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STEROID PHOTOCHEMISTRY

THE PHOTOCYCLOADDITION OF A 3-KETO-4-ENE STEROID TO CYCLIC AND ACYCLIC OLEFINS

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Abstract—The photocycloaddition of the 3-keto-4-ene steroid **1** to cyclic and acyclic olefins has been studied. The predominant product formed was the *cis*-4α,5α-cyclobutane, together with substantial amounts of the *trans*-4α,5β-isomer and lesser amounts of its epimer, the *cis*-4β,5β-cyclobutane. Unsymmetrical olefins add to give head-to-tail adducts. The stereochemistry of the adducts has been determined by a combination of NMR and ORD/CD measurements.

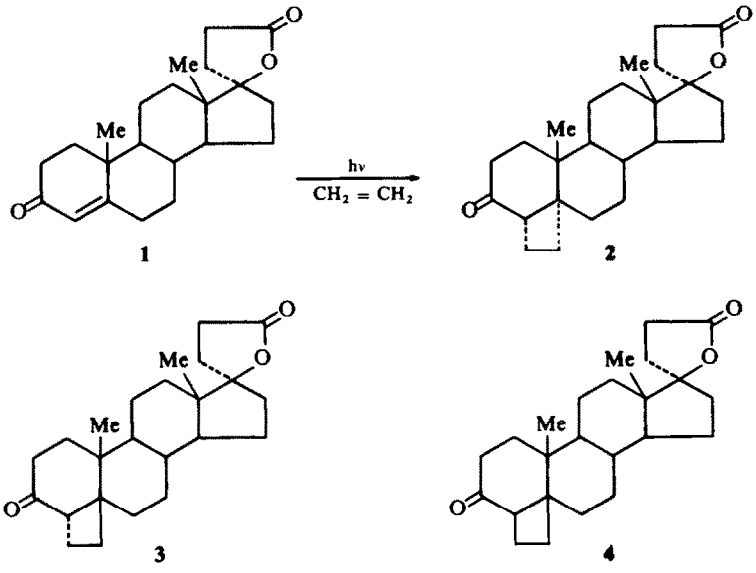
INTRODUCTION

THE PHOTOCHEMICAL CYCLOADDITION of cyclic α,β-unsaturated ketones to olefins has received considerable attention since its discovery.[1] However the use of this reaction in the steroid field has been usually limited to the study of a steroidal enone with one or two olefins. Fried's group has mentioned the addition of ethylene to testosterone and found only *cis*-α-addition.[2] Fried's group has also extensively studied cycloaddition reactions of 20-keto-16-ene steroids and found only *cis*-addition.[3] Recently, Rubin has studied the addition of ethylene and cyclopentene to testosterone propionate and presented evidence for *cis* and *trans*-fused adducts. We would like to report our results on the addition of a 3-keto-4-ene steroid (**1**) to a variety of substituted and unsubstituted cyclic and acyclic olefins.

RESULTS

Ethylene. In view of the conflicting results from Fried's and Rubin's experiments, we elected to study the addition of **1** to ethylene.[2,4] Irradiation of **1** in the presence of ethylene gave an 81% yield of three adducts (Table), detectable by TLC, which were cleanly separated on silica. The first isomer (**2**; 70%) was identified as the *cis*-fused cyclobutane by the unconjugated carbonyl at 1690 cm^{-1}, only $n \rightarrow \pi^*$ absorption in the uv, and stability towards methanolic NaOMe. The 4α,5α-stereochemistry was assigned on the basis of ORD/CD measurements, which showed a weak positive curve with a molecular amplitude of +26 (Fig. 1). The observed molecular amplitude, which is smaller than expected for a 5α-substituted steroid, indicates that the A-ring in **2** is either in a twist or boat conformation.[6] The conclusion is further strengthened by the position of the 19-Me resonance, which appears at 0·82 δ; compared with a calculated shift of 1·19 δ.[7]* This substantial shift is due to the 19-Me group experiencing the shielding effect of the 3-carbonyl in either the boat or twist form.

* Calculated using the 17β-acetoxy-17α-methyl values for the lactone ring in **1** from ref. 7.



The second isomer (**3**; 30%) off of the column possessed a *trans* 6-4 ring junction as indicated by ready epimerization with NaOMe. The strain inherent in this ring fusion was indicated by the cyclohexanone carbonyl band appearing at 1720 cm^{-1}. This frequency appears characteristic for all of the *trans*-fused cyclobutanes studied thus far in this work. The stereochemistry about the *trans*-ring junction was determined by ORD/CD. The curve of **3** had a molecular amplitude of +330, which, together with a positive CD curve, indicated that the hydrogen at C-4 was *beta*. Construction of the strained model demonstrates that **3** can exist either with the A-ring in the twist form with all carbon atoms in the positive octant or nodal planes or, alternatively, in the chair form with all the carbon atoms except C-1 in positive octants. This particular geometry accounts for the very large molecular amplitude observed, as compared to the ordinary unsubstituted AB-*trans* steroid.[8] Confirmatory evidence for the 4α,5β-stereochemical assignment was obtained by the *in situ* NaOMe epimerization to the 4β,5β-isomer (**4**). In the *in situ* epimerization, the ORD/CD curves of the 4α,5β-isomer were determined, and the solution treated with NaOMe for 18 hr., and the spectra

TABLE 1. THE PHOTOCYCLOADDITION OF **1** TO CYCLIC AND ACYCLIC OLEFINS*

Olefin	*cis*-4α,5α	*cis*-4β,5β	*trans*-4α,5β	Other
Ethylene	57% **2**	trace **4**	24% **3**	
Isobutylene	76% **5**	trace **7**	12% **6**	
1,1-Diethoxyethylene	—	—	—	11% **10**, 42% **B**, 27% **9**
Cyclopentene	43% **12**	9% **13**	35% **11**	1% **14**
1-Acetoxycyclopentene	30% **15**	trace	35% **16**	
Cyclohexene	40% **17**	12% **19**	25% **20**	15% **18**

* Yields are based on starting enone **1**.

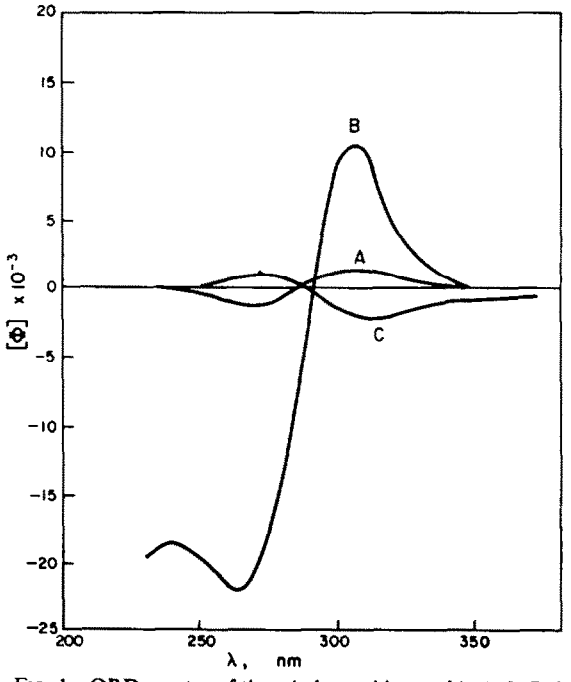


FIG. 1a. ORD spectra of the ethylene adducts of 1: A, 2; B, 3; C, 4.

