The Photocycloaddition of an 5α-Androst-1-en-3-one to Olefins

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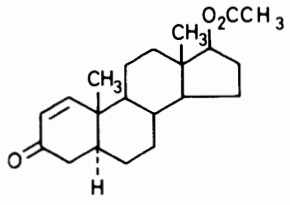
The triplet photocycloaddition of 17β-acetoxy-5α-androst-1-en-3-one to the olefins cyclopentene, a ketene acetal, and isobutylene is described. The addition to cyclopentene forms *cis*- and *trans*-fused cyclobutanes. The *trans*-adduct is remarkably stable to both strong acid and base at room temperature, requiring extended heating in alcoholic base for epimerization to occur. This stability is ascribed to steric shielding of the enolizable proton. Addition to the ketene acetal, followed by careful hydrolysis, yields the novel *trans*-fused cyclobutanone. Epimerization and deuteriation demonstrated the stereochemistry as being 1β,2α. Isobutylene, in addition to the *cis*- and *trans*-fused cyclobutanes, also yielded an ene-type product.

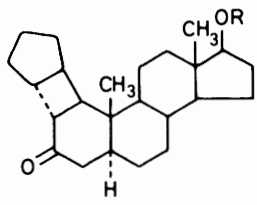
The photocycloaddition of enones to olefins to form cyclobutanes is a well known reaction with considerable synthetic utility and mechanistic ambiguity.[1] Currently, the reaction is thought to occur through an excited-state complex (exiplex) between the twisted $^3(\pi\pi^*)$ state of the enone and an olefin.[2] This highly ordered exiplex can collapse directly to a *trans*-fused cyclobutane.[3] Additionally, the exiplex can form a twisted 1,4-diradical which can form the same strained cyclobutane, rotate to form the more stable *cis*-fused cyclobutane, and undergo hydrogen transfer to form an ene-type product.[2,4] The *trans*-fused cyclobutanes thus formed are very susceptible to epimerizing conditions and are, in many cases, difficult to isolate. Steroidal enones differ from the simpler cyclohexenones in that only a single 1,4-diradical is formed, usually at the α-carbon.[5] Among the steroidal chromophores investigated, the 1-en-3-one system was reported not to form photoproducts with ethylene, acetylene, or maleic anhydride under either direct excitation or triplet photosensitization.[6] Successful cyclobutane formation was observed, however, with 1,1-dichloroethylene and vinyl acetate. Subsequent chemical manipulations in these adducts gave *cis*-fused cyclobutanones. In the present paper we describe the photocycloaddition of this same chromophore to various olefins and indicate the unusual properties of the adducts and report the isolation of a *trans*-fused cyclobutanone.[7]

Cyclopentene.—Irradiation of enone (**1**) in cyclopentene–ethyl acetate formed two photoadducts which were separated by a combination of crystallization and chromatography. The first, (**2**), isolated in 38% yield, was identified as a *trans*-fused cyclobutane because of a deshielded C-19 methyl group and a strained cyclohexanone carbonyl group.[8] The chiroptical properties indicated a 2α-cyclobutane and hence a 1β,2α-configuration. Attempted epimerization and acetate hydrolysis under the usual conditions of sodium methoxide in methanol yielded the alcohol (**3**) whose spectral characteristics were similar to those of (**2**).[8,9] Reacetylation surprisingly regenerated the *trans*-fused cyclobutane (**2**). Indeed, the 17β-alcohol group in (**2**) could be oxidized to give the unepimerized 17-ketone (**4**) using chromium trioxide in 12M sulphuric acid.[10] It was, however, possible to epimerize the *trans*-fused cyclobutane into the *cis*-fused cyclobutane by refluxing (**2**) in ethanolic sodium ethoxide solution for three days. The resultant alcohol (**5**) was reacetylated to yield (**6**) which was distinctly different from the *trans*-fused starting material (**2**). The positive chiroptical properties of (**5**) and (**6**) indicated a 1β,2β-ring fusion while the C-19 methyl group was no longer deshielded in the n.m.r. spectrum and the cyclohexanone carbonyl i.r. frequency was at the normal position.[8] Oxidation of the alcohol (**5**) to the ketone gave the 1β,2β-[2 + 2] dione (**7**) which was readily differentiated from the corresponding 1β,2α-dione (**4**).

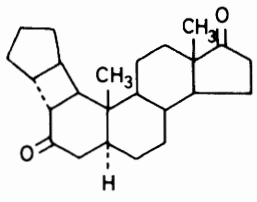
The other primary [2 + 2] photoadduct was isolated in 56% yield and identified as the *cis*-fused cycloadduct (**8**). The stereochemistry was determined to be 1α,2α by the negative chiroptical properties and its recovery when it was subjected to the successful epimerizing conditions used for (**2**), followed by reacetylation.



