PHOTOCHEMICAL TRANSFORMATIONS OF DIENES

IV. THE STEREOCHEMISTRY OF THE PHOTO-INDUCED ETHANOL ADDITION TO 3-METHOXYCHOLESTA-3,5-DIENE

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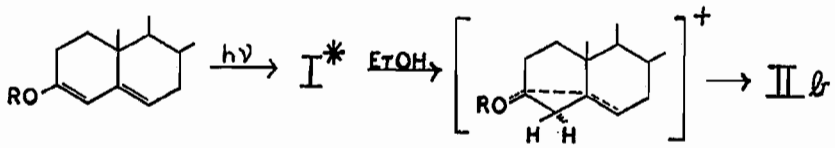
ABSTRACT

The photolysis of 3-methoxycholesta-3,5-diene in ethanol-*d* resulted in a 1:1 mixture of 4α- and 4β-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (II, II*a*). A stereospecific synthesis of 4β-deuterio-3α,5-cyclo-5α-cholestan-6β-ol is described.

Recently we have shown that the photo-induced addition of alcohols to 3-alkoxycholesta-3,5-dienes gave in reasonably good yield 3,3-dialkoxycholest-5-enes (1) (e.g. I $\rightarrow$ II). The addition of the alkoxy moiety seemed to be quite stereospecific (3β) (1). In this paper we wish to report on the stereochemistry of protonation of the diene system, and to propose a reaction scheme accounting for the products of these and related reactions (2, 3).



I A

The geminal protons at C-4 are clearly shifted away from most signals in the nuclear magnetic resonance (n.m.r.) spectrum of 3,3-dialkoxycholest-5-enes (1), but seem to be equivalent and hence give rise to a single two-proton peak. In order to determine the stereochemistry of the proton addition at C-4, it was necessary to devise a means of making the two protons at C-4 non-equivalent. In principle, this could be achieved by incorporating them into a cyclopropane ring. The C-4 deuterated product could then be compared by n.m.r. to 4β-deuterio-3α,5-cyclocholestan-6β-ol (VIII), stereospecifically synthesized by an independent route.

Cholest-4-en-3β-yl acetate (4) was treated with monoperphthalic acid (5) in ether and the resulting 4α,5α-epoxycholestan-3β-yl acetate (V) (6) reduced with lithium aluminium deuteride to give 4β-deuteriocholestan-3β,5α-diol (VI). These reductions are known to result in a *trans* diaxial opening of oxide rings (6, 7, 8). Monoacetylation and dehydration with thionyl chloride gave 4β-deuteriocholesteryl acetate (VII*a*), which, after hydrolysis, was transformed into 4β-deuteriocholesteryl tosylate (VII*b*). The n.m.r. spectrum of VII*b* in benzene showed a one-proton signal at 2.45 p.p.m. (doublet, J = 4.5 c.p.s.) corresponding to the C-4 α proton. Pure cholesterol tosylate shows a two-proton signal at

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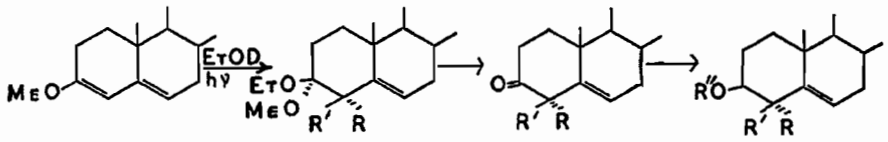
2.45 p.p.m. (doublet, J = 8.8 c.p.s.) due to the C-4 protons. Solvolysis of VII*b* yielded 4β-deuterio-3α,5-cyclocholestan-6β-ol (VIII) (9). Whereas 3α,5-cyclocholestan-6β-ol shows complex signals between 0.2 and 0.7 p.p.m. due to the cyclopropane protons, its 4β-deutero analogue showed in the high field region a one-proton doublet at 0.23 p.p.m. (J = 8.5 c.p.s.) only. The 4α-hydrogen is coupled with the hydrogen at C-3 and the coupling constant is that expected for *cis*-hydrogens on a cyclopropane ring (10, 11).