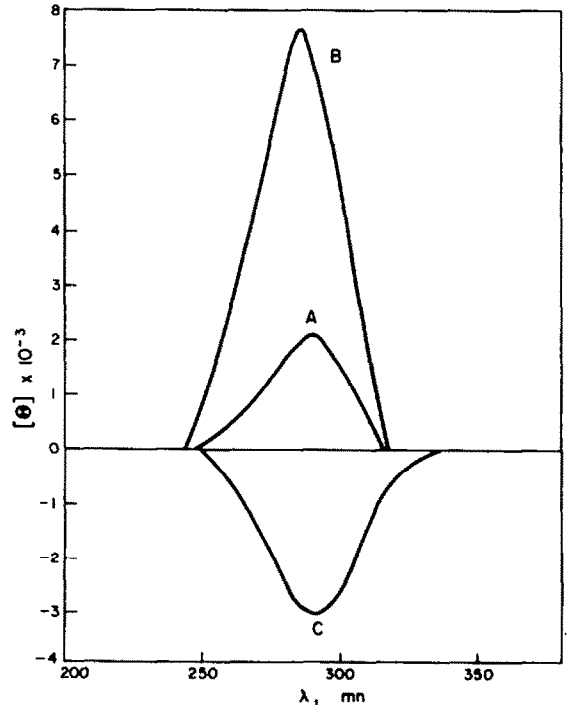
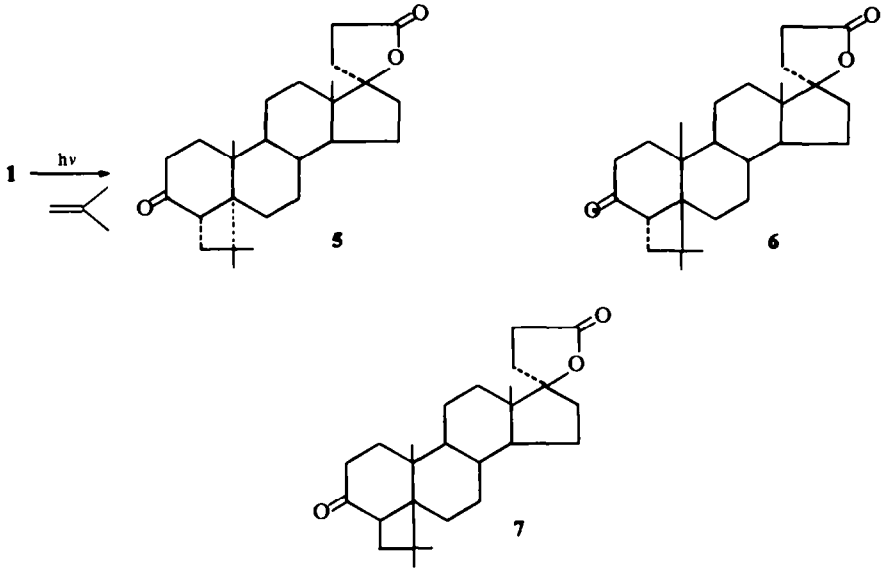


FIG. 1b. CD spectra of ethylene adducts of 1: A, 2; B, 3; C, 4.

rerecorded. The ORD curve of **3** had gone from a molecular amplitude of +330, to a negative molecular amplitude of −42 for the 4β,5β-isomer (**4**). Analogously the CD curve went from +8,000° (286 nm) for **3** to −3,050° (291 nm) for **4**. The 4β,5β-isomer was not characterized as a crystalline compound; however, preparative epimerization of the *trans*-isobutylene isomer gave ORD/CD curves indistinguishable from those obtained by *in situ* epimerization.

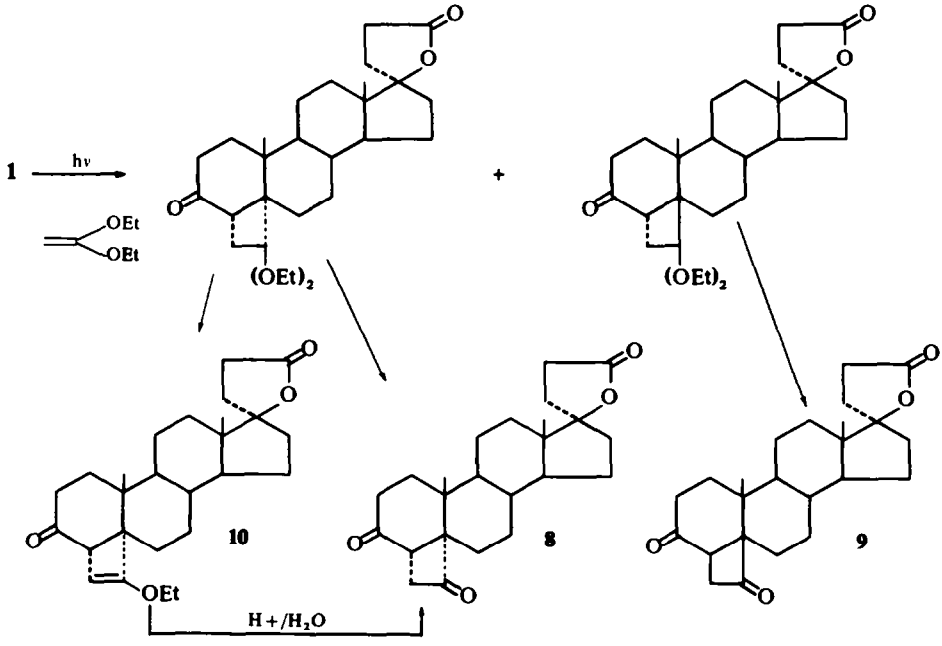
Isobutylene. To determine whether geminally substituted olefins add head-to-head or head-to-tail to **1**, the addition of **1** to isobutylene was studied. Irradiation of **1** in the presence of isobutylene resulted in three cyclobutane adducts being formed in 90% yield, which were separated by chromatography. The major adduct (85%) was the



cis-fused 4α,5α-adduct, as indicated by the positive Cotton effect in the ORD, and the inertness to alcoholic NaOMe. The *gem*-dimethyl group was assigned to the 3',3'-position (head-to-tail adduct) in **5** by analogy with the *trans*-adduct **6** where the Me groups could be securely located. Also only head-to-tail cyclobutanones were formed by the hydrolysis of the 1,1-diethoxyethylene adducts. The second compound isolated (**6**; 13%), was identified at the 4α,5β-*trans*-adduct (**6**) by its strong positive ORD curve (molecular amplitude +284), and the ready epimerization to the *cis*-4β,5β-adduct (**7**). That the isobutylene had added to form the head-to-tail adduct as indicated in **6** was demonstrated by the 4β-proton appearing as an ABX quartet at 3·43 δ. The *trans*-ethylene adduct (**3**) also shows the 4β-proton as the X-portion of an ABX spectrum at 3·25 δ. The third adduct (**7**; 3%) was identified as the 4β,5β-isomer by its negative Cotton effect, and the ready formation from **6** by base catalyzed epimerization.

Diethoxyethylene. The addition of **1** to 1,1-diethoxyethylene proceeded rapidly to give two isomers in a ratio of 70:30 by NMR analysis. Attempted chromatography on silica gave three products of differing R_f (**8**, **9**, **10**); resulting from hydrolysis and alcohol elimination from the cyclobutanone diethyl ketals.