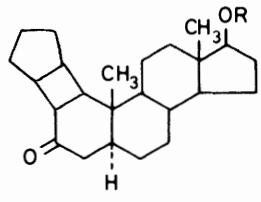
(**1**)



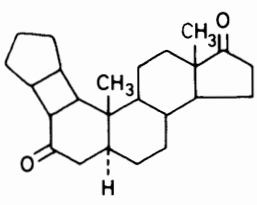
(**2**) R = $OCCH_3$
(**3**) R = H



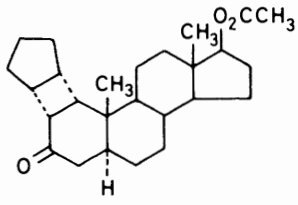
(**4**)



(**5**) R = H
(**6**) R = $OCCH_3$



(**7**)

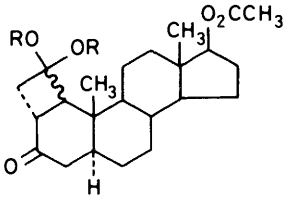


(**8**)

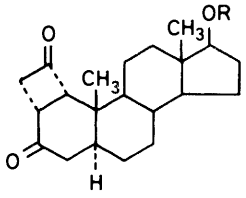
The photocycloaddition of enone (**1**) to cyclopentene was readily quenched by piperylene (penta-1,3-diene), indicating an enone triplet state for the cycloaddition.[11]

Ketene Acetals.—The photocycloaddition of enone (**1**) to ketene bis(methoxyethyl) acetal proceeded uneventfully and a portion of irradiation solution was chromatographed and the non-crystalline mixture of adducts isolated. The n.m.r. spectrum

of this mixture (**9**) showed a deshielded C-19 angular methyl group at δ 1.17 and an i.r. carbonyl absorption at 1 735 cm^{-1} indicating that the majority of the product was *trans*-fused. A further portion was transesterified and epimerized with sodium methoxide in methanol and the acetal was subsequently hydrolysed with acid. The mixture of two cyclobutanones was separated by silica gel chromatography to yield the 1α,2α-cyclobutanone alcohol (**10**) and the known 1β,2β-cyclobutanone alcohol (**11**) in the ratio 1 : 7.5.[6] The strong preponderance of the 1β,2β-epimer over the 1α,2α was taken to indicate that the initially isolated *trans*-acetal (**9**) was 1β,2α, analogous with the cyclopentene adduct. Reacetylation of these alcohols yielded the acetates (**12**) and (**13**) respectively. Oxidation of (**10**) and (**11**) with Jones reagent formed the known 17-ketones (**14**) and (**15**) respectively, thus confirming their structures.[6]

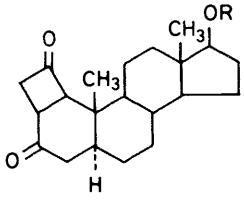


(**9**)



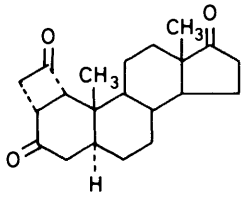
(**10**) R = H

(**12**) R = $OCCH_3$

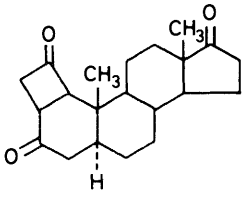


(**11**) R = H

(**13**) R = $OCCH_3$



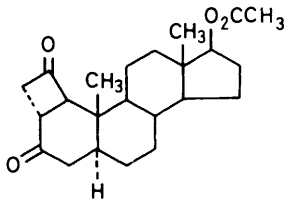
(**14**)



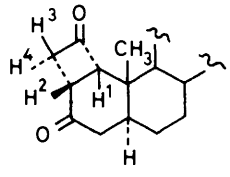
(**15**)

However, when the acetal photoadduct mixture (**9**), which was predominantly *trans*-fused, was hydrolysed in a two-phase system of ethyl acetate and aqueous toluene-*p*-sulphonic acid, a new compound was isolated. This cyclobutanone (**16**) was neither *cis*-fused adduct (**12**) or (**13**) and hence must be the long sought *trans*-fused cyclobutanone. Based on the structure of the *trans*-cyclopentene adduct (**2**) and the ketene acetal photoadducts (**9**) epimerization studies, the stereochemistry of the *trans*-fused cyclobutanone (**16**) was assigned as 1β,2α. Since there were two potentially epimerizable carbons alpha to a carbonyl group, epimerization studies could be ambiguous. When (**16**) was epimerized using aqueous toluene-*p*-sulphonic acid, an equimolar mixture of both *cis*-fused cyclobutanone 17β-alcohols (**10**) and (**11**) was formed. Because of the difficulty observed in the epimerization of the *trans*-fused cyclopentene adduct (**2**), it was felt that a weak base would result in selective epimerization at C-1. Refluxing (**16**) in pyridine gave only the 1α,2α-cyclobutanone (**12**) in greater than 95% yield.

