19B (a mixture of cis and trans isomers; ca. 2:3): IR (CCl_4) 3430, 1680, 1410, 1190 cm^{-1}; ^1H NMR (CCl_4) δ 1.42 and 1.49 (each s, 9 H), 1.82, 2.09, 2.14, and 2.18 (each s, 6 H), 5.24 and 5.42 (each s, 1 H), 6.63 and 6.70 (each s, 1 H), 6.9–7.1 (m, 5 H), 7.35–7.5 (m, 2 H); MS, for $C_{21}H_{24}O_4$ m/e 340.1674 (theory 340.1672).

22: colorless prisms, mp 130–132 °C; IR (CCl_4) 1645, 1470, 1425 cm^{-1}; ^1H NMR (CCl_4) δ 2.20 (s, 3 H) 2.27 (s, 3 H), 3.88 (s, 3 H), 7.0–7.5 (m, 7 H). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.57. Found: C, 76.85; H, 5.71.

25: colorless prisms, mp 153–155 °C; IR (CCl_4) 1630, 1470, 1425 cm^{-1}; ^1H NMR (CCl_4) δ 2.03 (s, 3 H), 2.26 (s, 3 H), 3.86 (s, 3 H), 7.14 (s, 1 H), 7.4–7.7 (m, 6 H). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.22; H, 5.75.

The syntheses of **22** and **25** by another route were reported in the previous paper.[9]

The reaction of **15** in acetone was also carried out under the same conditions. After removal of the solvent the residue was chromatographed on column with benzene as eluent. The first yellow component was recovered **15** (a mixture of cis and trans isomers, 81%), and the residue was eluted by ether. The ether eluent was further chromatographed on TLC ($CHCl_3$ containing 15% AcOEt). The colorless band at R_f 0.2 was chromone derivative **24** (16%), which was methylated to **25**.

After irradiation of **15** in acetone containing water (9%) under the same conditions, the solvent was removed under reduce pressure, and then the reaction products were extracted with chloroform from the residual water mixture. The extract was chromatographed on column (C_6H_6). The first yellow compound was recovered **15** (18%), and the residue was eluted by ether. The ether eluent was chromatographed on TLC ($CHCl_3$ containing 15% AcOEt). The colorless band at R_f 0.2 was a mixture of **21** (18%) and **24** (28%), which were determined after methylation, the fluorescence band (under expose to UV lamp) at R_f 0.1 was 5-hydroxy-2-(α-hydroxybenzyl)-2,6-dimethylbenzofuran-3(2*H*)-one (**17H**, 19%), and the origin was 5-hydroxy-4-methyl-2-[(α-methylstyryl)oxy]benzoic acid (**19H**, 13%).

17H: colorless solid, mp 153–154 °C; IR ($CHCl_3$) 3600, 3320, 1695, 1470 cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3COCD_3) δ 1.22 (s, 3 H), 2.31 (s, 3 H), 3.57 (d, J = 6 Hz, 1 H), 4.95 (d, J = 6 Hz, 1 H), 6.98 (s, 1 H), 7.05 (s, 1 H), 7.3–7.65 (m, 5 H), 7.98 (s, 1 H). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.02; H, 5.44.

19H (a mixture of cis–trans isomers; ca. 1:1): colorless oil; ^1H NMR (CCl_4) δ 2.00, 2.15, 2.23, and 2.28 (each s, 6 H), 6.08 and 6.18 (each s, 1 H), 6.85 and 6.95 (each s, 1 H), 7.15–7.6 (m, 7 H), 7.74 and 7.76 (each s, 1 H). **19H** was identified to convert it by the methylation with diazomethane to methyl 5-hydroxy-4-methyl-2-[(α-methylstyryl)oxy]benzoate (**19M**; a mixture of cis–trans isomers): colorless needles, mp 131–133 °C; IR ($CHCl_3$) 3400, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89, 2.19, 2.21, and 2.27 (each s, 6 H), 3.83 and 3.89 (each s, 3 H), 5.54 and 6.75 (each s, 1 H), 6.19 (br s, 1 H), 6.86 and 6.97 (each s, 1 H), 7.05–7.75 (m, 6 H). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.56; H, 6.01.

Acknowledgment. I am sincerely grateful to Professor K. Maruyama of Kyoto University for his continuing interest and useful suggestions, and I thank Drs. O. Soga and A. Takuwa for encouragement during this work.

