

PHOTOCHEMICAL TRANSFORMATIONS OF DIENES

I. THE PHOTOLYSIS OF 3-ALKOXYCHOLESTA-3,5-DIENES

GEORGE JUST AND CLIFFORD C. LEZNOFF^{1,2}

Department of Chemistry, McGill University, Montreal, Quebec

ABSTRACT

The photolysis of 3-alkoxycholesta-3,5-dienes in an alcohol has been found to result in a stereospecific addition of the alcohol to the Δ^3 double bond with formation of β,γ -unsaturated ketals. On silica gel, the non-cyclic β,γ -unsaturated ketals gave cholest-5-en-3-one.

As part of an investigation of the photoinduced transformations of heteroannular dienes, an ethanolic solution of 3-ethoxycholesta-3,5-diene (I) was irradiated with a high-pressure mercury lamp. The reaction was very fast as evidenced by the disappearance of the chromophore at 239 m μ . Evaporation and purification by chromatography on alumina resulted in a 60% yield of a crystalline compound (II), C₃₁H₅₄O₂, m.p. 49–50°. Treatment with acid resulted in the formation of cholest-4-en-3-one (VIII). Chromatography of II on silica gel gave cholest-5-en-3-one (IV).

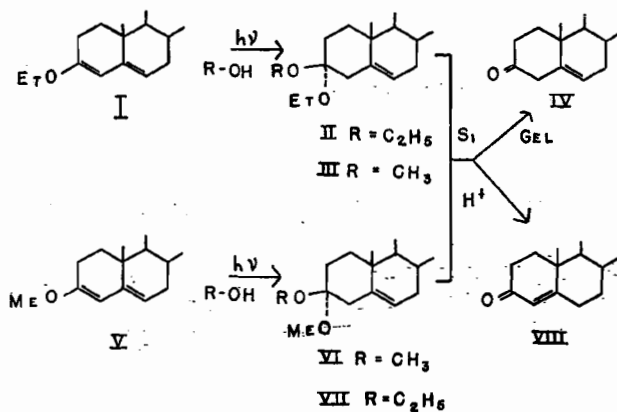


FIG. 1.

These results, in accord with the infrared (Fig. 2) and nuclear magnetic resonance (n.m.r.) data (Table I), indicated that the photoproduct was 3,3-diethoxycholest-5-ene (II). The structure was confirmed by synthesis in which cholest-5-ene-3-one was reacted with absolute ethanol in the presence of malonic acid (2).

Similarly, photolysis of 3-methoxycholesta-3,5-diene (V) in methanol gave 3,3-dimethoxycholest-5-ene (VI) in 50–60% yield, identical in all respects with a synthetic sample (2).

When 3,3-diethoxycholest-5-ene was recrystallized from methanol, a new compound

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TABLE I
Nuclear magnetic resonance data of photolysis products II, III, VI, and VII
(T.M.S. = 0, chemical shifts in p.p.m.)

Compound	Methylene group at C ₄ singlet	3 α -MeO singlet	3 β -MeO singlet	3 α -EtO quartet center	3 β -EtO quartet center	Vinyl proton at C ₆ singlet
3,3-Diethoxycholest-5-ene	2.25	—	—	3.40 _s	3.33	5.25
3,3-Dimethoxycholest-5-ene	2.23	3.12 _s	3.04 _s	—	—	5.25
3 α -Ethoxy-3 β -methoxycholest-5-ene	2.25	—	3.05 _s	3.44	—	5.25
3 β -Ethoxy-3 α -methoxycholest-5-ene	2.25	3.15	—	—	3.33	5.25