The first compound (**10**) was isolated by chromatography and analyzed for the addition of diethoxyethylene; followed by the elimination of EtOH. The NMR spectrum showed a doublet at 4·50 δ (J = 1·5 Hz) for the cyclobutene proton, which is in agreement with both experimental and extrapolated values for vinyl-allylic

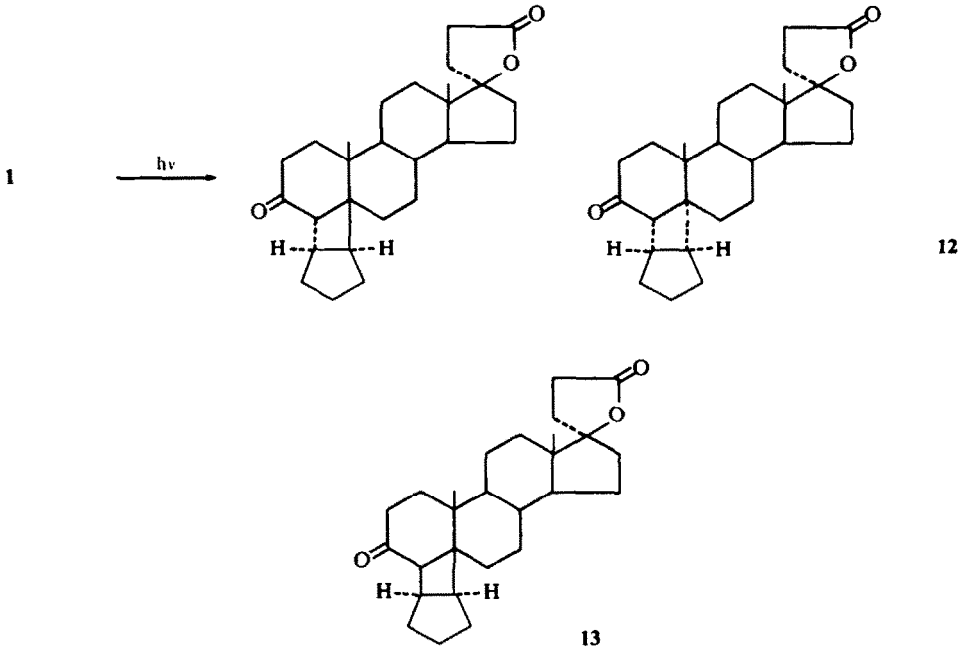


cyclobutene coupling constants.[9] The NMR spectrum also indicated the presence of one OEt group. The IR-spectrum shows an enol ether band at 1640 cm^{-1}, as well as the expected absorptions for the cyclohexanone and lactone carbonyls. The UV spectrum shows two maxima at 230 nm and 293 nm, indicating some degree of interaction between the cyclobutene double bond and the C-3 carbonyl. On this basis, **10** was formulated as an enol ether of cyclobutanone. Acid catalyzed hydrolysis of enol ether (**10**) gave the 4α,5α-cyclobutanone (**8**); thus establishing the stereochemistry of the adduct.

The second compound eluted (**8**) was identified as a cyclobutanone by an absorption at 1775 cm^{-1} in the IR spectrum. The lack of reaction with $FeCl_3$ indicated that the cyclobutanone formed by hydrolysis of ketal was 1,4 rather than 1,3.[10] Also the relative positions of the carbonyl groups were established by the appearance of an ABX system for the cyclobutanone hydrogens. The three spin system has been solved, and the coupling constants are in agreement with those from simpler cyclobutanones.[11] The most interesting observation was the occurence of a long range coupling on the order of 0·75 Hz between the axial 4β-hydrogen of the cyclobutanone and the axial 2β-hydrogen.

The third compound eluted, **9**, was also a cyclobutanone as evidenced by an IR absorption at 1780 cm^{-1}. The stability towards dilute base indicated a *cis*-fusion. That **9** was a cyclobutanone formed by head-to-tail addition of **1** to 1,1-diethoxyethylene, followed by hydrolysis was shown by lack of reaction with $FeCl_3$ and an ABX-spin system for the cyclobutanone protons.[10,11] The assignment of stereochemistry was accomplished in two ways. Construction and inspection of models of the 4α,5α- and 4β,5β-isomers indicated that in the 4β,5β-isomer the cyclobutanone carbonyl is coplanar and proximate to the angular C-19 Me group. This deshielding effect would cause the C-19 Me group of the 4β,5β-isomer to be at significantly lower field than the 4α,5β-isomer. The C-19 resonance at 1·10 δ for **9** compared to 0·87 δ for **8** indicates that **9** is the 4β,5β-isomer. The second method was to compare the ORD/CD curves. In the 6-dehydro-series of **1**, the 4α,5β- and 4β,5β-cyclobutanone ketals were stable and isolated, and the ORD/CD curves from these and the 4β,5β-cyclobutanone were determined, and the spectra of the 6-dehydrocyclobutanone was identical with **9**.[12]

Cyclopentene. The addition of **1** to cyclopentene proceeded rapidly and in 87% yield to form three photoadducts (**11**, **12**, **13**) which were separated by crystallization and chromatography. Crystallization of the residue gave the *trans*-isomer (**11**; 50%). The ORD curve of **11** shows a strong positive Cotton effect with a molecular amplitude of a = +308 (Fig. 2), and a positive CD curve, indicating the *trans*-adduct. The *trans*-



adduct (**11**) can be slowly epimerized to the 4β,5β-isomer (**13**). The NMR-spectrum of **11** in $CDCl_3$ shows an unresolved two proton multiplet at 3·03 δ. Perdeuteriobenzene resolves the multiplet at 3·03 δ into a one proton doublet at 4·52 δ (J = 9 Hz) and another one proton multiplet.[13]

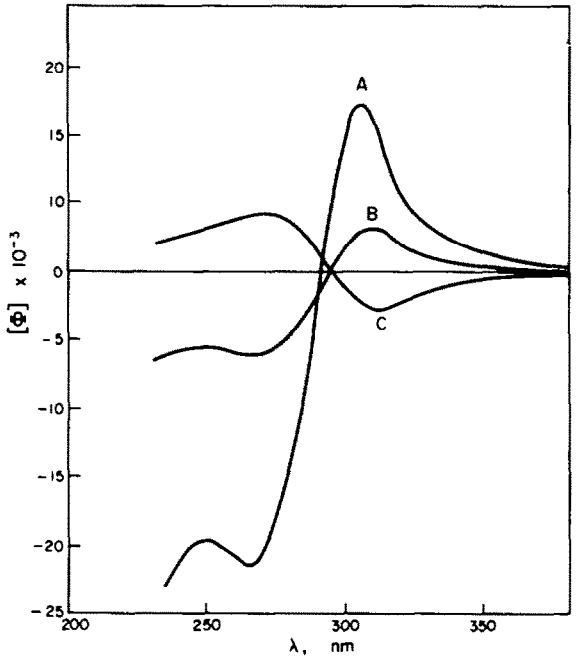


FIG. 2a. ORD spectra of the cyclopentene adducts of 1: A, 11; B, 12; C, 13.