Registry No. **1a**, 92777-31-6; **1b**, 92777-26-9; **1c**, 92777-27-0; **1d**, 92777-28-1; **1e**, 92777-29-2; **1f**, 92777-30-5; **1g**, 92777-31-6; **4aM**, 92777-45-2; **4aE**, 113008-35-8; **4aP**, 113008-36-9; **4aB**, 113008-37-0; **4bM**, 92777-47-4; **4bE**, 92777-34-9; **4bP**, 113008-38-1; **4bB**, 113008-39-2; **4cM**, 92777-48-5; **4cE**, 92777-35-0; **4cP**, 113008-40-5; **4cB**, 113008-41-6; **4dM**, 92777-49-6; **4dE**, 92777-36-1; **4dP**, 113008-42-7; **4dB**, 113008-43-8; **4eM**, 92777-50-9; **4eE**, 92777-37-2; **4eP**, 113008-44-9; **4eB**, 113008-45-0; **4eA**, 113008-79-0; **4fM**, 92777-52-1; **4fE**, 92777-39-4; **4fP**, 113008-46-1; **4fB**, 113008-47-2; **4gM**, 92777-53-2; **4gE**, 92777-41-8; **4gP**, 113008-48-3; **5aM**, 92777-46-3; **5aE**, 92777-32-7; **5aP**, 113008-49-4; **5aB**, 113008-50-7; **5bM**, 113008-51-8; **5bE**, 92777-33-8; **5bP**, 113008-52-9; **5bB**, 113008-53-0; **5dM**, 113008-54-1; **5dE**, 113008-55-2; **5dP**, 113008-56-3; **5dB**, 113008-57-4; **5eM**, 92777-51-0; **5eE**, 92777-38-3; **5eP**, 113008-58-5; **5eB**, 113008-59-6; **5eH**, 113008-78-9; **5fM**, 92777-20-3; **5fE**, 92777-40-7; **5fP**, 113008-60-9; **5fB**, 113008-61-0; **5gM**, 92777-19-0; **5gE**, 92777-42-9; **5gP**, 113008-62-1; **5gB**, 113008-63-2; **6**, 92812-34-5; **7**, 113008-75-6; **8**, 60-12-8; **10c**, 113008-64-3; **10d**, 113008-66-5; **10e**, 113008-77-8; (*E*)-**10e** acetate, 113008-80-3; (*Z*)-**10e** acetate, 113008-81-4; **11c**, 113008-65-4; **11d**, 113008-67-6; **13a**, 98231-01-7; **13e**, 113008-68-7; **13f**, 113008-69-8; **14a**, 113034-68-7; **14f**, 113008-70-1; **15**, 98230-47-8; **15** hydroquinone, 98230-54-7; **17B**, 113008-83-6; **17H**, 113008-84-7; **19M**, 113008-86-9; **19B**, 113008-82-5; **19H**, 113008-85-8; **21**, 98230-52-5; **22**, 98230-69-4; **24**, 98230-53-6; **25**, 98230-70-7; MeOH, 67-56-1; EtOH, 64-17-5; *i*-PrOH, 67-63-0; *t*-BuOH, 75-65-0; 2-(α-ethoxybenzyl)-5-hydroxy-4,6-dimethylbenzofurane, 92777-43-0; 5-acetoxy-2-(α-ethoxybenzyl)-4,6-dimethylbenzofuran, 113008-71-2; 3-methoxy-2,4-dimethyl-6-(styryloxy)benzyl alcohol, 113008-72-3; 3-methoxy-2,4-dimethyl-6-(styryloxy)benzyl acetate, 113008-73-4; ethyl 3-acetoxy-2,4-dimethyl-6-phenethylbenzoate, 113008-74-5; 2-hydroxy-6-methoxy-3,5,7-trimethylchroman-4-one, 113008-76-7.

Structure of Rearrangement Products Obtained on Treatment of 19-Hydroxyandrost-4-ene-3,17-dione under Epoxidation Conditions

Sophia Hrycko and Peter Morand*

Ottawa-Carleton Institute for Chemistry, Department of Chemistry, University of Ottawa, Ottawa, Canada K1N 6N5

F. L. Lee and E. J. Gabe

Division of Chemistry, National Research Council of Canada, Ottawa, Canada K1A 0R6

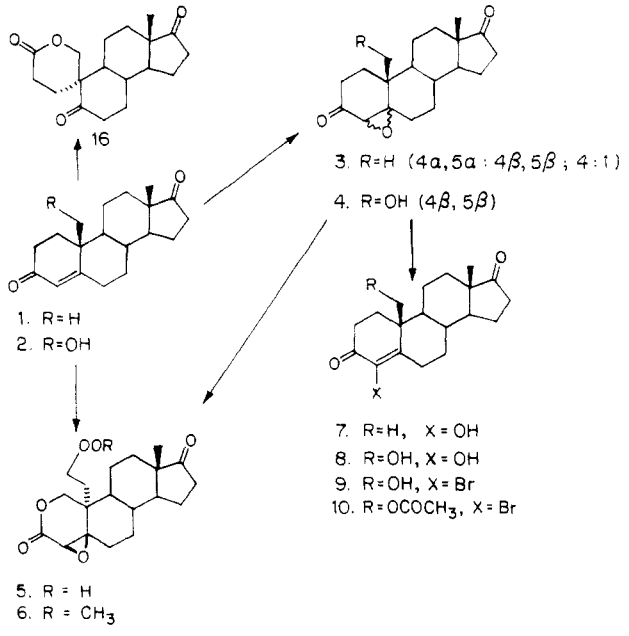
Received August 19, 1987

Treatment of 19-hydroxyandrost-4-ene-3,17-dione (**2**) with hydrogen peroxide in alkaline methanol at 0–4 °C for 60–90 min gave the corresponding 4β,5β-epoxide **4** in good yield. However, with a reaction period of 16 h and at 21 °C, only traces of the 4β,5β-epoxide **4** were obtained and a 20% yield of a second product was isolated. The structure of this product was determined by X-ray crystallography and found to be 19-(hydroperoxymethyl)-4β,5-epoxy-2-oxa-5β,10α-androstane-3,17-dione (**5**). The reactions of this hydroperoxide with hydrogen bromide, sodium iodide, and methyl iodide were examined. Under slightly different reaction conditions, the 3,5-seco compound **16** was isolated.

In connection with our studies on the active site of a 17β-hydroxy steroid dehydrogenase, 4,19-dihydroxyandrost-4-ene-3,17-dione (**8**) was required as a substrate for affinity labeling experiments. The synthesis of the

0022-3263/88/1953-1515$01.50/0

Scheme I



4-hydroxy compound **7** has previously been achieved[1,2] by acid-catalyzed opening of the 4,5-epoxides **3**, and these results have been confirmed in our laboratory.

