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PHOTOCHEMICAL TRANSFORMATIONS OF DIENES—V[1]

PHOTOLYSIS OF 6-FORMYLTESTOSTERONE METHYL ENOL ETHER ACETATE AND RELATED COMPOUNDS[2]

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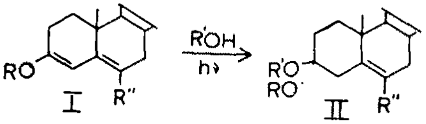
Abstract—Irradiation of dienolether aldehyde (III) in methanol leads to the ketal aldehyde (V) which is further converted to ketal acetal IV and to III. The relative rate constants for these reactions have been determined, thus permitting exclusion of alternate reaction pathways.

INTRODUCTION

Recently, it was shown[1,4] that the photolysis of an alcoholic solution of steroidal 3-alkoxy-3,5-dienes (I, R″ = H, CH_3, F) gives mixed ketals of type II in good yield.



$R = R' = CH_3$
$R'' = H, CH_3, F, NO_2$

When the 6-substituent (R″) is a nitrogroup,[4b] the reaction proceeds in a different manner and no product could be isolated in a useful yield. Substituents which conjugate with the enol ether chromophore hence exert a profound influence on the reaction course. In this paper, the reaction is applied to systems of type I in which R″ is a formyl group. In order to prove the reaction course and the structure of one of the photoproducts, ketal aldehyde V and 6-hydroxymethyl enol ether VI were also submitted to the action of UV light.

RESULTS

A methanolic solution of enol ether (III[5]) was irradiated until less than 5% of the original UV chromophore could be detected. TLC indicated the presence of one spot only. The NMR spectrum[6] of the product (IV) indicated the presence of an acetate and four methoxy groups, a single proton at 4·9 ppm ($C\underline{H}(OCH_3)_2$) and the absence of olefinic protons. The presence of a peak at 2·8 ppm (approximately 0·5 H) cast some

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[1] Part IV. C. C. Leznoff and G. Just, *Canad. J. Chem.* **42**, 2801 (1964).

[2] This work supported by the National Research Council of Canada.

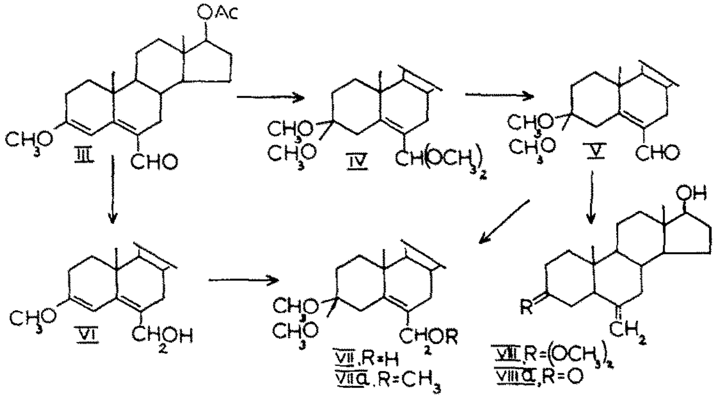
[3] Holder of a National Research Council of Canada Bursary, 1962–3, and Studentship, 1963–5.

[4] [a] G. Just and C. C. Leznoff, *Canad. J. Chem.* **42**, 79 (1964); [b] C. C. Leznoff and G. Just, *Ibid.* **42**, 2919 (1964).

[5] D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow and D. M. Williamson, *Tetrahedron* **20**, 597 (1964).

[6] We wish to thank Mr. K. Valentin for taking the spectra.

doubt on the structure assigned, and the possibility that the photoproduct was a 3,4-dimethoxyandrostane derivative could not be excluded at this point. Mild hydrolysis with aqueous methanol converted IV to the ketal aldehyde (V[8]). Sodium borohydride reduction of V gave the corresponding 6-hydroxymethyl ketal (VII[8]) which was also obtained when enol ether aldehyde III was reduced with sodium borohydride, and the resulting 6-hydroxymethyl enol ether (VI) photolyzed in methanol.[7]