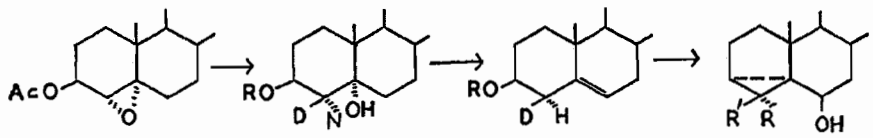


I

II R=H, R′=D
IIa R=D, R′=H
IIb R=H, R′=H

III R=H, R′=D
IIIa R=D, R′=H

IV R″=H, R=H, R′=D
IVa R″=H, R=D, R′=H
IVb R″=OTs, R=H, R′=D
IVc R″=OTs, R=D, R′=H



V

VI R=H
VIa R=OAc

VII R=OAc
VIIa R=H
VIIb R=OTs

VIII R=H, R′=D
VIIIa R=D, R′=H

Whereas the photolysis of 3-alkoxycholesta-3,5-dienes in methanol or ethanol proceeded without any difficulty, this was not the case for the corresponding reaction in deuterioethanol, prepared by decomposition of diethyl sulfite in heavy water (12). It seemed that in spite of all precautions taken in its preparation, a small amount of acidic material was present in the deuterated solvent. The reaction was hence carried out in deuterioethanol containing a small amount of pyridine. Mono-4-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (II, II*a*) (1) was isolated in approximately 50% yield by chromatography. Its n.m.r. spectrum showed a one-proton peak at 2.56 p.p.m. (benzene), indicating that one deuterium atom had been taken up per molecule of diene. The ketal was hydrolyzed with malonic acid in acetone to 4-deuteriocholest-5-en-3-one (III, III*a*), which showed a signal at 2.80 p.p.m. (benzene) due to one proton at C-4. No exchange with solvent could have taken place to any large extent at this stage, since any resulting non-deuterated cholest-5-en-3-one would have given (*vide infra*) non-deuterated 3α,5-cyclocholestan-6β-ol (9), which has a very characteristic n.m.r. spectrum in the 0.2–0.7 p.p.m. region. Lithium aluminium hydride reduction of III and treatment of the resulting alcohol with *p*-toluenesulfonyl chloride in pyridine overnight yielded 4-deuteriocholesteryl tosylate (IV*b*, IV*c*).

Solvolysis of (IV*b*, IV*c*) in buffered aqueous acetone gave 4-deuterio-3α,5-cyclocholestan-6β-ol (VIII, VIII*a*). Its n.m.r. spectrum showed two signals (approximately 0.5 protons each) in the region characteristic of cyclopropane protons. The signal at 0.23 p.p.m. (doublet, J = 8.5 c.p.s.) was identical to that of 4β-deuterio-3α,5-cyclocholestan-6β-ol. The low-field signal, centered at 0.48 p.p.m., showed up as a triplet. There is little doubt that this signal can be assigned to the 4β-hydrogen, and that this proton is spin–spin coupled with the hydrogen at C_3. In addition, some long range coupling similar to that observed in 3α-methyl-3β,5-cyclocholestane (2) must also be present. The results can only be interpreted by assuming that the deuteration at C-4 was non-specific and that an approximately 1:1 mixture of 4α- and 4β-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (II, II*a*) was obtained in the photo-induced reactions. This is in contrast with the stereochemistry of protonation of the 3β,5-cyclosteroids obtained in the photolysis of cholestadiene and its 3-methyl homologue, in which one deuterium atom was introduced stereospecifically at C-4β (2, 3). It seems therefore quite likely that no bicyclobutane intermediate was formed as a primary photoproduct, since a 3-ethoxybicyclobutane intermediate should be protonated by ethanol as specifically as the analogous 3-methyl and 3-unsubstituted bicyclobutanes.