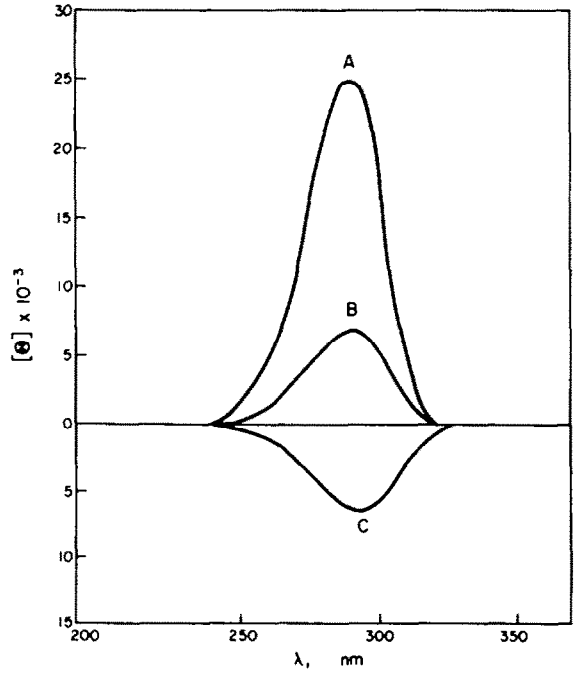
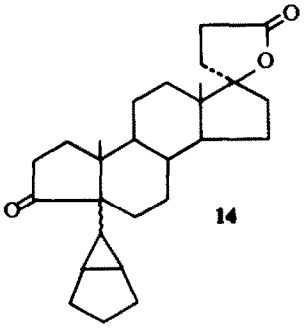


FIG. 2b. CD spectra of the cyclopentene adducts of 1: A, 11; B, 12; C, 13.

Chromatography of the residue, after crystallization of **11**, gave the 4α,5α-isomer (**12**; 40%). The structure was assigned on the basis of ORD/CD: the *cis*-adduct (**12**) showed a positive Cotton effect with a molecular amplitude of +92, and a positive CD curve. A 10% solution of **11** in $CDCl_3$ in the presence of 35 mg of tris(dipivalomethanato)europium shifted the 4β-proton to 3·77 δ ($J = 6$ Hz) at 100 MHz.[14] Closely following the 4α,5α-isomer, came the 4β,5β-isomer (**13**; 10%), identified by its negative Cotton effect and CD curve, and its ready preparation from the *trans*-isomer (**11**).

In the addition of cyclopentene, in contrast to the alicyclic olefins, there is the possibility of *syn*- and *anti*-isomerism. It is tempting to use the observed coupling constants for structural assignment, but the literature indicates the general undesirability of doing so.[11,15] However, addition of cyclopentene to excited enones is known to give almost exclusively the *anti*-isomer, and inspection of the model of the *syn*-isomer of **12** indicates that the cyclopentane protons would be touching the 1α- and 2α-protons of the steroid A-ring. For these reasons, the adducts are assigned the anti-configuration.[16]

In an early chromatography fraction, prior to elution of the cyclobutanes, a crystalline compound (**14**) was isolated in approximately 1% yield. The new compound analyzed correctly as an adduct of cyclopentene and steroid, but was not a cyclobutane.

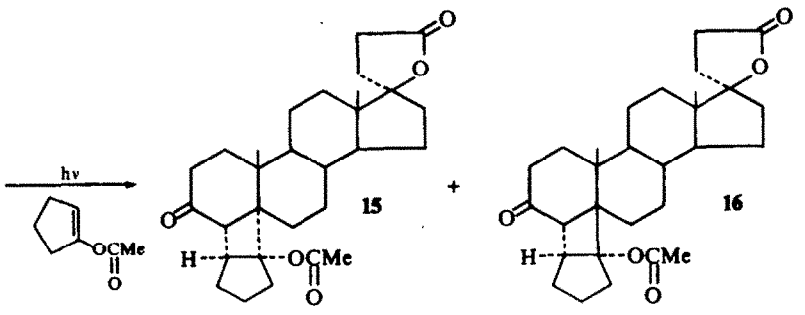


14

The IR spectrum of **14** showed the γ-lactone carbonyl at 1770 cm^{-1}, but instead of the usual cyclohexanone band, a cyclopentanone was evident from the band at 1740 cm^{-1}.[17] Only weak n → π* absorption was apparent in the UV. However, the NMR showed a cyclopropyl multiplet at 0·41 δ, and no olefinic unsaturation. On this basis, **14** was formulated as a A-nor-5-cyclopropyl steroid. Compound **14** could be formed from **12** by direct irradiation, along with many other products; indicating that **14** is a secondary irradiation product.

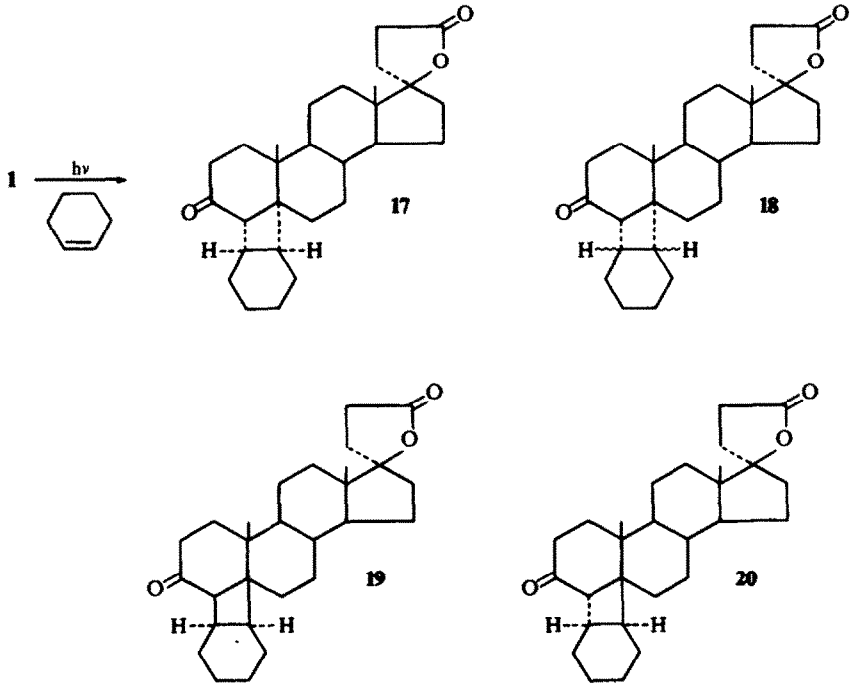
1-*Acetoxycylopentene.* The cycloaddition of **1** to 1-acetoxycyclopentene proceeded rapidly, with some photopolymerization of the olefin, to yield two adducts, **15** and **16**. Chromatography separated the two adducts, **15** being eluted first in 30% yield. Compound **15** was identified as the *cis*-4α,5α-isomer on the basis of a weak positive Cotton effect (a = +29) and a positive CD curve. The *anti*-stereochemistry was assigned on the similarity of the chemical shifts of the C-18 and C-19 Me groups with those of **12**. Continued elution gave a 35% yield of the *trans*-4α,5β-isomer (**16**).

Compound **16** showed the strong positive Cotton effect (a = +187) characteristic of the *trans*-isomer, and the strained cyclohexanone carbonyl band at 1725 cm^{-1}. The



NMR spectrum of **16** in perdeuteriobenzene indicated a doublet (J = 9 Hz) demonstrating the same stereochemistry as the *trans*-4α,5β-cyclopentene adduct (**11**).