Since some doubt persisted concerning the position of two of the methoxy groups in IV (3,3 or 3,4) and hence V and VII, IV was submitted to acid hydrolysis. Under well defined conditions, a crystalline hydrolysis product, identical with that obtained from hydrolysis of III, could be obtained in 26% yield. Its structure was not obvious and the reaction could not be used to exclude rigorously either possibility. Next, we turned to catalytic hydrogenation. TLC indicated that the product was a mixture. When an attempt was made to convert aldehyde V to the corresponding 6-methyl compound by sodium borohydride reduction of the *p*-toluenesulphonyl hydrazone of V[9], the main product isolated had spectral features consonant with structure VIIa[8]. The Huang–Minlon modification of the Wolff–Kishner reduction[10] of aldehyde V gave an amorphous product (VIII) which appeared homogeneous (TLC). Its NMR spectrum showed the presence of two methoxy groups (3·04 and 3·11 ppm) and two olefinic protons (4·40 and 4·55 ppm). The two olefinic protons must have been part of an exomethylene group, since the IR spectrum of VIII showed bands at 3075, 1650 and 890 cm^{-1}. The formation of olefin VIII rather than its Δ^5-6 methyl isomer is easily rationalized, since the carbanion[11] preceding the product forming step is allylic. Mild acid hydrolysis of olefinic ketal VIII gave a crystalline olefinic ketone VIIIa, ν 1720 cm^{-1} (3-ketone)[8]. This reaction sequence rigorously excludes the possibility that V, and therefore IV and VII, may be 3,4-dimethyl ethers.

KINETICS AND DISCUSSION

The addition of several molecules of methanol to enol ether aldehyde III proceeds either by formation of enol ether acetal A, followed by addition of methanol to the

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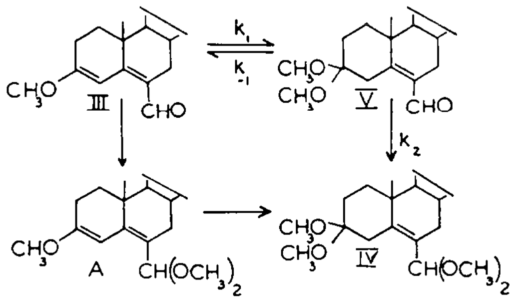
[7] None of the photochemical reactions occurred in the absence of UV light at a comparable rate.

[8] Detailed spectral and chemical characteristics are reported in the experimental section.

[9] L. Caglioti and P. Grasselli, *Chem. & Ind.* 153 (1964).

[10] Arthur I. Vogel, *Text-book of Practical Organic Chemistry* (3rd Edition) p. 516. Longmans.

[11] Donald J. Cram and George S. Hammond, *Organic Chemistry* p. 447, McGraw-Hill (1959).



enol ether function (III → A → IV), or by addition of methanol to the enol ether, followed by acetal formation (III → V → IV). In order to distinguish between these two possibilities, a methanolic solution of enol ether aldehyde (III) was irradiated. The transitory appearance of V could be detected spectrophotometrically (see below). Next, a solution of the ketal aldehyde (V) was irradiated. The product was quantitatively transformed to ketal acetal (IV).[12] When the reaction was monitored by TLC and UV, the transitory appearance of 1–2% of enol ether aldehyde (III) could be detected, and, using optimal conditions, isolated and identified. This evidence did not exclude either pathway.

We next turned to a kinetic approach to determine the reaction sequence. Using a constant light source, a constant initial concentration ($0{\cdot}5 \times 10^{-4}$ molar) of III and V, and determining the concentrations of III (λ_{max} 320 mμ), V (λ_{max} 250 mμ) and IV at various intervals spectrophotometrically, the following rate constants were obtained for the overall rate of disappearance of III (1) and V (2):[13]

$$-\frac{d\,III}{dt} = k_{III}\,(III) \qquad k_{III} = 0{\cdot}092\ \text{min}^{-1} \tag{1}$$

$$-\frac{d\,v}{dt} = k_V\,(V) \qquad k_V = 0{\cdot}642\ \text{min}^{-1} \tag{2}$$

Assuming that only reaction paths denoted by k_1, k_{-1} and k_2 are significant, the following expressions (3) and (4) can be written:

$$-\frac{d\,III}{dt} = k_1\,(III) - k_{-1}\,(V) \tag{3}$$

$$-\frac{d\,V}{dt} = k_2\,(V) + k_{-1}\,(V) - k_1\,(III) \tag{4}$$

From these equations, the values for k_1 ($0{\cdot}105\ \text{min}^{-1}$) $k_2 + k_{-1}$ ($0{\cdot}737\ \text{min}^{-1}$), k_{-1} ($0{\cdot}043\ \text{min}^{-1}$) and k_2 ($0{\cdot}696\ \text{min}^{-1}$) could be determined.[14] These values provide a self-consistent picture of the reaction and permit exclusion of pathway III → A → IV.