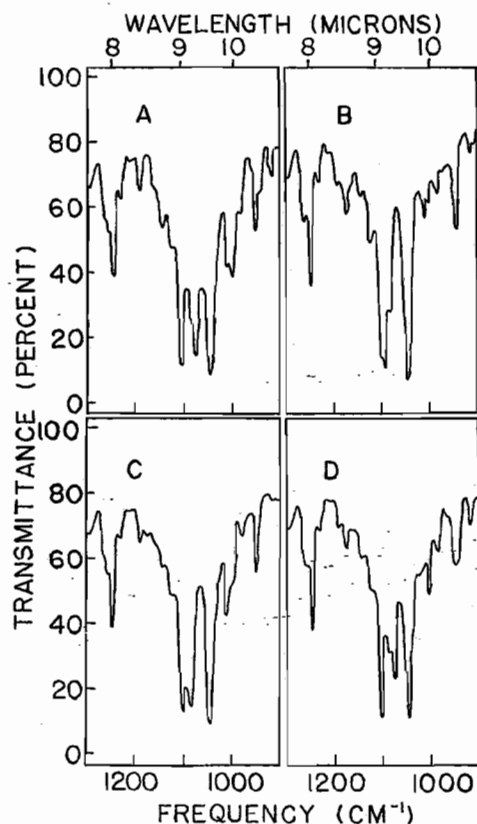


FIG. 2. The infrared spectra of (A) 3,3-diethoxycholest-5-ene; (B) 3,3-dimethoxycholest-5-ene; (C) 3 α -ethoxy-3 β -methoxycholest-5-ene; (D) 3 β -ethoxy-3 α -methoxycholest-5-ene.

(III), C₃₀H₅₂O₂, m.p. 105–106°, was obtained. The infrared spectrum (Fig. 2) showed strong absorption in the ether region and the n.m.r. spectrum showed the presence of one methoxy group, a singlet, and of one ethoxy group, a quartet (Table I), as well as a vinyl proton. The C₄ methylene group of these ketals at 2.25 p.p.m. is easily recognized and consistent with the structural assignments.

Since 3,3-dimethoxycholest-5-ene gives two distinct, unsplit signals for the two methoxy groups, compound III is a 3-ethoxy-3-methoxycholest-5-ene, in which one ethoxy group has been exchanged specifically for one methoxy group.

It is a well-known fact (4, 5, 7) that in solvolytic reactions of the cholesteryl type, the Δ^5 double bond participates to give a homoallylic carbonium ion and that the incoming group attaches itself at the 3β position in a stereospecific manner. It hence seems reasonable to assume that in this exchange reaction, the Δ^5 double bond assists preferentially the departure of the 3β substituent and that the resulting dialkoxy compound is 3α -ethoxy- 3β -methoxycholest-5-ene (III).

It was fortuitous that compound III was obtained in the pure state since a more detailed investigation of the exchange reaction of 3,3-diethoxy and 3,3-dimethoxycholest-5-ene in methanol and ethanol respectively revealed that the 3α -alkoxy group also exchanges. The rate of exchange of the 3β substituent is twice that of the 3α substituent.

In order to obtain some insight into the mechanism of the photolysis reaction, 3-methoxycholesta-3,5-diene (V) was photolyzed in absolute ethanol. The main product (VII) of the reaction, obtained in 60% yield, was isomeric with compound (III), obtained by the methanolysis of II. Nuclear magnetic resonance (Table I) showed the presence of one methoxy and one ethoxy groups. The chemical shifts of the methoxy and ethoxy groups coincide with one of the methoxy and ethoxy groups in VI and II. On silica gel, VII gave cholest-4-ene-3-one and cholest-5-ene-3-one. The compound is, hence, assigned the structure 3β -ethoxy- 3α -methoxycholest-5-ene (VII).