In order to gain further insight into the reaction, the photolysis of 3-ethoxycholesta-3,5-diene was carried out in the presence of oxygen, which is known to react as a rule rapidly with triplets (13, 14, 15), although exceptions are known (16). The yield of 3,3-diethoxycholest-5-ene was identical to that obtained in the absence of oxygen.

Since benzophenone is known to induce photoreactions to go through the triplet state (17, 18), 3-ethoxycholesta-3,5-diene was photolyzed in the presence of benzophenone, using a "pyrex" tube to filter out wavelengths below 330 mμ. This reaction led to a rapid disappearance of the chromophore. No ketal, however, was formed under these reaction conditions.[3]

The photolyses of cholesta-3,5-diene and 3-alkoxycholesta-3,5-dienes can be summarized as follows: the former is sensitive to oxygen (3), proceeds through a bicyclobutane which can be isolated (19), and the intermediate bicyclobutane is protonated stereospecifically by deuterioethanol (2, 3) to give 4β-deuterio-6β-ethoxy-3β,5-cyclo-5β-cholestane. The products of photolysis in ethanol are identical to those obtained when the photolysis is carried out in pentane, and the intermediate bicyclobutane (19) reacted with ethanol. In contrast, the photolysis of 3-alkoxycholestadienes is insensitive to oxygen. No intermediate bicyclobutane can be isolated, when the enol ether is photolyzed in pentane, and reaction of that photoproduct with ethanol does not give ketals (1). The protonation at C-4 is not stereospecific. Based on the evidence presented, it is not unreasonable to assume that these two reactions proceed through different pathways, in particular since the photolysis of 3-methylcholesta-3,5-diene cannot be explained in terms of only one reaction path (2).

Too little information is available at the present time to give a more detailed interpretation of reaction course of these photolyses.[4]

EXPERIMENTAL[5]

4β-Deuteriocholestan-3β,5α-diol-3β-acetate (VIa)

To 0.300 g of lithium aluminium deuteride in 20 ml of anhydrous ether was added 2.0 g of solid V (6). Anhydrous ether (20 ml) was then added and the mixture stirred for 2 h. After careful addition of water, the

[3]*The same reaction, in the absence of benzophenone, resulted in the recovery of most of the starting material.*
[4]*See, however, ref. 21.*
[5]*General procedures and instrumentation as in ref. 1.*

solution was washed neutral, dried over sodium sulfate, and evaporated to dryness to give 1.9 g of crystals, m.p. 198–218°. Recrystallization from ethyl acetate gave 1.2 g of 4β-deuteriocholestan-3β,5α-diol (VI), m.p. 221° (lit. m.p. 224.5–225.5° (22)).

About 1.2 g of VI in 40 ml pyridine and 15 ml of acetic anhydride were left standing overnight at room temperature. After the usual work-up, recrystallization from acetone–methanol gave 1.2 g of 4β-deuteriocholestan-3β,5α-diol-3β-acetate (VI*a*), m.p. 184–185° (lit. 184.6–185.6° (23)).

4β-Deuteriocholesteryl Acetate (VII)

To a solution of 1.15 g of VI*a* in 20 ml of pyridine at 0 °C, 3 ml of thionyl chloride was added and the solution stirred for 20 min. Ice water was added and after the usual work-up, the oily crystals were crystallized twice from acetone–methanol to give 500 mg of VII, m.p. 105–109°.

4β-Deuterio-3α,5-cyclocholestan-6β-ol (VIII) (9)

About 425 mg of VII was hydrolyzed (6) and 300 mg of 4β-deuteriocholesterol (VII*a*), m.p. 146–148°, was obtained after crystallization from acetone–methanol.

Tosylation of 260 mg of VII*a* gave 290 mg of 4β-deuteriocholesteryl tosylate (VII*b*), m.p. 131–132° (9).

A solution of VII*b* (238 mg) in 12 ml of acetone and 3 ml of water was refluxed with 200 mg of sodium acetate for 15 h. Ether extraction, and chromatography of the resulting oil on 4 g of alumina, gave 60 mg of crystals, eluted by hexane–benzene mixtures. Recrystallization from acetone afforded 50 mg of VIII, m.p. 61–63° (identified by melting point and mixed melting point with an authentic sample (9)).