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[12] IV and V had the same R_f value in all TLC systems used.

[13] The photoreaction of III could be suppressed by addition of a few drops of pyridine or by making the solution 0·006 molar in sodium acetate. However no significant change in reaction rate occurred when V was photolysed in the presence of sodium acetate.

[14] These values were determined several times. The experimental error is +10% for k_1 and k_2. It is considerably larger for k_{-1} (estimated error: +80%). Since the term k_1 (III) in (4) is very small, it could be neglected.

The values of the rate constants have no further significance. In order to make them meaningful, the relative magnitudes for k_1, k_{-1}, and k_2 would have to be corrected for the energy output of the lamp at the wavelength of the absorbing species. This has not been attempted and is beyond the scope of this study.

Further work is in progress to elucidate the mechanism of conversion of III $\leftrightarrows$ V $\rightarrow$ IV.

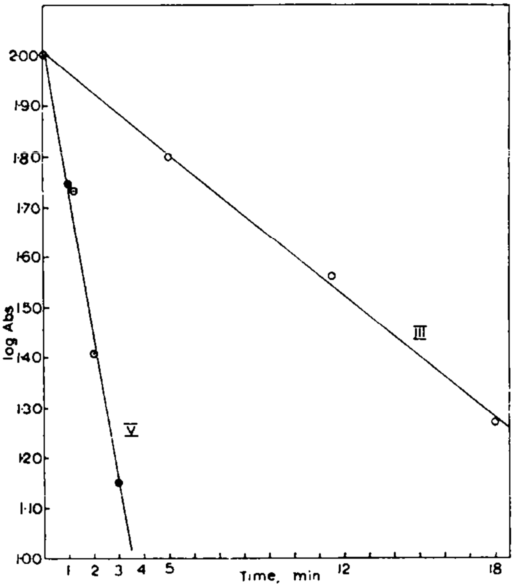

FIG. 1. The rate of disappearance of III and V.

EXPERIMENTAL

All m.ps were determined in a conc. H_2SO_4-bath and are uncorrected. Optical rotations were performed with a Carl Zeiss automatic polarimeter using a 0·5 dm tube. The IR spectra were taken on a Perkin-Elmer 337 grating spectrophotometer using 1 mm NaCl cells. NMR spectra were recorded on a Varian A.60 instrument at 60 megacycles using CCl_4 as solvent and tetramethylsilane (0 ppm) as internal standard. The UV absorption spectra were measured on a Beckman DK-1 recording spectrophotometer. Preparative TLC separation was effected on 0·75 mm thick (20 × 20 cm) unactivated plates coated with Merck A. G. Silica gel. All irradiations were performed in a Rayonet photochemical reactor (The Southern New England Co., Middletown, Conn., U.S.A.), using lamps with maximum output at 2537 Å. Analyses were carried out by Dr. C. Daesslé, Montreal, and Schwarzkopf Microanalytical Laboratory, Woodside 77, N.Y.

Photolysis of 17β-*acetoxy-6-formyl-3-methoxyandrosta-*3,5-*diene* (III)

A solution of III (0·600 g) in MeOH (200 ml) was irradiated in a He atm. for 16 hr. TLC (benzene–ether 4:1) revealed one spot only. Crystallization from MeOH containing a trace of pyridine gave IV (0·404 g), m.p. 119–120°. Recrystallization did not raise the m.p., $[\alpha]_D$ −68·95° (*c*, 1·23 in $CHCl_3$); ν CCl_4 1740, 1240 cm^{-1} (—OAc), 1660 cm^{-1} (C═C), 1100, 1075, 1055 cm^{-1} (OCH_3); δ 4·9 (s, 1H), 3·25 (s, 3H), 3·15 (s, 6H), 3·05 (s, 3H) 2·80 (poorly resolved signal, ~0·5H), 1·97 ppm (s, 3H). (Found: C, 69·48; H, 9·17. $C_{26}H_{42}O_6$ requires: C, 69·30; H, 9·40%.)