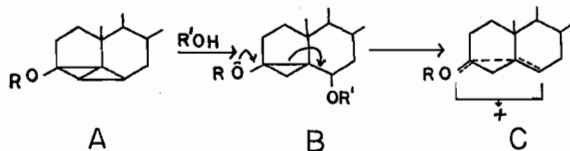
When 3-ethoxycholesta-3,5-diene (I) was photolyzed in methanol, 3,3-dimethoxycholest-5-ene (VI) was obtained. Obviously, the solvolysis exchange reaction was rapid. However, when the reaction was repeated in the presence of a small amount of pyridine, 3α -ethoxy- 3β -methoxycholest-5-ene (III) was obtained. The product was identical with the methanolysis product of 3,3-diethoxycholest-5-ene (II). The n.m.r. of the crude photolysis product revealed that the reaction was not completely stereospecific, but that 5-10% of the isomeric mixed ketal (VII) was present.

It should be noted that n.m.r. and infrared spectra were taken on all crude photolysis products, in order to ensure that no isomerizations occurred during chromatography and crystallization.

The n.m.r. and infrared spectra were very characteristic for photolysis products II, III, VI, and VII, and resulted in unambiguous identification (Table I and Fig. 2).

If the assignment of stereochemistry of the epimeric mixed ketals is correct, the chemical shifts of the 3α - and 3β -methoxy groups are 3.12 τ and 3.04 p.p.m. and of the 3α - and 3β -ethoxy groups are 3.40 τ and 3.33 p.p.m. respectively. The methoxy groups give signals which appear as singlets while the ethoxy groups give signals which appear as quartets.

All of these results are consistent with the intermediacy of the carbonium ion C, formed either directly by interaction of a photoexcited species with solvent, or indirectly by sequence A \rightarrow B \rightarrow C.



A similar sequence has been proposed some time ago by Dauben and Willey (8) to explain the photolysis of cholesta-3,5-diene (8, 9) in which an intermediate of type A (OR = H) was isolated. We were not able to isolate an intermediate of this nature, using the conditions described (8). In particular, the n.m.r. of the photolysis product (pentane, He atmosphere) did not show any peaks characteristic of alkoxy groups. Further work to determine the mechanism of the reaction is being carried out.

EXPERIMENTAL

The melting points were determined on a Kofler microscope hot-stage and are corrected. The analyses were carried out by Dr. C. Daesslé, Montreal. The infrared spectra were determined on a Perkin-Elmer 421 grating spectrophotometer using 1 millimeter sodium chloride cells and carbon disulphide as solvent. The ultraviolet absorptions spectra were measured by means of a Beckman recording spectrophotometer Model DK1. Nuclear magnetic resonance spectra were recorded on a Varian H.R. 60 instrument at 60 megacycles using carbon tetrachloride as solvent and tetramethylsilane (0 c.p.s.) as an internal standard. Optical rotations were performed with a Carl Zeiss automatic polarimeter using a 0.5-dm tube. All irradiations were performed with a Hanovia 450-watt lamp in a water-cooled immersion apparatus. Unless otherwise stated, Woelm alumina, activity II-III, was used for chromatography.

Irradiation of 3-Ethoxycholesta-3,5-diene (I) in Ethanol

A solution of 3.0 g of I, $\lambda_{\text{max}}^{\text{EtOH}}$, 239 $\text{m}\mu$ (ϵ 17,900), was irradiated until no absorption could be detected in the ultraviolet (1.5 hours). After evaporation, one-half of the crude material was chromatographed on silica gel (Davidson No. 923). Elution with hexane, hexane-benzene, and benzene-ether gave 0.5 g of crude cholest-5-ene-3-one (IV), m.p. 118-120°. Recrystallization from cyclohexane afforded 0.1 g of IV, m.p. 119-125°. The melting point was not depressed upon admixture of authentic IV (6a). The infrared spectra were superimposable.

The other half of the crude photolysis product was chromatographed on alumina. Elution with pentane gave crude 3,3-diethoxycholest-5-ene (II) in 60% yield. Several crystallizations from ethanol gave II, m.p. 49-50°, $[\alpha]_{\text{D}} -28.4^\circ$ (c , 1.06 in chloroform). Calc. for $\text{C}_{27}\text{H}_{44}\text{O}_2$: C, 81.16; H, 11.87%. Found: C, 81.26; H, 11.96%.