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

A solution of 2.1 g of I in 475 ml of dry pentane, 55 ml of ethanol-*d* (C_2H_5OD), and 0.25 ml pyridine was irradiated (Hanovia lamp, 450 W) for 3.5 h until little absorption could be detected in the ultraviolet After evaporation, the crude photolysis product was chromatographed on alumina. Elution with hexane gave 1.1 g of oily 4-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (II, II*a*). Crystallization from ethanol gave 500 mg of (II, II*a*), m.p. 92–93° (1).

4-Deuteriocholest-5-en-3-one (III, IIIa)

A solution of 500 mg of 4-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (II, II*a*) in 30 ml acetone and 3 ml of water containing 100 mg malonic acid was allowed to evaporate slowly at room temperature. After 66 h, 350 mg of 4-deuteriocholest-5-en-3-one (III, III*a*), m.p. 127–128°, was obtained by filtration. Its m.p. was not depressed upon admixture of cholest-5-en-3-one (24*a*).

4-Deuterio-3α,5-cyclocholestan-6β-ol (VIII, VIIIa)

To 350 mg of lithium aluminium hydride in 25 ml ether was added 350 mg of the 3-ketone (III, III*a*) obtained above. After stirring for 2 h, the reaction mixture was worked up and 355 mg of crystals were obtained. Recrystallization from acetone–methanol gave 210 mg of 4-deuteriocholesterol (IV, IV*a*), m.p. 138–140°. Its m.p. was not depressed upon admixture of cholesterol.

Tosylation of 4β-deuteriocholesterol obtained above gave 230 mg of 4-deuteriocholesteryl tosylate (IV*b*, IV*c*). The n.m.r. spectra of compounds (IV, IV*a*) and (IV*b*, IV*c*) were consistent with the structures assigned.

Solvolysis of 230 mg (see above) (9) of the tosylate gave 130 mg of (VIII, VIII*a*). Crystallization from acetone yielded 38 mg of (VIII, VIII*a*), m.p. 64–66°. Its melting point was not depressed upon admixture of an authentic sample (lit. m.p. 63–65° (9)).

Irradiation of 3-Ethoxycholesta-3,5-diene (IX) in Ethanol Saturated with Oxygen

A solution of 0.8 g of IX in 565 ml ethanol, through which oxygen had been bubbling for 40 min, was irradiated until the absorption maximum of IX had decreased to 2% of its original intensity (1 h). Chromatography on alumina gave, in the hexane fractions, 525 mg of 3,3-diethoxycholest-5-ene, m.p. 48–49°. Its melting point and infrared spectrum were identical to those of an authentic sample (1). Elution with ether yielded 75 mg of cholest-4-en-3-on-6β-ol, m.p. 182–183°, identified by mixed melting point with an authentic sample (24*b*). Both products had been formed in similar yields when oxygen had been excluded from the photolysis reaction (1).

Irradiation of 3-Ethoxycholesta-3,5-diene (IX) in Ethanol Using Benzophenone as a Photosensitizer

Irradiation (utilizing a pyrex sleeve to eliminate radiation below 330 mμ) of 0.5 g of IX in ethanol (525 ml), containing 0.5 g of benzophenone, for 2.5 h resulted in a decrease of the absorption maximum to less than 20% of the original absorbance. Evaporation of the solvent gave 0.2 g of benzpinacol as crystals. The remaining oil (0.6 g) was chromatographed on alumina. Elution with hexane gave 90 mg of IX. Further elution with hexane–benzene mixtures gave fractions which seemed to contain benzophenone, benzpinacol, and cholest-4-en-3-one. Elution with ether gave 190 mg crude cholest-4-en-3-on-6β-ol (X), from which 60 mg of X, m.p. 186–187°, was obtained by crystallization from hexane.

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