This regiospecific epimerization was used to confirm the 1β,2α-stereochemistry using deuterium exchange and a combination of mass spectrometry and 270 MHz n.m.r. spectrometry. At 270 MHz, the cyclobutanone protons in (**12**) are well resolved and the couplings are essentially first order. Since *cis*-vicinal cyclobutane and cyclobutanone hydrogens have larger coupling constants than *trans*, it was possible to differentiate H^3 and H^4.[12] The *cis* coupling constant ($J_{2,3}$ 10.8 Hz) is larger than the *trans* ($J_{2,3}$ 5.1 Hz). It was found empirically that keeping the *trans*-cyclobutanone (**16**) in pyridine–deuterium oxide (9 : 1) for ten days at room temperature resulted in complete epimerization to (**12**). Mass spectral deuterium analysis indicated the incorporation of up to five atoms of deuterium.[13] The amounts were as follows: D_0 (5%), D_1 (19%), D_2 (45%), D_3 (23%), D_4 (6%), and D_5 (2%). Using the 17α-proton in (**12**) as a standard, integration of the appropriate 270 MHz n.m.r. signals indicated complete exchange of hydrogen at C-1 (≥95%) while C-2 exchanged only to the extent of 26%. This exchange at C-2 was assumed to occur after epimerization to the *cis*-fused compound (**12**). The exocyclic proton H^3 exchanged almost twice as much (82% D) as the endocyclic proton H^4 (46% D). This experiment confirmed the assigned stereochemistry of (**16**) as 1β,2α.



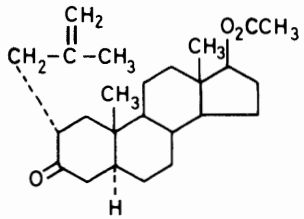
(**16**)



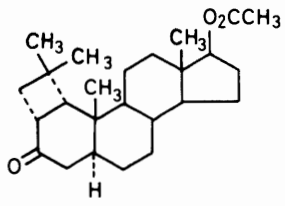
(**12**)

Since the formation of a *trans*-fused cyclobutane ring results in a significant shift in the cyclohexanone carbonyl frequency, it was of some interest whether this effect would be observed in the *trans*-fused cyclobutanone.[8] For example, the cyclohexanone carbonyl absorption occurs at 1 706.3 ± 0.7 cm^{-1} in 1α,2α-(**12**) and 1 712.3 ± 1.2 cm^{-1} in 1β,2β-(**13**) while it is at 1 731.4 ± 0.8 cm^{-1} in the *trans*-fused (**16**). However, when the cyclobutanone frequencies were measured there was only a small difference between the *trans*-cyclobutanone and its two *cis*-epimers. The 1α,2α-(**12**) cyclobutanone carbonyl appears at 1 773.9 ± 0.2 cm^{-1} and that of the 1β,2β-(**13**) at 1 769.6 ± 0.9 cm^{-1}, while that of the *trans*-1β,2α-(**16**) is at 1 776.4 ± 0.6 cm^{-1}, a shift of only 2—7 cm^{-1} from the *cis* to the *trans*.

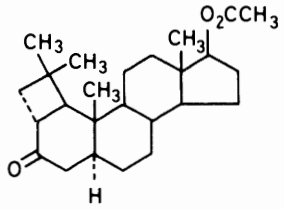
Isobutylene.—The photocycloaddition of enone (**1**) to isobutylene was unique among the olefins studied in that an ene-type product was observed. Irradiation of enone (**1**) in the presence of isobutylene formed three photoadducts which are separable by chromatography. The initial photoproduct (**17**) was not a cyclobutane but contained unsaturation. The n.m.r. spectrum showed two olefinic protons and a vinylic methyl group and only two aliphatic tertiary methyl groups. A one-proton multiplet occurred at δ 2.55 which we ascribe to the 2β-hydrogen which is tertiary and alpha to a carbonyl group. The next adduct was identified as the 1α,2α-*cis*-cyclobutane (**18**) based on its spectral properties and stability to epimerizing conditions. The n.m.r. spectrum showed a multiplet at δ 2.58 for the 2β-hydrogen, indicating a head-to-tail adduct. The final



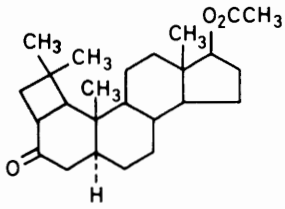
(17)



(18)



(19)



(20)

photoadduct (**19**) was the 1β,2α-*trans*-fused adduct as indicated by a strained cyclohexanone carbonyl frequency and strongly negative chiroptical properties. The head-to-tail addition of the enone to isobutylene was indicated by a multiplet for the 2β-hydrogen at δ 3.08. Epimerization in an analogous manner to the *trans*-cyclopentene adduct (**2**), followed by reacetylation, gave the 1β,2β-*cis*-cyclobutane (**20**).