Cyclohexene. The reaction of **1** with cyclohexene proceeded rapidly as with the other olefins. However, in this case, four isomeric adducts were detected by TLC and separated by chromatography. The first compound eluted was the *cis*-4α,5α-cyclobutane (**17**; 40%). The *cis*-4α,5α-stereochemistry was assigned on the basis of a positive Cotton effect (a = +56), inertness to NaOMe, and the cyclohexanone carbonyl at 1695 cm^{-1}. The *anti*-stereochemistry was assigned on the basis of Tris-(dipivalomethanato)europium induced chemical shifts.[14] A 10% $CDCl_3$ solution of



17 showed, in the presence of 35 mg of europium complex, a doublet at 6·33 δ with a coupling constant of 7 Hz, comparable with that of **12**. Continued elution gave 15% of **18** which was assigned the 4α,5α-stereochemistry on the basis of the positive Cotton effect and CD spectrum. Compound **18** also possessed a cyclohexanone carbonyl absorption at 1695 cm^{-1}, and was inert to NaOMe. The C-18 Me group of **18** was identical to that of **17**, and the C-19 Me groups of **17** and **18** differed by only one hertz.

Chemical shifts induced by the europium complex (35 mg) caused the C-2 protons and the C-4 cyclobutane proton to overlap and form a broad multiplet from which no meaningful coupling constants could be extracted.[14] Smaller amounts of europium caused no significant shifts. As a result, stereochemistry beyond that of the 4α,5α-cyclobutane fusion was not assignable. The third compound eluted (**19**; 12%) was the *cis*-4β,5β-cyclobutane. Compound **19** possessed a negative Cotton effect (a = −56) and a negative CD spectrum, and was easily formed by epimerization of the *trans*-compound (**19**). Tris(dipivalomethanato)europium allowed the determination of the C-4 cyclobutane coupling constant, as a doublet (J = 8·2 Hz) at 4·57 δ. The final compound eluted was the *trans*-4α,5β-cyclobutane (**20**) formed in 25% yield. The *trans*-cyclobutane followed from the strong positive Cotton effect (a = +367) and positive CD spectrum, and the cyclohexanone carbonyl at 1720 cm^{-1}. Epimerization cleanly gave the 4β,5β-isomer (**19**). In contrast to the other *trans*-isomers obtained during this study, the axial C-4 proton was not shifted out of the methylene envelope. However, tris(dipivalomethanato europium (35 mg) shifted the C-4 proton to 4·21 δ (J = 10 Hz). The observed coupling constant is comparable with that of the *trans*-cyclopentene adduct (**11**), indicating the *trans*-anti-stereochemistry.

DISCUSSION

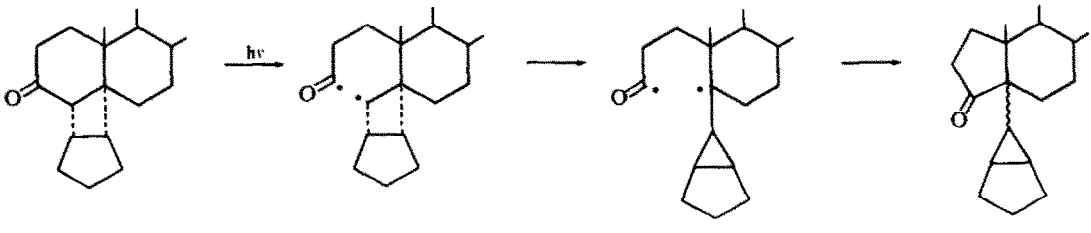
The original mechanism described by Corey for enone-olefin cycloaddition is still generally accepted as valid.[1] This mechanism envisages excitation of the enone, and intersystem crossing followed by complex formation to form a diradical and subsequent ring closure. One of the initial questions still unanswered is whether the initial bonding to form the diradical is between the olefin and the α- or β-carbon of the enone. However, there is substantial evidence for the nonconcerted nature of the reaction.[18] The addition of the steroidal enone **1** also proceeds *via* the triplet as the reaction is quenched by both piperylene and ferric acetylacetonate.[19] The nature of the excited state is not known, but recent measurements indicate the $\pi \rightarrow \pi^*$ triplet is slightly lower than the $n \rightarrow \pi^*$ triplet in 4-en-3-one steroids.[20] This is in direct contrast to the results from the 4,6-dien-3-one steroids where the reaction appears to proceed *via* the singlet.[12]

The addition of the enone to ethylene is an interesting reaction. Until recently, there have been very few cases where the excited enone was able to add to ethylene, and these have either involved negatively substituted enones, or been conducted in a specially constructed low temperature apparatus.[21, 22] This lack of reactivity has been attributed to two factors: (a) the relative insolubility of ethylene in common organic solvents at room temperature, and (b) that the excited enone is moderately electrophilic; reacting faster with electron rich olefins.[1] Then the reaction of **1** at room temp and low ethylene concentration is rather remarkable, and implies a long-lived triplet. Kearns has found the triplet lifetime of testosterone acetate to be 28 msec, compared with a few nanoseconds for cyclohexenone.[20, 23]

The orientation of the addition of substituted olefins to **1** was of considerable interest to us, since the steroidal enone is similar to 3-methylcyclohexenone. Corey has shown that in cyclohexenone, olefins add predominantly in head-to-tail fashion, while addition to 3-methylcyclohexenone proceeded at the same rate but with dramatically altered orientation, giving head-to-head adducts.[12] It was expected that **1** would add to olefins to give head-to-head adducts, and it was surprising that only head-to-tail adducts were formed from the substituted ethylenes and cyclopentene. The reason for this unexpected orientation is obscure, but may be the result of the methylene group in **1** being constrained as part of the steroid B-ring and therefore generating less steric interference than the freely rotating methyl group in 3-methylcyclohexenone.

The difference in the products of the addition of **1** to five and six membered cyclic olefins was interesting. The addition of cyclopentene gave only three isomers, one *trans* and two *cis*, analogous to the acyclic olefins. Inspection of models, indicates that the adducts are probably in the *anti*-configuration, since, in the 4α,5α-*cis*-adduct, hydrogens on the cyclopentane ring would be actually touching hydrogens on the steroid A-ring. However, with cyclohexene there is sufficiently more flexibility in the ring so that an additional isomer is formed. Inspection of models indicates that all three possibilities are structurally feasible, one syn-configuration, and two *trans*-conformations in the cyclohexane ring. DeMayo has found that cyclopentenone adds cyclohexene to give four isomeric cyclobutanes, but has not determined their structures.[24] Griffin has studied the addition of cycloheptene to cyclopentenone and determined the structures of the four adducts, finding that both *syn*-, *anti*- and the two possible *trans*-cycloheptane/cyclobutane adducts are formed.[25] The europium shift reagent was used in an attempt to determine the coupling constant of the 4β-proton of the new isomer (**18**) but no success was attained, and the detailed stereochemistry about the cyclohexane-cyclobutane ring remains unknown.[14]

The formation of the 5-cyclopropyl-A-norsteroid (**14**) from cyclobutane **12** is unique, and may be envisaged as proceeding through Norrish Type I cleavage to generate an acyl and a cyclobutyl radical. The cyclobutyl radical then rearranges to the cyclopropyl carbonyl radical followed by ring closure to give the observed product. Alternatively ring closure of the cyclobutyl radical with the acyl radical would regenerate starting material, or possibly *trans*-isomer. It is not known whether the stereochemistry about the steroid A/B ring is maintained. There is some documenta-



tion in the literature for the interconvertibility of cyclobutyl and cyclopropylcarbinyl radicals.[26] Finally, it should be pointed out that **14** was eluted from silica gel along with other products, and was isolated due to its ready crystallization, and also to the large amount of steroid irradiated.