Treatment of 19-hydroxyandrost-4-ene-3,17-dione (**2**) (200 mg) with hydrogen peroxide and 0.2 N NaOH in methanol at 0–4 °C for 16 h gives a 65% yield[3] of the 4β,5β-epoxide **4** (Scheme I). We have since confirmed that the reaction is complete after 60–90 min under these conditions, as reported by Fishman and Hosoda.[4] However, on a larger scale (~1 g) and with a reaction period of 16 h, only traces of the 4β,5β-epoxide **4** were obtained and a 20% yield of a second product was isolated. An 85% yield of this product could be isolated from the 4β,5β-epoxide **4**, under optimized conditions of time and temperature, confirming that the latter is an intermediate in the formation of the second product from **2**.

The mass spectrum of the unknown product indicated a molecular weight of 350, corresponding to the addition of three atoms of oxygen to the 19-hydroxy-Δ^4 3-ketone **2**. The fragment at m/z 334 (loss of one atom of oxygen) is characteristic of hydroperoxides.[5-8] Examination of the proton NMR spectrum also indicated the presence of a hydroperoxide (signal at δ 8.16, exchangeable with D_2O). Other resonances in the proton NMR spectrum included signals at δ 4.32 (cf. δ 3.97 for 19-CH_2 in **4**), δ 3.45 (cf. δ 2.90 for 4α-H in **4**), and δ 4.12 (multiplet integrating for two protons). The ^{13}C NMR spectrum showed no change for the C-17 carbonyl group, but the C-3 carbonyl group resonance which normally appears at ca. δ 200 was absent and a signal at δ 168 was observed. This is consistent with a lactone carbonyl group.

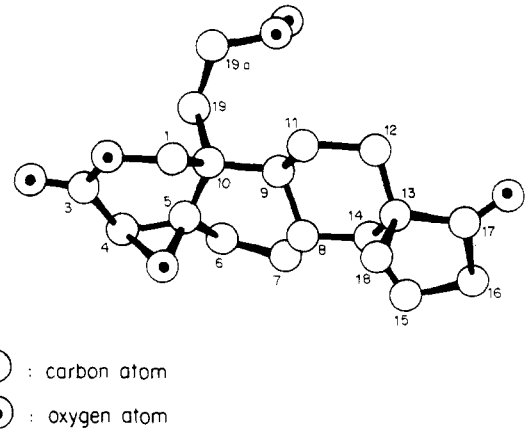


Figure 1. Structure of **5** determined by X-ray crystallography.

Treatment of a few crystals of the unknown product with potassium iodide in ethanol liberated iodine, which confirmed the presence of a hydroperoxy group. Repeating this reaction on a larger scale led to the isolation of a compound whose mass spectrum showed a molecular ion peak at m/z 334, indicating a loss of 16 mass units from the starting material (m/z 350). Also the proton NMR spectrum of the product showed a fine doublet at δ 3.10, exchangeable with D_2O, and the signal of the hydroperoxide group at δ 8.16 was no longer present in the spectrum. Similarly, the 4α-H resonance of the starting material was absent from the proton NMR spectrum and another fine doublet was observed at δ 4.41, which became a singlet upon addition of D_2O.

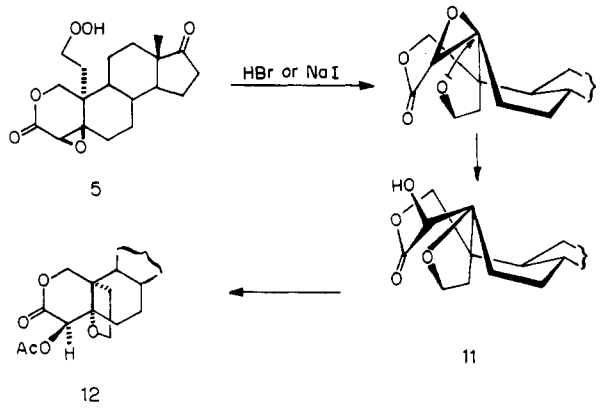
Methylation[6] of the hydroperoxide group of the unknown product obtained from **2** or **4** gave a compound corresponding to the hydroperoxymethyl ether as indicated by the resonance at δ 3.80 (OCH_3) in the proton NMR spectrum and δ 62.2 (OCH_3) in the ^{13}C NMR spectrum.

To determine whether the unknown hydroperoxide still retained the epoxide function, we treated it with 2% HBr in acetic acid. In an earlier experiment, it was found that the 4β,5β-epoxide **4** gave rise to a 71% yield of the 4-bromo-Δ^4 3-ketone **9** under these conditions. However, when the hydroperoxide was treated with 2% HBr in acetic acid, two products were formed, neither of which contained bromine. The major product had a molecular weight of 334, corresponding to the cleavage of the hydroperoxy group, and the proton and ^{13}C NMR spectra of this product were identical with those obtained for the product generated by the reduction of the peroxide by sodium iodide.

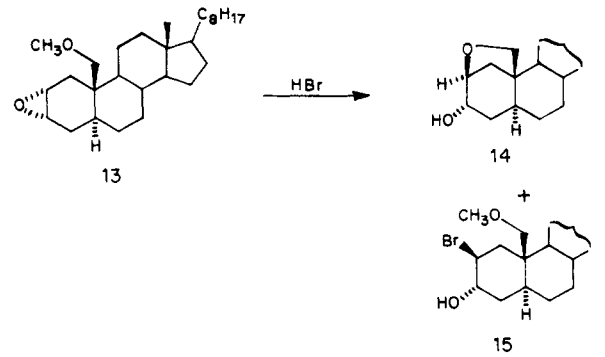
Although the foregoing experiments and spectroscopic data provided useful information about structural features of the unknown hydroperoxy compound, it was not possible to deduce its molecular structure with certainty. After many unsuccessful attempts, the appropriate solvent and conditions were found for the formation of a suitable crystal for X-ray analysis. The X-ray crystallographic analysis provides unequivocal proof that the structure of the rearranged product is 19-(hydroperoxymethyl)-4β,5-epoxy-2-oxa-5β,10α-androstane-3,17-dione (**5**) (Figure 1; for details, see the Experimental Section). Formation of this product with a C-10 angular substituent below the plane of the molecule can be rationalized by assuming that the A-ring seven-membered lactone formed by Baeyer–Villiger rearrangement was cleaved and the 19-hydroxyl group participated in the formation of the six-membered lactone ring found in **5**. The characteristic arrangement of the A ring of **5** occurs in natural products such as limonoids.[9,10]