Previous studies of the photochemical addition of other cyclohexenones to isobutylene have demonstrated that both the cyclobutanes and ene-products can be derived from the same 1,4-diradical.[4] The structures of the isobutylene adducts of enone (**1**) are consistent with a 1,4-diradical formed between the α-carbon of the enone (C-2) and isobutylene with subsequent partitioning among the three products.

Discussion

The isolation and characterization of the strained *trans*-fused [2 + 2] adducts of cyclohexenone with olefins was originally described by Corey.[9] The ready epimerization of these adducts to the more stable *cis*-fusion adducts using acid, base, heat, or even filtration through alumina was immediately noted. Thus the stability of the *trans*-ring fusion in the cyclopentene and isobutylene adducts (**2**) and (**19**) to strong base and acid is very unusual. The same adducts in the 3-keto-4-ene series epimerize readily.[8] The reason for the unusual stability of these adducts of the enone (**1**) appears to be steric. Assuming that the five- and six-membered rings have a *syn*-relationship about the cyclobutane ring,[14] a model of (**2**) then indicates the reason for the stability. The epimerizable axial 2β-hydrogen in (**2**) is buried underneath the cyclopentane ring and the C-19 angular protons. Attack by base across the β-face of the A-ring of the steriod is effectively hindered by the C-3 carbonyl and the axial hydrogens at C-4 and C-6. This sterically inaccessible proton is the reason for the isolation for the *trans*-fused cyclobutanone (**16**).

A *trans*-fused cyclobutanone, while formally obtainable from a *trans*-fused ketone acetal enone adduct, has remained an elusive goal. For instance, hydrolysis of the *trans*-ketene acetal adducts from 3-keto-4-ene and 4,6-dienes results only in the *cis*-fused cyclobutanone.[8,15] Even though the 2β-hydrogen in (**9**) is less hindered than that in the cyclopentene or isobutylene adducts, it is still sufficiently hindered to permit acidic hydrolysis of the acetal without epimerization to form the desired *trans*-fused cyclobutanone.

Experimental

M.p.s were run on a Thomas-Hoover Unimelt Capillary Apparatus and are uncorrected. I.r. spectra were run in potassium bromide pellets unless otherwise stated on a Beckman IR-12 spectrophotometer. U.v. spectra were run in methanol on a Beckman DK-2A spectrophotometer and optical rotations were determined in chloroform on a Perkin-Elmer Model 141 polarimeter. ^{1}H N.m.r. spectra were recorded on Varian T-60, A-60, XL-100, or Bruker 270 MHz instruments and were run in deuteriochloroform using tetramethylsilane as internal standard. Mass spectra were determined on an A.E.I. MS-30 spectrometer using electron impact at 70 eV. The o.r.d. and c.d. spectra were obtained on methanol solutions using a Jasco ORD/UV-5 spectrometer. Elemental analyses were performed by the Searle Laboratories Microanalytical Service under the direction of Mr. E. Zielinski. Light petroleum refers to the fraction boiling in the range 40—60 °C.

Cyclopentene Photoadducts.—A solution of 17β-hydroxy-5α-androst-1-en-3-one acetate (**1**) (5.00 g) in ethyl acetate (65 ml) and cyclopentene (95 ml) was irradiated under argon with a 450-W medium-pressure mercury arc (Pyrex filter).[16] After 1.25 h, t.l.c. [(1:4 and 1:9) ethyl acetate–toluene] indicated consumption of enone and the formation of two major adducts. After evaporation of the solvent, the residual oil was dissolved in light petroleum (75 ml) and refrigerated for several days whereupon the 1β,2α-trans-*adduct* (**2**) (1.67 g) crystallized, m.p. 193—196 °C (Found: C, 78.5; H, 9.8. $C_{26}H_{38}O_3$ requires C, 78.35; H, 9.61%); δ 4.57 (1 H, t), 2.02 (3 H, s, COMe), 1.10 (3 H, s, 19-H_3), and 0.80 (3 H, s, 18-H_3); $\nu_{max.}$(KBr) 1 735, 1 715, and 1 250 cm^{-1}; $[\alpha]_{589}^{25}$ +69° (*c* 1.04), $[\alpha]_{365}^{25}$ −221°; $[\Phi]_{300}$ −6 370°, $[\Phi]_{283}$ 0°, and $[\Phi]_{262}$ + 5 800°; *a* − 121; $[\theta]_{284}$ − 8 775°.