17β-*Acetoxy-6-formyl-*3,3-*dimethoxyandrost-5-ene* (V)

A methanolic solution of IV containing a few drops water was allowed to stand for 18 hr at room temp, after which time crystals appeared. When necessary, the crystallization could be completed by further addition of water or cooling. The product, m.p. 159–160·5°, was recrystallized twice from moist MeOH and gave pure V, m.p. 164–165°; $[\alpha]_D$ −126·9° (*c*, 0·98 in $CHCl_3$); ν CCl_4 2750 cm^{-1} (—CHO), 1660 cm^{-1} (α,β-unsaturated aldehyde), 1740, 1230 cm^{-1} (—OAc), 1100, 1050 cm^{-1} (—OCH_3); δ 10·3 (s, 1H), 3·95 (poorly resolved signal, ~0·5H), 3·70 (poorly resolved signal, ~0·5H), 3·30 (s, 3H), 3·15 (s, 3H), 2·06 ppm (s, 3H); λ_{max}^{MeOH} 250 mμ (ε 12,620). (Found: C, 71·44; H, 8·90. $C_{24}H_{36}O_5$ requires: C, 71·25; H, 8·97%.)

*17β-Acetoxy-6-hydroxymethyl-*3,3*-dimethoxyandrost-*5*-ene* (VII)

1. *From* 17*β-acetoxy-6-formyl-*3,3*-dimethoxyandrost-*5*-ene* (V). To a stirred solution of V (60 mg) in MeOH (2 ml) was slowly added $NaBH_4$ (64 mg) and the mixture was stirred for 15 min at room temp. Water was added and the mixture extracted with ether. The organic phase was washed several times with water and dried over $MgSO_4$. Evaporation of the solvent gave 60 mg of a crystalline residue. Recrystallization from ether gave 21 mg needles, m.p. 180·5–181°; ν CCl_4 3470 cm^{-1} (—OH), 1740, 1240 cm^{-1} (—OAc), 1100, 1050 cm^{-1} (—OCH_3).

2. *From the photolysis of* 17*β-acetoxy-6-hydroxymethyl-*3*-methoxyandrosta-*3,5*-diene* (VI). A solution of VI (99 mg) in MeOH (70 ml) was irradiated in a He atm. for 0·5 hr, after which time TLC (benzene–ether, 3:2) revealed only one spot. Evaporation of the solution and crystallization from MeOH gave 73 mg needles, m.p. 174·5–176·5°. Recrystallization raised the m.p. to 180–181°; $[\alpha]_D$ −50·64° (*c*, 0·93 in $CHCl_3$). This product was identical by IR, TLC, and mixed m.p. with that obtained from the $NaBH_4$ reduction of V; δ 4·41, 4·22, 3·91, 3·71 (AB quartet, J = 12 c/s, —CH_2OH), 3·3 (s, 3H), 3·8 (s, 3H), 2·95 (poorly resolved signal, ~0·5H), 2·09 (s, 3H) ppm. (Found: C, 70·74; H, 9·67. $C_{24}H_{38}O_5$ requires: C, 70·90; H, 9·42%.)

Hydrolysis of III

A solution of III (530 mg) in dioxan (20 ml), 50% aqueous perchloric acid (0·3 ml) and water (6 ml) was stirred at room temp for 4 hr. It was then diluted with water and the solution extracted with ether. The organic layer was washed with 10% $NaHCO_3$aq and water, and dried. Evaporation gave a light yellow foam. TLC (benzene–ether, 4:1) separated the mixture into two main components. Elution of the slower band with $CHCl_3$ gave 102 mg plates, m.p. 207·5–209°; $[\alpha]_D$ −49·9° (*c*, 1·10 in $CHCl_3$); ν $CHCl_3$ 1725 cm^{-1} (—OAc), 1680 cm^{-1} (α,β-unsaturated ketone); ν KBr 1740, 1220, 1020 cm^{-1} (—OAc), 1675 cm^{-1} (broad peak, unsaturated carbonyl (s)), 1600 cm^{-1} (weak), 870 cm^{-1} (medium): δ_{CHCl_3} 6·19 (s, 1H), peaks on the methylene envelope at 2·62, 2·46, 2·40, 2·12 and 2·05 (s, 3H) ppm; λ_{max}^{MeOH} 249 mμ (ε 8600). (Found: C, 73·80; H, 8·44. $C_{22}H_{30}O_4$ requires: C, 73·71; H, 8·44%.)

Hydrolysis of IV

A solution of IV (102 mg) in acetone (8·0 ml) containing water (2·0 ml) and conc. H_2SO_4 (0·05 ml) was stirred at room temp for 16 hr. The mixture was extracted with ether and the organic layer washed neutral with H_2O. Evaporation of the dried ethereal solution gave a light yellow foam which was purified by preparative TLC (benzene–ether 4:1): the main component consisted of 20 mg of a crystalline material identical by IR, TLC and mixed m.p. with that obtained previously from the hydrolysis of III.