(1) Brodie, A. M. H.; Schwarzel, W. C.; Shaikh, A. A.; Brodie, H. J. *Endocrinology (Baltimore)* **1977**, *100*, 1684.
(2) Burnett, R. D.; Kirk, D. N. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1830.
(3) Morand, P.; Williamson, D. G.; Layne, D. S.; Lompa-Krzymien, L; Salvador, J. *Biochemistry* **1975**, *14*, 635.
(4) Hosoda, H.; Fishman, J. *J. Am. Chem. Soc.* **1974**, *96*, 7325.
(5) Schwarz, H.; Schiebel, H.-M. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley: New York, 1983; p 105.
(6) Doskotch, R. W.; El-Feraly, F. S.; Fairchild, E. H.; Huang, C. T. *J. Org. Chem.* **1977**, *42*, 3614.
(7) van Lier, J. E.; Smith, L. L. *J. Org. Chem.* **1971**, *36*, 1007.
(8) Feinberg, A. M.; Nakanishi, K.; Barciszenski, J.; Rafalski, A. J.; Augustyniak, H.; Wiewiórowski, M. *J. Am. Chem. Soc.* **1974**, *96*, 7797.

Scheme II



Scheme III



With the structure of the rearranged product **5** established, it is now possible to understand what happened on treatment with methyl iodide, i.e., methylation of the hydroperoxy group to give the peroxyether **6**. The proton NMR spectrum of **6** is identical with that of the starting material **5** except for the methyl ether resonance at δ 3.80, which replaced the hydroperoxide proton resonance at δ 8.16 in **5**.

Similarly, the product obtained when the hydroperoxide **5** was treated with sodium iodide or hydrogen bromide is identified as **11** (Scheme II). The peroxide function is first cleaved. Then follows cyclization induced by the 19a-oxygen atom opening the epoxide at C-5 and generating a 4β-hydroxyl group. This 4β-hydroxyl group is acetylated to give **12**. The ^{13}C NMR data of compound **11** are in agreement with the proposed structure, namely, a methine resonance at δ 70.4, which is attributed to C-4, and a quaternary carbon at δ 85.4, which is assigned to C-5. Such participation of the 19-oxygen atom has previously been observed by Kocovsky and Cerny.[11,12] These authors found that the cleavage of the 2α,3α-epoxide **13** with hydrobromic acid yielded a mixture of the cyclic ether **14** (48%) as a product of methoxyl group participation and the bromohydrin **15** (52%), arising by normal diaxial opening of the epoxide ring by bromide anion as external nucleophile (Scheme III).

Another rearranged product, different from the hydroperoxide **5**, was isolated when the 19-hydroxy compound **2** was treated with hydrogen peroxide and base in methanol under slightly different conditions of time and amount of sodium hydroxide used to generate the hydroperoxide **5**. This product is identified as the 3,5-seco compound **16** (Scheme I) on the basis of the following evidence. The elemental analysis indicated a formula of $C_{18}H_{24}O_4$ corresponding to the loss of one carbon and two hydrogen atoms and the addition of one atom of oxygen to the starting alcohol **2**. The presence of a saturated ketone was deduced from the carbonyl absorption at 1710 cm^{-1} in the IR spectrum as well as from the resonance at δ 210.1 in the ^{13}C NMR spectrum. The proton NMR spectrum indicated a resonance at δ 0.94, unchanged from the C-18 resonance of the starting material **2**, along with a quartet at δ 4.48 assigned to the C-19 methylene group. Also in agreement with the proposed structure, compound **16** did not react when treated under acetylating conditions. The 5-keto 3-acid functionality has been obtained by treatment of a 5β-3-ketone with potassium superoxide[13] and by treatment of androst-4-ene-3,17-dione with lithium peroxide and water.[14] Oxidation of a Δ^4 3-ketone with $NaIO_4$–$KMnO_4$[15] also generates a 3,5-seco acid. The isolation of **16** illustrates the sensitivity of the Baeyer–Villiger reaction to small variations of the reaction conditions. In this case, as in the formation of the hydroperoxide **5**, the participation of the 19-oxygen atom is observed.

Experimental Section

Melting points were determined on a Hoover Uni-melt apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter and are for chloroform solutions. Ultraviolet spectra were obtained with 95% ethanol solutions on a Varian DMS 90 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 783 infrared spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian XL-300 (300 MHz) instrument, and ^{13}C nuclear magnetic resonance spectra were obtained on a Varian FT-80 (80 MHz) instrument. Chemical shifts (ppm) are given relative to deuteriochloroform for protons and carbons. Brackets are used to indicate carbon resonances that are tentatively assigned; an asterisk is used to indicate carbon resonance assignments that can be interchanged (when more than one pair is involved, the symbol * is used). Mass spectra were obtained from a V.G. 7070-E double-focusing instrument. Microanalyses were carried out by M-H-W Laboratories, Phoenix, AZ. Terochem silica gel 1918 (equivalent to Merck 9385, 20–45 μm) was used for column chromatography. Workup involved pouring the reaction mixture into water, extracting with methylene chloride, and washing the extracts with water (and with 5% HCl if pyridine was present). The extracts were then dried with anhydrous sodium sulfate, and the solvent was removed on a rotary evaporator.