The residue obtained after evaporation of the mother liquors was flash chromatographed[17] [(1.5:98.5) ethyl acetate–methylene dichloride] to yield the 1α,2α-cis-*fused cyclobutane adduct* (**8**) (3.34 g), m.p. 150—152 °C (Found: C, 78.35; H, 9.6%); δ 2.03 (3 H, s, COMe), 0.78 (3 H, s, 18-H_3), and 0.70 (3 H, s, 19-H_3); $\nu_{max.}$(KBr) 1 735 and 1 700 cm^{-1}; $[\alpha]_{589}^{25}$ +1° (*c* 0.097), $[\alpha]_{365}^{25}$ −151°; $[\Phi]_{314}$ −2 866°, $[\Phi]_{296}$ 0°, and $[\Phi]_{262}$ +4 458°; *a* − 73; $[\theta]_{301}$ −4 935°. The initial fractions of the 1α,2α-adduct contained small amounts of the 1β,2β-adduct. Continued elution gave an additional amount of the *trans*-adduct (0.62 g).

Basic Transesterification of the trans-*Adduct* (**2**) *without Epimerization.*—A solution of the 1β,2α-*trans*-adduct (**2**) (274 mg) in methanol (25 ml), tetrahydrofuran (THF) (35 ml), and sodium methoxide (1 g) was stirred magnetically under nitrogen. After 2 h, the reaction mixture was quenched with citric acid (1 g) in water (50 ml). After the majority of the organic solvents had been removed under reduced pressure, the 17β-*alcohol* (**3**) (227 mg) still containing the 1β,2α-*trans*-fused cyclobutane ring crystallized, m.p. 220—223 °C (Found: C, 80.8; H, 10.25. $C_{24}H_{36}O_2$ requires C, 80.85; H, 10.18%); δ 3.62 (1 H, t, 17α-H), 2.6—3.05 (2 H, m), 1.11 (3 H, s, 19-H_3), and 0.76 (3 H, s, 18-H_3); $\nu_{max.}$(KBr) 3 530, 1 720sh, and 1 712 cm^{-1}; $[\alpha]_{589}^{25}$ + 28° (*c* 0.096, $[\alpha]_{365}^{25}$ +10°; $[\Phi]_{300}$ −4 510°, $[\Phi]_{281}$ 0°, and $[\Phi]_{256}$ +8 579°; *a* − 131; $[\theta]_{281}$ −8 033°.

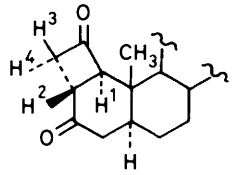
Oxidation of the 1β,2α-*Cyclopentene* [2 + 2] *Adduct* 17β-*Alcohol to the Ketone.*—The alcohol (**3**) (168 mg) in acetone solution (40 ml) was oxidized with Jones reagent[10] (1 ml) for 7 min after which the excess of reagent was quenched with isopropyl alcohol. After dilution with water, the organic solvents were removed under reduced pressure to give a blue precipitate which was redissolved in acetone and the solution filtered twice through a filter-aid to give a clear solution. Slow dilution with water gave crystals of the 17-*ketone* (**4**) (75 mg), m.p. 204—210 °C (Found: C, 81.0; H, 9.8. $C_{24}H_{34}O_2$ requires C, 81.31; H, 9.67%); δ 1.13 (3 H, s, 19-H_3) and 0.88 (3 H, s, 18-H_3); $\nu_{max.}$(KBr) 1 745 and 1 715 cm^{-1}; $[\alpha]_{589}^{25}$ +75° (*c* 0.108), $[\alpha]_{365}^{25}$ +331°.

Epimerization of the trans-*Photoadduct*.—The *trans*-fused cyclopentene photoadduct (**2**) (285 mg) was suspended in ethanol (25 ml) and sodium methoxide (1 g) was added. After being refluxed under nitrogen for 2 d, the cooled solution was acidified with dil. hydrochloric acid. The gummy precipitate was flash chromatographed using ethyl acetate–methylene dichloride as eluant (5:95) to yield the 1β,2β-*cis*-[2 + 2] cyclopentene adduct 17β-alcohol (**5**) (163 mg), m.p. 114—120 °C (Found: C, 81.0; H, 9.85. $C_{24}H_{36}O_2$ requires C, 80.85; H, 10.18%); δ 3.62 (1 H, t, 17α-H), 0.93 (3 H, s, 19-H_3), and 0.73 (3 H, s, 18-H_3); $\nu_{max.}$(KBr) 3 450 and 1 705 cm^{-1}; $[\alpha]_{589}^{25}$ +79° (*c* 0.103), $[\alpha]_{365}^{25}$ +527°; $[\Phi]_{316}$ +9 218°, $[\Phi]_{295}$ 0°, and $[\Phi]_{275}$ − 5 605°; *a* +148; $[\theta]_{297}$ +12 083°.