Catalytic hydrogenation of IV

A solution of IV (217 mg) in MeOH (10 ml) was hydrogenated at 2000 p.s.i. in the presence of PtO_2 (100 mg) for 18 hr. TLC of the product revealed at least six components. NMR of the major components showed that they lacked the required spectral features (namely, four methoxyl groups and two tertiary protons).

*17β-Acetoxy-6-methoxymethyl-*3,3*-dimethoxyandrost-*5*-ene* (VIIa)

Aldehyde V (252 mg) was slowly added to a stirred solution of *p*-tosylhydrazine (125 mg) in MeOH (10 ml) at room temp. After 30 min, TLC revealed one spot and the disappearance of starting material. The solvent was evaporated *in vacuo* at room temp to give an orange foam, which could not be crystallized; ν_{CCl_4} 3200, 1740, 1620, 1240, 1170, 1100, 1050, 950, 660, 570 cm^{-1}. The product was dissolved in MeOH (25 ml) and $NaBH_4$ (500 mg) was slowly added. The stirred solution was refluxed for 1·5 hr, after which time no tosylhydrazone could be detected by TLC. Separation of the resulting mixture by TLC gave one component in 25% yield. Two recrystallizations from MeOH containing a trace of pyridine gave crystals, m.p. 126–127°; $[\alpha]_D$ −20·08° (*c*, 1·24 in $CHCl_3$); ν_{CCl_4} 1740, 1240 cm^{-1} (—OAc), 1660 cm^{-1} (C=C), 1110, 1100, 1050 cm^{-1} (—OCH_3); pair of doublets centred at 3·91 and 3·60, (AB quartet, J = 11 c/s, —$\underline{CH_2}$—O), 3·19 (s, 3H), 3·11 (s, 3H), 3·00 (s, 3H), 2·75 (broad signal ~0·5H), 1·95 (s, 3H) ppm. (Found: C, 72·00; H, 9·41. $C_{25}H_{40}O_5$ requires: C, 71·39; H, 9·59%.)

3,3-*Dimethoxy-6-methyleneandrostan*-17β-*ol* (VIII)

A solution of V (256 mg), diethylene glycol (5·0 ml), hydrazine hydrate (0·25 ml) and KOH (250 mg) was heated under reflux for 1 hr. The condenser was then removed and the temp allowed to rise to 210°. After an additional 3 hr heating, the cooled colourless solution was extracted with ether. The usual workup gave a foamy residue which was purified by preparative TLC yielding VIII (132 mg); ν_{CCl_4} 3620 cm^{-1} (—OH), 3075, 1650, 890 cm^{-1} (—C=CH_2), 1100, 1055 cm^{-1} (—OCH_3).

6-*Methyleneandrostan*-17β-*ol*-3-*one* (VIIIa)

Ketal VIII (113 mg) was heated under reflux for 15 hr in acetone (20 ml) and water (5 ml) containing *p*-toluenesulphonic acid (113 mg). Ether extraction gave a crystalline residue. Two recrystallizations from ether gave VIIIa, m.p. 194·5–196°; $[\alpha]_D$ −21·03° (*c*, 1·25 in $CHCl_3$); ν_{CHCl_3} 3600, 1120 cm^{-1} (—OH), 1720 cm^{-1} (saturated ketone), 1650, 895 cm^{-1} (C=CH_2). (Found: C, 79·48; H, 10·07. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%.)

Kinetic experiments

A magnetically stirred solution of III (200 cc; 0·5 × 10^{-4} molar) in abs MeOH was irradiated in a He atm. in a quartz cell fitted with a cold water jacket and a cold water condenser. At various time intervals, aliquots (3 ml) were pipetted out and immediately transferred into a stoppered UV cell, and the spectrum recorded on a Beckman DKI recording spectrophotometer. Aldehyde V was similarly irradiated. Several runs were made in each case. The table below shows the concentrations of III, V and IV at various time intervals of a particular run in the controlled photolysis of III, and the rate constants k_{-1} and k_2.

Time min^{-1}	Conc. III	Conc. V	Conc. IV	k_{-1} min^{-1}	k_2 min^{-1}
0	1·00	0	0	0	0
5	0·635 ± 0·020	0·160	0·205	0·064 ± 61%	0·677 ± 5%
11·5	0·335 ± 0·035	0·170	0·465	0·033 ± 91%	0·704 ± 4%
18	0·189 ± 0·050	0·177	0·634	0·030 ± 98%	0·707 ± 4%

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