19-(Hydroperoxymethyl)-4β,5-epoxy-2-oxa-5β,10α-androstane-3,17-dione (5). 19-Hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**4**) (2.00 g, 6.29×10^{-3} mol) was dissolved in methanol (70 mL), and the solution was cooled in an ice–water bath. Ice-cold 4 N NaOH (15 mL) and ice-cold 30% H_2O_2 (44 mL) were added to the stirred solution. The solution was kept in ice for 4 h and then stirred, without addition of more ice, overnight (12 h). The reaction was terminated by the addition of water (50 mL), and the mixture was extracted with methylene chloride to afford 19-hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**4**) (63 mg, 3%). Following acidification, the aqueous phase was extracted with methylene chloride to afford **5** (1.86 g, 85%): mp 187–188 °C (needles from 95% ethanol); $[\alpha]_D$ +27° (*c* 0.79); IR (KBr) ν_{max} 3315 (OOH), 1735 and 1705 (3-CO and 17-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3 H, 18-CH_3), 3.45 (s, 1 H, 4α-H), 4.32 (q, 2 H, δ_a 4.04, δ_b 4.60, J_{ab} = 10.5 Hz, 19a-CH_2), 4.15 (m, 2 H, 1-CH_2), 8.16 (br s, 1 H, exchanges with D_2O, 19a-OOH);

(9) Barton, D. H. R.; Pradhan, S. K.; Sternhell, S.; Templeton, J. F. *J. Chem. Soc.* **1961**, 255.
(10) Dreyer, D. L.; Bennett, R. D.; Basa, S. C. *Tetrahedron* **1976**, *32*, 2367.
(11) Kocovsky, P.; Cerny, V. *Collect. Czech. Chem. Commun.* **1979**, *44*, 1496.
(12) Kocovsky, P.; Cerny, V. *Collect. Czech. Chem. Commun.* **1979**, *44*, 226.
(13) Alvarez, E.; Betancor, C.; Friere, R.; Martin, A.; Suárez, E. *Tetrahedron Lett.* **1981**, *22*, 4335.
(14) Holland, H. L.; Riemland, E.; Daum, U. *Can. J. Chem.* **1982**, *60*, 1919.
(15) Milewich, L.; Axelrod, L. R. *Org. Synth.* **1976**, *55*, 67.

^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.7 (CH_3, C-18), 21.3 (CH_2, C-11), 21.7 (CH_2, C-15), 23.7 (CH_2, [C-6]), 24.8 (CH_2, [C-7]), 31.4 (CH_2, C-12), 33.3 (CH, C-8), 34.4 (CH_2, C-19), 35.5 (CH_2, C-16), 38.8 (C, C-10), 47.3 (C, C-13), 48.5 (CH, C-9), 51.6 (CH, C-14), 55.2 (CH, C-4), 66.7 (C, C-5), 68.9 (CH_2, C-19a), 73.3 (CH_2, C-1), 168.2 (C, C-3), 219-7 (C, C-17); MS, m/z 350 (M^+), 334 (M–O). Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.10; H, 7.48. Found: C, 65.20; H, 7.52.

X-ray crystal structure analysis of 5: $C_{19}O_6H_{26}$, orthorhombic, a = 7.5904 (3) Å, b = 7.9968 (5) Å, c = 28.3470 (12) Å, Z = 4, D_{calcd} 1.353 g cm^{-3}, space group $P2_12_12_1$. Intensity data were collected on a CAD-4 diffractometer, with the NRCCAD[16] control program and profile analysis[17] in the $\vartheta/2\vartheta$ mode, with Cu Kα (λ = 1.54056 Å) radiation. A total of 1891 reflections was collected (2ϑ (max) = 140°), of which 1348, with $I > 2.5\sigma(I)$, were used in the analysis. The structure was solved by direct methods and refined by full-matrix least-squares techniques and unit weights, by using the NRCVAX[18] program system. The final R index was 0.047.

19-[(Methyldioxy)methyl]-4β,5-epoxy-2-oxa-5β,10α-androstane-3,17-dione (6). The hydroperoxide **5** (102 mg, 2.91 × 10^{-4} mol) was dissolved in 10 mL of 95% ethanol. It was necessary to heat gently the ethanol solution to get all the steroid into solution. Methyl iodide (540 mg, 3.80 × 10^{-3} mol) and silver oxide (500 mg, 2.16 × 10^{-3} mol) were added, and the solution was stirred at room temperature for 16 h. The solution was again heated gently, and the gray–brown precipitate was filtered. The solvent was removed under reduced pressure. The residue was purified by chromatography using methylene chloride–ethyl acetate, 90:10, as eluant. **6** was obtained in 57% yield: mp 127–128 °C; $[\alpha]_D$ +47° (c 0.52); IR (KBr) ν_{max} 1735 and 1725 sh (17-CO and 3-OCO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3 H, 18-CH_3), 3.40 (s, 1 H, 4α-H), 3.80 (s, 3 H, 19a-$OOCH_3$), 4.27 (q, 2 H, δ_a 4.02, δ_b 4.52, J_{ab} = 10.9 Hz, 19a-CH_2), 4.12 (m, 2 H, 1-CH_2); ^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.6 (CH_3, C-18), 21.6 (CH_2, C-11), 21.6 (CH_2, C-15), 23.7 (CH_2, [C-6]), 24.5 (CH_2, [C-7]), 31.3 (CH_2, C-12), 33.5 (CH, C-8), 33.9 (CH_2, C-19), 35.4 (CH_2, C-16), 38.4 (C, C-10), 47.2 (C, C-13), 47.5 (CH, C-9), 51.4 (CH, C-14), 54.6 (CH, C-4), 62.2 (CH_3, $OOCH_3$), 66.7 (C, C-5), 67.7 (CH_2, C-19a), 69.8 (CH_2, C-1), 167.3 (C, C-3), 219.6 (C, C-17); MS, m/z (M^+ at 364 is absent even under chemical-ionization conditions) 334. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.89; H, 7.75. Found: C, 65.76; H, 7.62.