The 17β-alcohol (**5**) (103 mg) was dissolved in acetic anhydride (0.8 ml) and pyridine (1 ml) and left at room temperature overnight. Upon slow dilution with water, the 17β-acetate (**6**) (110 mg) recrystallized, m.p. 148—152 °C (Found: C, 78.4; H, 9.4. $C_{26}H_{38}O_3$ requires C, 78.35; H, 9.61%); δ 2.02 (3 H, s, COMe), 0.92 (3 H, s, 19-H_3), and 0.78 (3 H, s, 18-H_3); $\nu_{max.}$(KBr) 1 740, 1 705, and 1 250 cm^{-1}; $[\alpha]_{589}^{25}$ +70° (*c* 0.100), $[\alpha]_{365}^{25}$ +512°; $[\Phi]_{315}$ +5 616°; $[\Phi]_{296}$ 0°, and $[\Phi]_{276}$ −4 446°; *a* +101; $[\theta]_{296}$ +8 424°.

Oxidation of the Alcohol (**5**) *to the* 17-*Ketone* (**7**).—A solution of the 17β-alcohol (**5**) (29 mg) in acetone (10 ml) was oxidized with a slight excess of Jones reagent. After quenching the excess of oxidant with isopropyl alcohol, the solution was diluted with water to give immediate crystallization of the 17-ketone (**7**) (18 mg) which was filtered off and washed with water. The *ketone* (**7**) had m.p. 138—145 °C (Found: C, 80.8; H, 9.7; $C_{24}H_{34}O_2$ requires C, 81.21; H, 9.67%); δ 0.97 (3 H, s, 19-H_3) and 0.87 (3 H, s, 18-H_3); $\nu_{max.}$(KBr) 1 742 and 1 703 cm^{-1}; $[\alpha]_{589}^{25}$ +171° (*c* 0.114), $[\alpha]_{365}^{25}$ +1 100°.

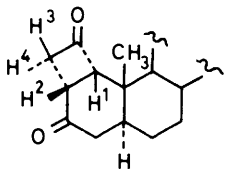
Ketene Acetal Photoadducts.—A solution of the steroidal enone (**2**) (4.0 g) in ethyl acetate (25 ml) and ketene bis(methoxyethyl) acetal[18] (20 ml) was irradiated under argon in a Rayonet preparative photoreactor using eight 3 500 Å lamps (Pyrex filter). After 32 h, the irradiation was terminated and the reaction mixture was added to additional ethyl acetate (100 ml) and cooled in an ice-bath. Water (50 ml) containing a few crystals of toluene-*p*-sulphonic acid was added to hydrolyse excess of ketene acetal. After 1 h, additional toluene-*p*-sulphonic acid (5 g) was added and the mixture was stirred overnight and then partitioned with additional water and toluene. The organic layer was neutralized with aqueous sodium hydrogen carbonate and then dried with sodium sulphate. The residue obtained after evaporation was crystallized from methanol (20 ml) to yield the trans-*fused cyclobutanone* (**16**) (1.75 g), m.p. 206—212 °C (Found: C, 74.3; H, 8.65. $C_{23}H_{32}O_4$ requires C, 74.16; H, 8.66%); δ 4.63 (1 H, t, 17-H), 2.06 (3 H, s, COMe), 1.13 (3 H, s, 19-H_3), and 0.83 (3 H, s, 18-H_3); $\nu_{max.}$ 1 776.4 ± 0.6 and 1 731.4 ± 0.9 cm^{-1}; $[\alpha]_{589}^{25}$ +23° (*c* 0.117), $[\alpha]_{365}^{25}$ +108°; $[\Phi]_{304}$ +3 353°, $[\Phi]_{289}$ 0°, and $[\Phi]_{264}$ −3 849°; $[\theta]_{287}$ +5 215°.



