out on a 0.025 M solution of the enedione **1** in a solvent consisting of 12.5% (V/V) cyclopentene in ethyl acetate. Irradiations were carried out in Pyrex tubes mounted in a merry-go-round apparatus in a Rayonet Preparative Photoreactor using eight 3000-Å lamps as the light source. The quencher employed was 3,3,4,4-tetramethyl-1,2-diazetidine 1,2-dioxide.[22] Aliquots containing the reaction mixture both in the absence and presence of 0.01 M quencher were degassed by two successive freeze–thaw cycles at the temperature of liquid nitrogen. Samples were removed at 0.5-h intervals and analyzed by GLC on a 6 ft 1.5% OV-17 column at 270 °C on a Perkin-Elmer 900 gas chromatograph. Under these conditions, the ratio of the formation of [4 + 2] dihydropyran adduct **7** in the quenched to the unquenched reaction was 2.1 ± 0.2. The [2 + 2] adduct **9** did not survive the GLC conditions and reverted to starting materials.

Acknowledgments. The enedione **1** was first prepared, in a different manner, by Dr. Roy H. Bible, Jr., Analytical Resources and Methods, G. D. Searle and Co. The physical spectra were obtained under the direction of Mr. A Damascus, and the chromatographies were conducted under the supervision of Mr. Robert Nicholson.

Registry No.—**1**, 38753-78-5; **2**, 55665-77-5; **3**, 69429-71-6; **4**, 69429-72-8; **5**, 69429-73-8; **6**, 69429-74-9; **7**, 66175-76-6; **8**, 69429-75-0; **9**, 66175-77-7; **10**, 69469-70-4; **11**, 69429-76-1; **12**, 69460-71-5; **13**, 69429-77-2; **14**, 69429-78-3; **15**, 69429-79-4; **16**, 69429-80-7; **17**, 69429-81-8; **18**, 69429-82-9; **19**, 69429-83-0; cyclopentene, 142-29-0; dihydropyran, 110-87-2; 2,3-dimethylbutadiene, 513-81-5; 1,3-cyclohexadiene, 592-57-4; 4-methyl-1,3-pentadiene, 926-56-7; propionic anhydride, 123-62-6; 2-propanol, 67-63-0.

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