[5β(*R*)]-α,19-Dihydroxy-17-oxo-*A*-nor-3-oxaandrostane-5-acetic Acid, δ-Lactone (11). The hydroperoxide **5** (320 mg, 9.14 × 10^{-4} mol) was dissolved in a solution of 95% ethanol (10 mL) and ether (8 mL). To the resulting milky solution were added sodium iodide (800 mg, 5.34 × 10^{-3} mol) and 2 drops of acetic acid. The solution turned dark yellow and was stirred at room temperature for 7 h. After the workup, the residue was purified by column chromatography. Elution with methylene chloride–ethyl acetate, 85:15, afforded 3,5-seco-5,17-dioxoandrostane 3,19-lactone **16** (9 mg). Elution with methylene chloride–ethyl acetate, 80:20 gave **11** (47 mg, 16%): mp 74–75 °C; $[\alpha]_D$ +9° (c 0.32); IR (KBr) ν_{max} 3450 (br, OH), 1735 (17-CO and 3-OCO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3 H, 18-CH_3), 3.10 (d, 1 H, exchanges with D_2O, J = 2.9 Hz, 4β-OH), 3.97 (m, 2 H, 1-CH_2), 4.35 (q, 2 H, δ_a 4.19, δ_b 4.52, J_{ab} = 12.6 Hz, 19a-CH_2), 4.41 (d, 1 H, becomes a s upon addition of D_2O, 4α-H); ^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.7 (CH_3, C-18), 21.5 (CH_2, C-11), 21.6 (CH_2, C-15), 22.1 (CH_2, [C-6]), 24.6 (CH_2, [C-7]), 31.4 (CH_2, C-12), 33.2 (CH, C-8), 35.6 (CH_2, C-16), 37.1 (CH_2, C-19), 46.0 (CH, C-9), 46.9 (C, C-13), 47.9 (C, C-10), 51.6 (CH, C-14), 64.1 (CH_2, C-19a), 68.6 (CH_2, C-1), 70.4 (CH, C-4), 85.4 (C, C-5), 174.1 (C, C-3), 219.9 (C, C-17); MS, m/z 334 (M^+), 277. Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.22; H, 7.84. Found: C, 68.02; H, 8.00. The compound **11** was also obtained when the hydroperoxide **5** (391 mg, 1.12 × 10^{-3} mol), dissolved in acetic acid (1.5 mL) and placed in an ice–water bath, was treated with a solution of hydrogen bromide (0.1 mL) in acetic acid (6 mL). After the mixture was stirred for 1 h, water (30 mL) was added, and the pale yellow residue obtained after the workup was purifed by column chromatography. Elution with methylene chloride–ethyl acetate, 78:22, afforded **11** (43%).

[5β(*R*)]-α,19-Dihydroxy-17-oxo-*A*-nor-3-oxaandrostane-5-acetic Acid, δ-Lactone Acetate (12). The alcohol **11** (42 mg, 1.26 × 10^{-4} mol) was treated with acetic anhydride in pyridine overnight. **12** (39 mg, 9.84 × 10^{-5} mol) was isolated in 78% yield: IR (KBr) ν_{max} 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 3 H, 18-CH_3), 2.22 (s, 3 H, 4β-$COCH_3$), 3.95 (q, 2 H, 1-CH_2), 4.37 (q, 2 H, δ_a 4.26, δ_b 4.47, J_{ab} = 12.6 Hz, 19a-CH_2), 5.58 (s, 1 H, 4α-H); ^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.9 (CH_3, C-18), 20.7 (CH_3, $COCH_3$), 21.6 (CH_2, C-11), 21.7 (CH_2, C-15), 22.7 (CH_2, [C-6]), 25.9 (CH_2, [C-7]), 31.6 (CH_2, C-12), 33.7 (CH, C-8), 35.7 (CH_2, C-16), 36.4 (CH_2, C-19), 45.9 (CH, C-9), 47.3 (C, C-13), 47.9 (C, C-10), 51.4 (CH, C-14), 64.1 (CH_2, C-19a), 68.7 (CH_2, C-1), 70.0 (CH, C-4), 84.0 (C, C-5), 168.1* (C, C-3), 169.8* (C, $COCH_3$), 219.4 (C, C-17); MS, m/z 376 (M^+), 334.

4-Bromo-19-hydroxyandrost-4-ene-3,17-dione (9). 19-Hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**4**) (200 mg, 6.29 × 10^{-4} mol) dissolved in acetic acid (3 mL) was cooled in an ice–water bath. A solution of HBr in acetic acid (0.2 mL of HBr in 12 mL of acetic acid) was added to the stirred steroid solution. After 15 min, the reaction was terminated by adding cold water (100 mL). **9** (171 mg, 71%) was isolated as a white precipitate: mp 163 °C; $[\alpha]_D$ +214° (c 0.285); UV λ_{max} 262 nm (ε 12 136); IR ($CHCl_3$) ν_{max} 1735 (17-CO), 1680 (3-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (s, 3 H, 18-CH_3), 4.02 (q, 2 H, δ_a 3.92, δ_b 4.12, J_{ab} = 10.6 Hz, 19-CH_2); ^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.8 (CH_3, C-18), 21.1 (CH_2, C-11), 21.6 (CH_2, C-15), 30.1 (CH_2, C-12), 31.6 (CH_2, C-7), 32.2* (CH_2, C-6), 33.2* (CH_2, C-1), 34.9 (CH_2, C-2), 35.4 (CH, C-8), 35.7 (CH_2, C-16), 47.4* (C, C-10), 47.6* (C, C-13), 51.0 (CH, C-14), 54.0 (CH, C-9), 65.8 (CH_2, C-19), 124.1 (C, C-4), 163.7 (C, C-5), 191.2 (C, C-3), 220.1 (C, C-17); MS, m/z 382/380 (M^+, ^{81}Br–^{79}Br), 352/350; HRMS calcd for $C_{19}H_{25}O_3Br$ 380.0980, found 380.0987.