Further elution with benzene gave 20% of cholest-4-en-3-one (VIII), m.p. 81-82° not depressed upon admixture of authentic (VIII). Infrared and ultraviolet spectroscopy further proved the identity of the two products.

Further elution with ether gave 25 mg of cholest-4-en-6 β -ol-3-one (IX) (6b), m.p. 181-182°, $\lambda_{\text{max}}^{\text{EtOH}}$, 237 $\text{m}\mu$ (ϵ 12,800), ν_{OH} , 3570 cm^{-1} (free O-H), 3380 cm^{-1} (hydrogen-bonded O-H), 1685 cm^{-1} (α,β -unsaturated ketone). The melting point was not depressed on admixture with authentic IX.

3,3-Diethoxycholest-5-ene (II) and 3,3-Dimethoxycholest-5-ene (VI)

Following the procedure described by Ueberwasser *et al.*, a solution of cholest-5-en-3-one (1.0 g) and 0.5 g of malonic acid in 60 ml absolute ethanol was stirred for 20 hours at 20-25°. The solution was worked up as described and the resulting oil chromatographed on alumina. Elution with pentane yielded 0.38 g of pure 3,3-diethoxycholest-5-ene (II), m.p. 48-49°, in 32% yield, identical (infrared, melting point, mixed melting point) with that obtained by photolysis.

Similarly, the reaction of cholest-5-en-3-one, 1.0 g, and 0.5 g of malonic acid in 60 ml of absolute methanol yielded 0.685 g of pure 3,3-dimethoxycholest-5-ene (VI), m.p. 96°, identical (infrared, melting point, and mixed melting point) with that obtained by photolysis.

3-Methoxycholesta-3,5-diene (V)

To cholest-4-en-3-one (10 g) and 10 ml of trimethylorthoformate in 50 ml of dioxane, was added two drops of concentrated sulphuric acid in 1.5 ml of dioxane and the mixture refluxed for 0.5 hours. Pyridine (0.25 ml) was then added and the solution evaporated to an oil which was covered with methanol and allowed to crystallize. Recrystallization from ether-methanol yielded 5.8 g of pure V, m.p. 67-68°, $[\alpha]_{\text{D}} -97.1^\circ$ (c , 1.12 in pyridine), $\lambda_{\text{max}}^{\text{EtOH}}$, 239 $\text{m}\mu$ (ϵ 19,900). Calc. for $\text{C}_{28}\text{H}_{46}\text{O}$: C, 84.35; H, 11.63%. Found: C, 84.19; H, 11.97%.

Irradiation of 3-Methoxycholesta-3,5-diene (V) in Methanol

Irradiation of 0.5 g of V in 1800 ml of absolute methanol for 30 minutes yielded, after evaporation, 0.6 g of an oil. Chromatography on alumina and elution with pentane gave 200 mg of 3,3-dimethoxycholest-5-ene (VI), m.p. 93°. Recrystallization from acetonitrile-ether gave pure VI, m.p. 95.7-96.0°, $[\alpha]_{\text{D}} -35.5^\circ$ (c 1.07 in chloroform), identical (infrared, melting point, and mixed melting point) with that described above. Calc. for $\text{C}_{28}\text{H}_{46}\text{O}_2$: C, 80.87; H, 11.70%. Found: C, 81.19; H, 11.82%.

Methanolysis of 3,3-Diethoxycholest-5-ene (II)

The crude irradiation product of 1.65 g of 3-ethoxycholesta-3,5-diene (I) in ethanol was chromatographed on alumina. The oily hexane eluate (0.90 g) was covered with methanol. After a few days, 0.36 g of 3 α -ethoxy-3 β -methoxycholest-5-ene (III), m.p. 88-91°, was obtained. Two recrystallizations from methanol raised the m.p. to 105-106°. Calc. for $\text{C}_{28}\text{H}_{48}\text{O}_2$: C, 81.02; H, 11.79%. Found: C, 80.70; H, 12.05%.