In general, the photocycloaddition of the Δ^4-3-keto steroid (1) to olefins generates *cis*-4α,5α-cyclobutanes, *trans*-4α,5β-cyclobutanes, and lesser amounts of the *cis*-4β,5β-cyclobutane easily and in high yield. The 4β,5β-isomer may be formed as the result of fortuitous epimerization of the *trans*-isomer. Also only head-to-tail adducts are formed from geminally substituted olefins, and the substituted and unsubstituted cyclopentenes give only the *anti*-adducts. Cyclohexene, on the other hand, resembles the simpler cyclohexenone in the formation of several products thereby lessening its synthetic utility.

EXPERIMENTAL

M.ps were taken on a Thomas–Hoover Uni-Melt capillary apparatus and are uncorrected. IR spectra were taken in KBr, unless otherwise noted, and UV spectra were run in MeOH and are not recorded if only $n \rightarrow \pi^*$-absorption was observed. A Varian Associates A-60 or HA-100 spectrophometer was used to record NMR spectra. All spectra were run in $CDCl_3$ solution, TMS as an internal standard unless otherwise noted. ORD/CD curves were run in MeOH on a Jasco ORD/UV-5 spectrometer.

Irradiation procedures. A 450 watt Hanovia medium pressure arc, 679A-36, was used as the source of UV light, and was contained in a pyrex 51 immersion well. The irradiation vessel consisted of a reservoir of 550 ml capacity with provision for magnetic stirring and a gas inlet tube. All irradiations were run under N_2, or, if a gaseous olefin was used, the olefin served to exclude oxygen. All irradiations were monitored by TLC, and were run until essential disappearance of starting material.

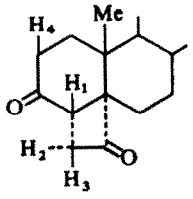
Photocycloaddition of 3-(3-*oxo*-17β-*hydroxy*-4-*androsten*-17α-*yl*)*propionic acid lactone* (1) *to ethylene.* A solution of 6·00 g of 1 in 500 ml EtOAc was stirred magnetically and irradiated for 6 hr while a slow stream of ethylene was passed through the solution. Evaporation of solvent and chromatography on 700 g of Baker silica with 5% EtOAc/benzene gave 3·68 g of 17β-hydroxy-1′βH-cyclobut(4,5)-5α-3-oxo-androstane-17α-propionic acid-γ-lactone, m.p. 267–70° (EtOAc): IR, 1770, 1690 cm^{-1}; NMR ($CDCl_3$), 0·92 δ (s, 3H), 0·82 δ (s, 3H); ORD, $[\phi]_{306}$ + 1550°, $[\phi]_{292}$ 0°, $[\phi]_{287}$ −1100°, a = +26; CD, $[\theta]_{289}$ +2100°. (Calc. for $C_{24}H_{34}O_3$: C, 77·80; H, 9·25. Found: C, 77·63; H, 9·43%). Continued elution gave 1·59 g of the *trans*-fused isomer, 17β-hydroxy-1′βH-cyclobut(4,5)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 232 – 5° (EtOAc). IR, 1765, 1720 cm^{-1}; NMR, 3·26 δ (q, ABX, J = 6, 10 Hz), 1·00 δ (S, 3H), 0·89 δ (S, 3H); ORD, $[\phi]_{303}$ +10,700°, $[\phi]_{290}$ 0°, $[\phi]_{263}$ −22,200°, $[\phi]_{240}$ −18,500°, a = +330; CD, $[\phi]_{286}$ +8,000°. (Calc. for $C_{24}H_{34}O_3$: C, 77·80; H, 9·25. Found: C, 77·77; H, 9·45%). A small fraction intermediate between the 4α,5α- and 5α,5β-isomers was identified as the 4β,5β-epimer by TLC, but was not isolated.

Epimerization of the 4α,5β-trans-*ethylene-adduct.* The ORD/CD curves of a 100 mg% solution of the 4α,5β-*trans*-ethylene adduct were recorded, and then solution was equilibrated overnight with 5 mg of NaOMe to produce a solution of the 4β,5β-adduct, 17β-hydroxy-1′αH-cyclobut(4,5)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone: ORD, $[\phi]_{308}$ −3150°, $[\phi]_{288}$ 0°, $[\phi]_{272}$ +1050°, a = −42; CD, $[\phi]_{291}$ −3,050°.

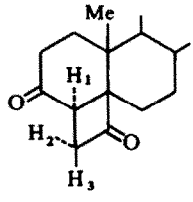
Photochemical cycloaddition of 1 *to isobutylene.* A solution of 10·0 g of 1 in 550 ml EtOAc was irradiated for 7 hr in the presence of isobutylene. The solvent was removed and the residue crystallized from EtOAc to give 3·50 g of the 4α,5α-isomer, 3′,3′-dimethyl-17β-hydroxy-1′βH-cyclobut(4,5)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 200–2° (EtOAc/petroleum ether): IR, 1775, 1695 cm^{-1}; NMR, 1·27 δ (s, 3H), 0·92 δ (s, 6H), 0·80 δ (s, 3H); ORD, $[\phi]_{312}$ +1,800°, $[\phi]_{297}$ 0°, $[\phi]_{272}$ −4,000°, a = +58; CD, $[\theta]_{295}$ +3,750. (Calc. for $C_{26}H_{38}O_3$: C, 78·35; H, 9·61. Found: C, 78·15; H, 9·72%). A second crop of 900 mg was collected which was found by TLC to consist of two compounds in equal amounts; the previously described 4α,5α-isomer and the 4α,5β-*trans*-isomer, 3′,3′-dimethyl-17β-hydroxy-1′βH-cyclobut(4,5)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 230–2° (EtOAc/petroleum ether): IR, 1765, 1720 cm^{-1}; NMR: 3·34 δ (q, ABX, J = 7, 10 Hz), 1·37 δ (s, 3H), 1·21 δ (s, 3H), 1·12 δ (s, 3H), 0·93 δ (s, 3H); ORD, $[\phi]_{306}$ +9,400°, $[\phi]_{294}$ 0°, $[\phi]_{268}$ −19,000°, $[\phi]_{246}$ −16,250°, a = +284; CD, $[\theta]_{288}$ +21,500°. (Calc. for $C_{26}H_{38}O_3$: C, 78·35; H, 9·61. Found: C, 78·18; H, 9·75%). The residue was chromatographed on 700 g of Baker silica gel. Elution with 10% EtOAc/benzene gave a further 4·87 g of the 4α,5α-isomer. Continued elution gave 1·17 g of a mixture of the 4α,5β- and 4β,5β-isomers. Epimerization of this mixture with NaOMe in MeOH gave the 4β,5β-isomer, 3′,3′-dimethyl-17β-hydroxy-1′αH-cyclobut(4,5)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 224–30° (ether/petroleum ether): IR, 1775, 1695 cm^{-1}; NMR 1·27 δ

(s, 3H), 0·93 δ (s, 6H), 0·80 δ (s, 3H); ORD, $[\phi]_{314}$ −2,800°, $[\phi]_{296}$ 0°, $[\phi]_{276}$ +2,350°, a = −51; CD, $[\theta]_{297}$ −5,100°. (Calc. for $C_{26}H_{38}O_3$: C, 78·35; H, 9·61. Found: C, 78·14; H, 9·63%). The ORD/CD curves of the crystalline 4β,5β-isomer and the 4β,5β-isomer formed by *in situ* epimerization with methoxide were identical.