4-Bromo-19-acetoxyandrost-4-ene-3,17-dione (10). To a solution of **9** (30 mg, 7.89 × 10^{-5} mol) in pyridine was added acetic anhydride, and the reaction mixture was stirred overnight. Workup afforded **10** as an oil (23 mg, 67%): mp 155 °C (methanol); UV λ_{max} 260 nm (ε 8607); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3 H, 18-CH_3), 2.00 (s, 3 H, 19-$COCH_3$), 4.42 (q, 2 H, δ_a 4.15, δ_b 4.69, J_{ab} = 11.0 Hz, 19-CH_2); ^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.8 (CH_3, C-18), 20.9 (CH_3, $COCH_3$), 21.1 (CH_2, C-11), 21.6 (CH_2, C-15), 30.1 (CH_2, C-12), 31.5 (CH_2, C-7), 32.3* (CH_2, C-6), 32.9* (CH_2, C-1), 34.5 (CH_2, C-2), 35.4 (CH, C-8), 35.6 (CH_2, C-16), 45.5 (C, C-10), 47.5 (C, C-13), 51.0 (CH, C-14), 54.1 (CH, C-9), 66.5 (CH_2, C-19), 124.4 (C, C-4), 162.1 (C, C-5), 170.5 (C, $COCH_3$), 190.4 (C, C-3), 219.5 (C, C-17); MS, m/z 424/422 (M^+, ^{81}Br–^{79}Br); HRMS calcd for $C_{21}H_{27}O_2Br$ 422.1085, found 422.1085.

19-Hydroxy-5,17-dioxo-*A*-nor-3,5-secoandrostan-3-oic Acid, δ-Lactone (16). 19-Hydroxyandrost-4-ene-3,17-dione (**2**) (1.00 g, 3.31 × 10^{-3} mol) was dissolved in methanol (17 mL) and cooled in an ice–water bath. Ice-cold 4 N NaOH (2 mL) and 30% H_2O_2 (4 mL) were successively added, and the reaction mixture was stirred in an ice–water bath, without adding more ice, for 15 h 30 min. Water (30 mL) was added to the reaction mixture, which was extracted with methylene chloride to afford 19-hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (**4**) (60 mg, 6%). The remaining aqueous phase was acidified with HCl and extracted with methylene chloride. The residue obtained after evaporation of the solvent was purified by column chromatography. Elution with methylene chloride–ethyl acetate, 85:15, afforded **16** (265 mg, 26%): mp 223–224 °C; $[\alpha]_D$ +50° (c 0.415); IR ($CHCl_3$) ν_{max} 1735 (17-CO and 3-OCO), 1710 (5-CO) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 3 H, 18-CH_3), 4.43 (q, 2 H, δ_a 4.38, δ_b 4.48, J_{ab} = 13.2 Hz, 19-CH_2); ^{13}C NMR ($CDCl_3$, 80 MHz) δ 13.8 (CH_3, C-18), 21.6 (CH_2, C-11), 22.5 (CH_2, C-15), 23.1 (CH_2, [C-7]), 28.1 (CH_2, [C-1]), 30.1 (CH_2, [C-2]), 31.2 (CH_2, C-12), 35.4 (CH_2, C-16), 35.5 (CH, C-8), 38.1 (CH_2, C-6), 47.5 (C, C-13), 50.6 (CH, C-9), 51.4 (CH, C-14), 51.6 (C, C-10), 68.8 (CH_2, C-19), 172.0 (C, C-3), 210.1 (C, C-5), 219.0 (C, C-17); MS, m/z 304 (M^+), 276 (M – CO); HRMS calcd for $C_{18}H_{24}O_4$ 304.1668, found 304.1660. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found: C, 70.71; H, 7.91.

Acknowledgment. We thank Dr. J. M. Koekenoer, Rand Afrikaans University, Johannesburg, South Africa

(16) Le Page, Y.; White, P. S.; Gabe, E. J. A.C.A. Annual Meeting, Hamilton, Ontario, Canada, June 1986; Abstract PA23.
(17) Grant, D. F.; Gabe, E. J. *J. Appl. Crystallogr.* **1978**, *11*, 114.
(18) Gabe, E. J.; Lee, F. L.; Le Page, Y. *Crystallographic Computing 3: Data Collection, Structure Determination, Proteins and Databases*; Sheldrick, G. M., Kruger, C., Goddard, R., Ed.; Clarendon: Oxford, 1985; p 167.

for a generous gift of 19-hydroxyandrost-4-ene-3,17-dione. We are grateful for financial assistance from the Natural Sciences and Engineering Research Council of Canada and for a 1967 Science and Engineering Scholarship (S.H.).

Registry No. 2, 510-64-5; 4, 53875-00-6; 5, 113055-68-8; 6, 113055-69-9; 9, 113035-98-6; 10, 113035-99-7; 11, 113055-70-2; 12, 113055-71-3; 16, 113036-00-3.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond lengths, and bond angles for compound 5 (18 pages). Ordering information is given on any current masthead page.