In a second run, 100 mg of pure 3,3-diethoxycholest-5-ene (II) was heated for 12 hours in methanol on a steam bath and the solvent allowed to evaporate. Crystallization of the reaction product from methanol gave 40 mg of III, m.p. 96-98°. The very characteristic infrared and n.m.r. spectra of the products, m.p. 96-98°, and m.p. 105-106°, were indistinguishable.

Cholest-4-en-3-one (VIII) from 3 α -Ethoxy-3 β -methoxycholest-5-ene (III)

When a 90-mg sample of III in carbon tetrachloride was taken to dryness on the steam bath, an oily

mixture was recovered. Chromatography on aluminum oxide and elution with hexane-benzene mixtures gave cholest-4-en-3-one (VIII), m.p. 81-82°. The melting point was not depressed on admixture of authentic (VIII). Comparison of the infrared spectra confirmed the identity of the two compounds.

Further elution with ether gave 25 mg of a crystalline material, which melted at 182-183° after recrystallization from hexane. The melting point was not depressed on admixture with the material obtained in the chromatogram of the photolysis product of I in ethanol and V in methanol.

Rate of Alcoholysis of the 3,3-Dialkoxycholest-5-enes

Ketals VI and II were heated under reflux with ethanol and methanol respectively. Aliquots were withdrawn periodically and their n.m.r. spectra recorded.

In the methanolysis of II the 3 β -ethoxy group was replaced at a rate twice as fast as the 3 α -ethoxy group. The 3 β group was replaced after 10 hours, the 3 α group after 20 hours.

When 3,3-diethoxycholest-5-ene in 55 ml of methanol plus two drops of pyridine was refluxed overnight, 3,3-dimethoxycholest-5-ene was obtained.

Irradiation of 3-Methoxycholesta-3,5-diene (V) in Absolute Ethanol

Irradiation of 2.0 g of V in 1800 ml of absolute ethanol for 3 hours gave 2.3 g of product, which, on chromatography on alumina, yielded 1.1 g of 3 β -ethoxy-3 α -methoxycholest-5-ene (VII). The n.m.r. spectrum of this material indicated the presence of some epimeric 3 α -ethoxy-3 β -methoxycholest-5-ene (III) in small amounts. Recrystallization from ethanol gave pure VII, m.p. 98-99°, $[\alpha]_D -32.3$ (*c* 1.26 in chloroform). Calc. for C₃₀H₅₂O₂: C, 81.02; H, 11.79%. Found: C, 81.43; H, 12.07%.

Effect of Silica Gel on β,γ -Unsaturated Ketals

3 β -Ethoxy-3 α -methoxycholest-5-ene (70 mg) was chromatographed on 20 g of silica gel (Davidson No. 923). A mixture of cholest-4-en-3-one (VIII) and cholest-5-en-3-one (IV) was obtained as indicated by the infrared spectrum of the eluate, ν 1735 cm⁻¹ (saturated ketone), 1690 cm⁻¹ (α,β -unsaturated ketone).

Chromatography of pure cyclic diethylene ketal of cholest-5-ene-3-one (3) resulted in complete recovery of starting material.

Irradiation of 3-Ethoxycholesta-3,5-diene (I) in Methanol with Pyridine

Irradiation of 0.8 g of I in 1500 ml of methanol for 30 minutes and subsequent slow evaporation of the solvent resulted in the formation of 0.28 g of pure 3 α -ethoxy-3 β -methoxycholest-5-ene (III), m.p. 110-112°. Recrystallization from ether-methanol gave pure III, m.p. 112-113°, $[\alpha]_D -30.1$ (*c* 1.13 in chloroform). The infrared and n.m.r. spectra further proved the identity of this material.

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