Photochemical cycloaddition of **1** *to* 1,1-*diethoxyethlene.* A solution of 10·0 g of **1** in 15 ml of 1,1-diethoxyethylene and 550 ml EtOAc was irradiated for 6 hr. The solvent was removed at reduced pressure, and dissolved in 200 ml of 80% aqueous AcOH, containing a few drops of con. HCl. A precipitate formed which was collected, dried, and crystallized from CH_2Cl_2/EtOAc to give 3·32 g of the 4α,5α-isomer, 17β-hydroxy-1′βH-3′-oxocyclobut(4,5)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 322–5°: IR, 1775, 1765, 1700 cm^{-1}; NMR 0·93 δ (s, 3H), 0·88 δ (s, 3H), 4·55 δ (H_1, $\underline{A}BX$), 4·65 δ (H_2, $A\underline{B}X$), 5·73 δ (H_3, $AB\underline{X}$)



$J_{1,4}$ = 0·8, $J_{1,2}$ = 4·5 Hz, $J_{1,3}$ = 11·1, $J_{2,3}$ = −18·7 Hz. (Calc. for $C_{24}H_{32}O_4$: C, 74·97: H, 8·39. Found: C, 74·78; H, 8·33%). Limited solubility in the usual ORD/CD solvents precluded accurate determination of molecular rotations. Slow addition of water (300 ml) to the AcOH aq. gave a gummy solid, which, upon recrystallization from CH_2Cl_2/EtOAc, gave 3·15 g of the 4β,5β-isomer, 17β-hydroxy-1′αH-3′-oxocyclobut-(4,5)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 221–5°: IR, 1780, 1760, 1725 cm^{-1}; NMR, 1·10 δ (s, 3H), 0·95 δ (s, 3H), 5·75 δ (H_1, $\underline{A}BX$), 5·61 δ (H_2, $A\underline{B}X$) 4·30 δ (H_3, $AB\underline{X}$), $J_{1,2}$ = 10·7, $J_{1,3}$ = 8·1,



$J_{2,3}$ = −16·0 Hz; ORD, $[\phi]_{301}$ +6,550°, $[\phi]_{285}$ 0°, $[\phi]_{262}$ −9,800°, a = +163; CD, $[\theta]_{284}$ +13,100°. (Calc. for $C_{24}H_{32}O_4$: C, 74·97; H, 8·39. Found: C, 74·66; H, 8·32%).

In a different experiment utilizing the same amounts and irradiation conditions, the residue, after solvent removal, was chromatographed on 1500 g of Mallinckrodt CC-7. Elution with 10% EtOAc/benzene gave 1·30 g of 3′-ethoxy-17-hydroxy-1′βH-cyclobut-3′-eno(4,5)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 199–203° (EtOAc/petroleum ether); IR, 1760, 1695, 1640 cm^{-1}; UV, 230 nm (ε 2000), 293 nm (ε 300); NMR, 4·50 δ (d, J = 1·5 Hz, 1H), 3·95 δ (q, 2H), 1·37 δ (t, 3H), 0·97 δ (s, 3H), 0·87 δ (s, 3H); ORD, $[\phi]_{312}$ +22,700°, $[\phi]_{296}$ 0°, $[\phi]_{264}$ −39,200°, a = +619; CD, $[\phi]_{296}$ +38,200°. (Calc. for $C_{26}H_{36}O_4$: C, 75·69; H, 8·80. Found: C, 75·84; H, 8·94%). Continued elution gave 4·70 g of the 4α,5α-cyclobutanone, and elution with 15% EtOAc/benzene gave 3·02 g of the 4β,5β-cyclobutanone.

Hydrolysis of the cyclobutanone enol ether in MeOH/water with dil. HCl gave the 4α,5α-cyclobutanone.

Photochemical cycloaddition to cyclopentene. A solution of 10·0 g of **1** in 20 ml cyclopentene and 550 ml EtOAc was irradiated for 6 hr. The residue, after removal of solvent, gave 2·70 g of the *trans*-isomer, 1′α,5′α-dihydro-17β-hydroxy-6′βH-4,5-(6′7′-bicyclo[3.2.0.]heptano)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 244–8°: IR, 1780, 1725 cm^{-1}; NMR ($CDCl_3$), 3·06 δ (m, 2H), 1·13 δ (s, 3H), 0·93 δ (s, 3H); (C_6D_6), 4·51 δ (d, J = 9 Hz, 1H), 0·82 δ (s, 3H), 0·77 δ (s, 3H); ORD, $[\phi]_{304}$ +12,300°, $[\phi]_{296}$ 0°, $[\phi]_{268}$ −22,500°, a = +308; CD, $[\theta]$ +25,000°. (Calc. for $C_{27}H_{38}O_3$: C, 78·98; H, 9·33. Found: C, 79·28; H, 9·32%). Chromatography of the residue on 800 g of Mallinckrodt CC-7 gave, with 10% EtOAc/benzene, 0·255 g of a compound homogeneous by TLC. Crystallization from ether/petroleum ether gave 0·120 g of

5ξ-(6'-bicyclo[3.1.0]hexanyl)-17β-hydroxy-A-norandrostane-17α-propionic acid-γ-lactone, m.p. 242–4°: IR, 1770, 1740 cm^{-1}; NMR, 0·42 δ (m, cyclopropyl), 1·12 δ (s, 3H), 0·97 δ (s, 3H); ORD, $[\phi]_{326}$ +1·750°, $[\phi]_{316}$ +1,200°, $[\phi]_{308}$ 0°, $[\phi]_{305}$ −200°, $[\phi]_{280}$ −1,050°, $[\phi]_{254}$ −350°: CD, $[\theta]_{320}$ +1,450°, $[\theta]_{310}$ 2,200°, $[\theta]_{300}$ +1,900, $[\theta]_{255}$ +200°. (Calc. for $C_{27}H_{38}O_3$: C, 78·98; H, 9·33. Found: C, 78·83; H, 9·30%). Continued elution gave 3·72 g of the 4α,5α-isomer, 1'α,5'α-dihydro-17β-hydroxy-6'βH-4,5-(6'7'-bicyclo-[3.2.0]heptano)-5α-3-oxoandrostane-17α- propionic acid-γ-lactone, m.p. 233–5° (EtOAc/petroleum ether): IR, 1775, 1705 cm^{-1}; NMR, 0·92 δ (s, 3H), 0·83 δ (s, 3H); ORD, $[\phi]_{309}$ +3,100°, $[\phi]_{294}$ 0°, $[\phi]_{263}$ −6,100°, $[\phi]_{247}$ −5,700°, a = +92; CD, $[\theta]_{290}$ +6,900. (Calc. for $C_{27}H_{38}O_3$: C, 78·98; H, 9·33. Found: C, 79·13; H, 9·04%). Continued elution gave 1·14 g of the 4β,5β-isomer, 1'α,5'α-dihydro-17β-hydroxy-6'αH-4,5-(6'7'-bicyclo[3.2.0]heptano)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 210–2° (ether/petroleum ether): IR, 1785, 1775 sh, 1695 cm^{-1}; NMR, 0·92 δ (s, 3H), 0·85 δ (s, 3H); ORD, $[\phi]_{311}$ −2,000°, $[\phi]_{295}$ 0°, $[\phi]_{271}$ +2,900°, a = −69, CD, $[\theta]_{291}$ −4,300°. (Calc. for $C_{27}H_{38}O_3$: C, 78·98; H, 9·33. Found: C, 79·04; H, 9·18%). Continued elution gave an additional 1·26 g of the *trans* 4α,5β-isomer.