Photochemical Reactions of Model *cis*-Stilbenes: The [2 + 2]-Cycloaddition Reaction

John H. Penn,* Li-Xian Gan, Thomas A. Eaton, Edward Y. Chan, and Zhe Lin

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045

Received June 8, 1987

The photochemical [2 + 2]-reactions of three model *cis*-stilbenes have been examined. 1,2-Diphenylcyclobutene was found to undergo photochemical [2 + 2]-cycloaddition reactions with 2,5-dimethyl-2,4-hexadiene and with itself but did not undergo reaction with tetramethylethylene. 1,2-Diphenylcyclopentene and 1,2-diphenylcyclohexene were unreactive in photochemical [2 + 2]-cycloaddition reactions. The singlet excited-state lifetimes of these compounds were measured. The results show that the observation of the *cis*-stilbene [2 + 2]-reaction is dependent upon the rate of deactivation of the excited state.

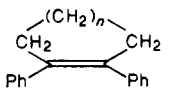
Introduction

The [2 + 2]-photocycloaddition reaction is a very well-known reaction.[1] The generality of this reaction is attested to by the fact that a recent review deals with the utility of this reaction in the synthesis of natural products.[1b] Although the reaction has achieved general usage, the mechanism is still incompletely understood. Caldwell has recently developed a method for predicting relative reactivity in [2 + 2]-reactions.[2] Although this method has achieved success in predicting reactivity in a large number of reactions,[3] a recent report shows a reactivity pattern other than would be predicted by Caldwell's method.[4] We reasoned that further examples of [2 + 2]-reactivity would serve to provide further constraints upon the limits of [2 + 2]-reactivity and lead to a more generally useful reaction.

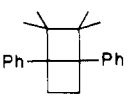
Our approach to defining the boundary conditions of this reaction was to employ the *cis*-stilbene chromophore. To date, only a few unequivocal examples[5] of the [2 + 2]-cycloaddition reaction of an excited *cis*-stilbene chromophore have been reported.[6] Yet, several examples of *trans*-stilbene intermolecular [2 + 2]-reactions abound in the literature.[7-9] One would anticipate that the reactivity of this chromophore would be similar to the reactivity of *trans*-stilbene. In one school of photochemical thought, a higher excited-state energy would result in a faster and more efficient reaction, since the energy of the excited state is closer to the transition-state energy.[10] Thus, based on the similar singlet excited-state energies of *cis*- and *trans*-stilbene and the higher triplet excited-state energy of *cis*-stilbene as compared to the trans isomer, a similar rate of [2 + 2]-cycloaddition would be predicted for these compounds. Caldwell's method for predicting [2 + 2]-reactivity predicts that *cis*-stilbene should have a slower rate of reaction than *trans*-stilbene due to the higher triplet excited-state energy of *cis*-stilbene. In order to test which of these hypotheses were correct, or if another intervening factor (such as steric hindrance of the phenyl groups) was operative, we undertook a systematic study of the [2 + 2]-cycloaddition reactions of a series of *cis*-stilbenes. These stilbenes vary only in the size of the ring in which the *cis*-stilbene chromophore is constrained. This systematic variation of size may be expected to yield effects related to the lifetime of the excited state.

Results

The compounds 1,2-diphenylcyclobutene (4), 1,2-diphenylcyclopentene (5), and 1,2-diphenylcyclohexene (6), were synthesized by the literature methods.[11] Using tetramethylethylene (TME) as a solvent, we irradiated a 0.2 M solution of 4. To our surprise, no 8 was formed!



4: $n = 0$
5: $n = 1$
6: $n = 2$



8

Only the previously known dimeric product was isolated from the reaction mixture.[12] Even when the concentration of 4 was lowered to 0.01 M, dimer 7 was still the predominant product.[5] This result is made even more startling when the strain energy of these two potential products are

(1) (a) Trecker, D. J. *Org. Photochem.* **1969**, *2*, 63–116. (b) Schreiber, S. L. *Science (Washington, D.C.)* **1985**, *227*, 857–863.
(2) Caldwell, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 4004.
(3) (a) Caldwell, R. A.; Mizuno, K.; Hansen, P. E.; Vo, L. P.; Frentrup, M.; Ho, C. D. *J. Am. Chem. Soc.* **1981**, *103*, 7263. (b) McCullough, J. J.; MacInnis, W. K.; Lock, C. J. L.; Faggiani, R. *J. Am. Chem. Soc.* **1982**, *104*, 4644.
(4) Smothers, W. K.; Meyer, M. C.; Saltiel, J. *J. Am. Chem. Soc.* **1983**, *105*, 545.
(5) (a) White, E. H.; Anhalt, J. P. *Tetrahedron Lett.* **1965**, *3937*–3945. (b) DeBoer, C. D.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 803–804. (c) Kaupp, G.; Stark, M. *Chem. Ber.* **1978**, *111*, 3608. (d) Lewis, F. D. *Adv. Photochem.* **1986**, *13*, 165.
(6) Chapman[7] has reported that irradiation of *cis*-stilbene in TME produces *trans*-1,2-diphenyl-3,3,4,4-tetramethylcyclobutane. It is not clear whether this reaction proceeds directly from the *cis*-stilbene or results from the photochemical isomerization of *cis*-stilbene to *trans*-stilbene, followed by cycloaddition.
(7) Chapman, O. L.; Adams, W. R. *J. Am. Chem. Soc.* **1968**, *90*, 2333.
(8) Chapman, O. L.; Lura, R. D. *J. Am. Chem. Soc.* **1970**, *92*, 6352–6354.
(9) Lewis, F. D. *Acc. Chem. Res.* **1979**, *12*, 152.
(10) Zimmerman, H. E.; Welter, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 4131.
(11) (a) Baumstark, A. L.; Bechara, E. J. H.; Semigran, M. J. *Tetrahedron Lett.* **1976**, 3265. (b) Baumstark, A. L.; McCloskey, C. J.; Witt, K. E. *J. Org. Chem.* **1978**, *43*, 3609–3611.
(12) This product was characterized by its melting point, NMR, and GCMS data to be the product previously obtained in the irradiation of 4 in hexane.[5]

0022-3263/88/1953-1519$01.50/0