H¹ δ 2.94, $J_{2,3}$ 10.2 Hz
H² δ 2.55, $J_{2,4}$ 6.0 Hz
H³ δ 3.22, $J_{3,4}$ 14.7 Hz
H⁴ δ 3.04, $J_{1,3}$ 1.5 Hz

(**16**)

The mother liquor from the crystallization was evaporated and the residue acetylated with pyridine and acetic anhydride. After the usual work-up, the mixture was flash chromatographed using ethyl acetate–toluene (7:93) as eluant. The faster moving component was the 1α,2α-*cyclobutanone* (**12**) (354 mg), m.p. 199.5—203 °C (Found: C, 74.0; H, 8.6%); δ 2.06 (3 H, s, COMe), 0.88 (3 H, s, 19-H_3), and 0.79 (3 H, s, 18-H_3); $\nu_{max.}$ 1 773.9 ± 0.2, 1 731.6 ± 1, and 1 706.3 ± 0.7 cm^{-1}; $[\alpha]_{589}^{25}$ +2.9° (*c* 0.103), $[\alpha]_{365}^{25}$ −154°. The following fractions (269 mg) were a mixture of the 1β,2α- and 1β,2β-cyclobutanone.



H¹ δ 3.67, $J_{1,2}$ 9.3 Hz
H² δ 3.17, $J_{2,3}$ 10.8 Hz
H³ δ 3.35, $J_{2,4}$ 5.1 Hz
H⁴ δ 2.99, $J_{3,4}$ −18.0, $J_{1,3}$ 3.6, $J_{1,4}$ 0.9 Hz

(**12**)

In a similar experiment, the enone (**2**) (1.5 g) was irradiated and the irradiation solution concentrated to give the ketene acetal which was diluted with THF (25 ml) and methanol (75 ml). After the addition of sodium methoxide (1.5 g), the mixture was stirred overnight under nitrogen. After acidification with toluene-*p*-sulphonic acid (3.5 g) and water (25 ml), the mixture was refluxed for 2 h to hydrolyse the epimerized acetals. After dilution with water, the mixture was extracted with methylene dichloride (3 × 100 ml) and the organic extracts were dried with sodium sulphate. Flash chromatography of the residue using ethyl acetate–toluene (1:4) as eluant yielded the 1α,2α-cis-fused alcohol (**10**) (160 mg), m.p. 198—201 °C (acetone–water) (Found: C, 76.0; H, 9.2. $C_{21}H_{30}O_3$ requires C, 76.32; H, 9.15%); δ 2.75—3.80 (5 H, m), 0.88 (3 H, s, 19-H_3), and 0.74 (3 H, s, 18-H_3); $\nu_{max.}$ 3 470, 1 783, and 1 705 cm^{-1}; $[\alpha]_{589}^{25}$ −1° (*c* 0.095), $[\alpha]_{365}^{25}$ −202°.

Continued elution yielded the 1β,2β-*cis*-cyclobutanone alcohol (**11**)[6] (1.21 g), m.p. 182.5—187.5 °C (decomp.) (acetone–water) (lit.,[6] 194—195 °C) (Found: C, 75.9; H, 9.5%), δ 2.9—3.3 (3 H, m), 3.4—4.3 (2 H, m), 0.74 (6 H, s, 18- and 19-H_3); $\nu_{max.}$ 3 500, 1 790, and 1 718 cm^{-1}; $[\alpha]_{589}^{25}$ +101° (*c* 0.118), $[\alpha]_{365}^{25}$ +702°. Acetylation with pyridine and acetic anhydride gave the 17β-acetate (**13**), m.p. 168.5—171.5 °C (decomp.) (acetone–water) (Found: C, 73.8; H, 8.8. $C_{23}H_{32}O_4$ requires C, 74.16; H, 8.66%); δ 4.50 (1 H, t, 17α-H), 3.5—3.8 (1 H, m), 2.9—3.4 (3 H, m), 2.03 (3 H, s, COMe), 0.78 (3 H, s, 18-H_3), and 0.74 (3 H, s, 19-H_3); $\nu_{max.}$ 1 769.6 ± 0.9, 1 731.6 ± 0.7, and 1 712.3 ± 1.2 cm^{-1}; $[\alpha]_{589}^{25}$ +69.5° (*c* 0.107), $[\alpha]_{365}^{25}$ +562°; $[\Phi]_{320}$ +6 836°, $[\Phi]_{300}$ 0°, and $[\Phi]_{274}$ −6 476°; $[\theta]_{300}$ +10 115°.

Pyridine-catalysed Epimerization of the trans-*Cyclobutanone* (**16**).—A solution of the 1β,2α-*trans*-fused cyclobutanone (**16**) (1.011 g) in pyridine (200 ml) was placed under argon and refluxed for 21 h. Evaporation of the solvent and recrystallization from acetone–water gave the 1α,2α-*cis*-fused cyclobutanone (**12**) (940 mg). There was no t.l.c. evidence for the 1αβ,2β-isomer.