Epimerization of the *trans*-4α,5β-isomer with NaOMe gave the 4β,5β-isomer, identical with the compound isolated from the chromatography.

Photocycloaddition of **1** *to 1-acetoxycyclopentene.* A solution of **1** (10·0 g) in 15 ml of 1-acetoxycyclopentene and 600 ml EtOAc was irradiated (pyrex filter), under N_2, for 9 hr. During irradiation, the solution became opaque and was treated with decolorizing carbon. Evaporation of the solvent and chromatography on 1600 g of Mallinckrodt CC-7 silica gave, with 10% EtOAc/benzene, 3·09 g of the 4α,5α-isomer, 1'α-acetoxy-5'α-hydro-17β-hydroxy-6'βH-4,5-(6',7'-bicyclo[3.2.0]heptano)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 273–6°: IR, 1775, 1735, 1710 cm^{-1}; NMR ($CDCl_3$), 3·18 δ (m, 1H), 2·03 δ (s, 3H), 0·96 δ (s, 3H), 0·88 δ (s, 3H); (C_6D_6), 3·18 δ (m, 1H), 2·60 δ (broad, s, 1H), 1·61 δ (s, 3H), 0·80 δ (s, 3H), 0·64 δ (s, 3H); ORD $[\phi]_{314}$ +1,360°, $[\phi]_{295}$ 0°, $[\phi]_{274}$ −1500°, a = +29; CD; $[\theta]_{296}$ +2000°. (Calc. for $C_{29}H_{40}O_5$: C, 74·32; H, 8·60. Found: C, 74·38; H, 8·62%). Continued elution with 10% EtOAc/benzene gave 3·78 g of the *trans*-4α,5β-isomer, 1'α-acetoxy-5α-hydro-17β-hydroxy-6'βH-4,5-(6',7'-bicyclo[3.2.0]heptano)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 251–5°: IR, 1770, 1735, 1725 cm^{-1}; NMR ($CDCl_3$) 3·15 δ (m, 1H), 2·80 δ (broad s, 1H), 2·03 δ (s, 3H), 1·35 δ (s, 3H); 1·00 δ (s, 3H); (C_6D_6), 3·20 δ (m, 1H), 2·32 δ (d, J = 10 Hz, 1H), 1·63 δ (s, 3H); 1·04 δ (s, 3H); 0·90 δ (s, 3H); ORD, $[\phi]_{304}$ +6,400°, $[\phi]_{291}$ 0°, $[\phi]_{274}$ −12,300°, a = +187; CD, $[\theta]_{288}$ +14,100°. (Calc. for $C_{29}H_{40}O_5$: C, 74·32; H, 8·60. Found: C, 74·26; H, 8·90%). In the fraction just preceeding the 4α,5β-*trans*-isomer, the 4β,5β-isomer was found in low yield. This compound could not be induced to crystallize, but was solidified to a foam by heating under vacuum in an Abderhalden apparatus: IR, 1770, 1735, 1695 cm^{-1}; NMR ($CDCl_3$), 3·10 δ (m, 1H), 1·20 δ (s, 3H), 0·92 δ (s, 3H), 0·84 δ (s, 3H).

Photocycloaddition of **1** *to Cyclohexene.* A solution of 10 g of **1** in 50 ml of cyclohexene and 550 ml of EtOAc was irradiated for 3 hr. The solvent was evaporated and the residue chromatographed on 1500 g of Mallinckrodt CC-7 silica. Elution with 5% EtOAc/benzene gave 4·81 of 7'α,8'α-dihydro-17β-hydroxy-6'βH-4,5-(7',8'-bicyclo[4.2.0]octano)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 220–5°: IR, 1780 cm^{-1}, 1695 cm^{-1}; NMR ($CDCl_3$), 0·93 δ (s, 3H), 0·78 δ (s, 3H); ORD, $[\phi]_{308}$ +2,300°, $[\phi]_{291}$ 0°, $[\phi]_{266}$ −3,300°, a = +56; CD, $[\phi]_{289}$ +4,250. (Calc. for $C_{28}H_{40}O_3$: C, 79·20; H, 9·50. Found: C, 79·14; H, 9·52%). Tris (dipivalomethanato) europium (35 mg) in a 10% solution of the 4α,5α-isomer in $CDCl_3$ showed the following shifts at 60 MHz: 6·33 δ (d, J = 7 Hz, 1H), 2·22 δ (s, 3H), 1·62 δ (s, 3H). Continued elution gave 1·89 g of 7'ξ,8'ξ-dihydro-17β -hydroxy-6'βH-4,5-(7',8'-bicyclo[4.2.0]octano)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 198–200°; IR, 1770, 1695 cm^{-1}; NMR 0·93 δ (s, 3H), 0·80 δ (s, 3H); ORD, tion gave 1·89 g of 7'ξ,8'ξ-hydroxy-6'βH-4,5-(7',8'-bicyclo[4.2.0]octano)-5α-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 198–200°; IR, 1770, 1695 cm^{-1}; NMR 0·93 δ (s, 3H), 0·80 δ (s, 3H); ORD, $[\phi]_{309}$ +4,400°, $[\phi]_{291}$ 0°, $[\phi]_{269}$ −5,100°, a = +95: CD, $[\phi]_{290}$ +7,800°. (Calc. for $C_{28}H_{40}O_3$: C, 79·20; H, 9·50. Found: C, 79·33; H, 9·72%). Tris(Dipivalomethanato)europium (35 mg) in a 10% $CDCl_3$ solution of the steroid showed the following shifts: 2·58 δ (s, 3H), 1·70 δ (s, 3H). Continued elution gave 1·59 g of 7'α,8'α-dihydro-17β-hydroxy-6'αH-4,5-(7'8'-bicyclo[4.2.0]octano)-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 224–26°: IR, 1765, 1695 cm^{-1}; NMR, 0·97 δ (s, 3H), 0·90 δ (s, 3H); ORD, $[\phi]_{313}$ − 2,150°, $[\phi]_{296}$ 0°, $[\phi]_{272}$ + 3,500, a = − 56; CD, $[\theta]_{293}$ − 10,600°. (Calc. for $C_{28}H_{40}O_3$: C, 79·20: H, 9·50. Found: C, 79·11; H, 9·48%). Tris(dipivalomethanato)europium (35 mg) in a 10% solution of the 4β,5β-isomer showed the following shifts: 4·57 δ (d, J = 8·2, 1H), 1·53 δ (s, 3H), 1·42 δ (s, 3H). Continued elution gave 3·03 g of the 4α,5β-*trans*-isomer, 7'α,8'α-17β-hydroxy-6'βH-4,5(7',8'-bicyclo[4.2.0]-5β-3-oxoandrostane-17α-propionic acid-γ-lactone, m.p. 239–41°: IR, 1770, 1720 cm^{-1}; NMR, 1·02 δ (s, 3H), 0·92 δ (s, 3H): ORD, $[\phi]_{306}$ +13,600°, $[\phi]_{292}$ 0°, $[\phi]_{264}$ −23,100°, a = +367; CD, $[\theta]_{288}$ +30,800°.

(Calc. for $C_{28}H_{40}O_3$: C, 79·20; H, 9·50. Found: C, 79·04; H, 9·56%). Tris(dipivalomethanato)europium (35 mg) in a 10% solution of the 4α,5β-isomer showed the following shifts: 4·21 δ (d, J = 10 Hz, 1H), 1·40 δ (s, 3H), 1·28 δ (s, 3H).

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