The 1α,2α-*Cyclobutanone*-17-*ketone* (**14**).—The 1α,2α-cyclobutanone-17β-alcohol (**10**) (452 mg) was dissolved in acetone (100 ml) and oxidized with an excess of Jones reagent. After excess of oxidant had been quenched with isopropyl alcohol, the solution was diluted with water to give the 17-ketone (**14**) (328 mg), m.p. 207—208.5 °C (lit.,[6] 207 °C) (Found: C, 76.3; H, 8.9. Calc. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%); δ 0.90 (3 H, s, 19-H_3) and 0.87 (3 H, s, 18-H_3); $\nu_{max.}$ 1 775, 1 740, and 1 705 cm^{-1}; $[\alpha]_{589}^{25}$ +74.5° (*c* 0.106), $[\alpha]_{365}^{25}$ +308.5°.

The 1β,2β-*Cyclobutanone* 17-*Ketone* (**15**).—The 17β-alcohol (**11**) (260 mg) was dissolved in acetone (50 ml) and oxidized as

above to yield the 17-ketone (**15**) (250 mg), m.p. 232—236 °C (lit.,[6] 246—248 °C) (Found: C, 76.4; H, 8.6%); δ 3.5—3.85 (1 H, m), 2.9—3.4 (3 H, m), 0.87 (3 H, s, 18-H_3), and 0.76 (3 H, s, 19-H_3); $[\alpha]_{589}^{25}$ +159° (*c* 0.103), $[\alpha]_{365}^{25}$ +1 121°.

Isobutylene Photoadducts.—The irradiation reservoir was placed in a large Dewar flask. A solution of the enone (**1**) (4.0 g) in ethyl acetate (200 ml) was added. A solid-CO_2–acetone mixture was placed in the Dewar flask and, at the same time, isobutylene was condensed into the irradition vessel until a volume of 600 ml was reached. The mixture was irradiated with a 450-W medium-pressure mercury arc through a Pyrex filter for 17 h with isobutylene being added as needed to maintain the volume at 600 ml. The residue obtained after evaporation was chromatographed on silica using ethyl acetate–benzene (1:98) as eluant. The initially eluted photoproduct was the *ene-product* (**17**) (0.86 g), m.p. 156—158 °C (ether–light petroleum) (Found: C, 77.7; H, 10.0. $C_{25}H_{38}O_3$ requires C, 77.67; H, 9.91%); δ 4.7 (2 H, m), 2.00 (3 H, s, COMe), 1.68 (3 H, s, vinyl Me), 1.07 (3 H, s, 19-H_3), and 0.80 (3 H, s, 18-H_3); $\nu_{max.}$ 1 740, 1 710, 1 655, and 1 255 cm^{-1}. Continued elution gave the cis-1α,2α-*cyclobutane* (**18**) (0.96 g), m.p. 152—154 °C (methanol–water) (Found: C, 77.8; H, 9.9%); δ 2.53 (1 H, m, 2β-H), 2.03 (3 H, s, COMe), 1.27 (3 H, s), 0.92 (3 H, s), and 0.78 (6 H, s); $\nu_{max.}$ 1 738, 1 695, and 1 250 cm^{-1}; $[\Phi]_{314}$ −2 360°, $[\Phi]_{292}$ 0°, and $[\Phi]_{278}$ +850°; *a* −32; $[\theta]_{296}$ −3 440°.

Further elution gave the trans-1β,2α-*cyclobutane* (**19**) (1.45 g), m.p. 209—212 °C (ether–light petroleum) (Found: C, 77.7; H, 10.1%); δ 3.08 (1 H, m, 2β-H), 2.02 (3 H, s, COMe), 1.20 (3 H, s), 1.10 (6 H, s), and 0.81 (3 H, s, 18-H_3); $\nu_{max.}$ 1 735, 1 715, and 1 250 cm^{-1}; $[\Phi]_{301}$ −4 830°, $[\Phi]_{258}$ 0°, and $[\Phi]_{273}$ +8 700°; *a* −135; $[\theta]_{285}$ −11 020°.

Epimerization of the *trans*-adduct (**19**) in a manner analogous to the cyclopentene adduct (**2**), followed by reacetylation with acetic anhydride and pyridine, furnished the cis-1β,2β-*adduct* (**20**), m.p. 137—140 °C (methanol–water) (Found: C, 77.4; H, 9.9%); δ 2.03 (3 H, s, COMe), 1.17 (3 H, s), 1.13 (3 H, s), 0.92 (3 H, s), and 0.81 (3 H, s); $\nu_{max.}$ 1 735, 1 705, and 1 255 cm^{-1}; $[\Phi]_{304}$ +930°, $[\Phi]_{286}$ 0°, and $[\Phi]_{265}$ −1 276°; *a* +22; $[\theta]_{287}$ +1 585°.

The same attempted epimerization on the *cis*-1α,2α-cyclobutane (**18**) regenerated the starting material (**18**) after reacetylation.

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