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PHOTOCHEMICAL TRANSFORMATIONS—II[1]

PHOTOCHEMISTRY OF 6-NITROCHOLESTERYL ACETATE AND RELATED COMPOUNDS

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Abstract—Photochemical rearrangement of 6-nitrocholesteryl acetate in ethanol is shown to give as the major product 3-oximinocholest-4-en-6-one. The same oxime is obtained from 3β-chloro-6-nitrocholest-5-ene but not from 6-nitrocholesterol on irradiation in ethanol. The photochemically-induced rearrangement of 6-nitrocholesteryl acetate in cyclohexane is also reported.

β-NITROSTYRENES are known to undergo dimerization,[2] addition to olefins,[3] and rearrangement[3] under the influence of UV light. It was considered of interest to study the photochemistry of an α,β-unsaturated nitro group in which this function was not further conjugated with an aromatic system.

6-Nitrocholesteryl acetate[4] (Ia) and some of its derivatives are readily available, and these have been investigated. Two preliminary accounts[5,6] of the photochemistry of 6-nitrocholesteryl acetate have recently been published. The results in this paper are substantially different from those previously reported and show these transformations to be sensitive to the solvent employed and to the nature of the substituent on $C_{(3)}$.

The photolysis of 6-nitrocholesteryl acetate was studied in ethanol using light from a medium-pressure mercury arc; the major product was 3-oximinocholest-4-en-6-one (II) obtained in 38% yield and not 3β-acetoxy-6-nitrocholest-4-ene (IIIa) as previously reported[5,6] in other solvents when light of wavelength greater than 290 mμ was employed. The same oxime has been isolated in lower yield (22%) on irradiation in acetone, where its formation has been attributed to the ability of acetone to act as a sensitiser.[6] The yield of oxime obtained on irradiation in ethanol is not reduced by the use of a pyrex filter, indicating that the nature of the solvent rather than the wavelength of light is the determining factor in the formation of 3-oximinocholest-4-en-6-one. Furthermore, the presence of a sensitiser is not essential for the formation of the oxime II, and the role assigned to acetone in the photolysis of 6-nitrocholesteryl acetate is therefore questionable.

The structure of this oxime was established by an unambiguous synthesis from the known 6-ethoxycholesta-4,6-dien-3-one[7] (IV); this was converted into the oxime V, which on selective acid hydrolysis of the enol ether gave the oxime II. Treatment of

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[1] For Part 1, see S. T. Reid and G. Subramanian, *Chem. Comm.* 245 (1966).

[2] R. D. Campbell and R. F. Ofstead, *Proc. Iowa Acad. Sci.* 71, 197 (1964).

[3] O. L. Chapman, A. A. Griswold, E. Hoganson, G. Lenz and J. Reasoner, *Pure and Appl. Chem.* 9, 585 (1964).

[4] C. E. Anagnostopoulos and L. F. Fieser, *J. Amer. Chem. Soc.* 76, 532 (1954).

[5] J. T. Pinhey and E. Rizzardo, *Chem. Comm.* 362 (1965).

[6] O. L. Chapman, P. G. Cleveland and E. D. Hoganson, *Chem. Comm.* 101 (1966).

[7] W. C. J. Ross, *J. Chem. Soc.* 737 (1946).

cholest-4-ene-3,6-dione with hydroxylamine hydrochloride also gave the oxime II which is the product expected by analogy with the known relative rates of oxime formation in 3- and 6-oxo-steroids.[8] The oxime II was reconverted to cholest-4-ene-3,6-dione in good yield by the action of pyruvic acid in acetic acid.

6-Nitrocholesta-3,5-diene (VI) was also isolated from the irradiation of 6-nitrocholesteryl acetate in ethanol, and separated in low yield by chromatography on silica gel. An authentic sample of this diene was prepared from 3β-chloro-6-nitrocholest-5-ene[9] by elimination in quinoline. The same nitrodiene was previously isolated from the photolysis of 6-nitrocholesteryl acetate in hexane or aqueous dioxan, where it was postulated[10] to be an intermediate in the formation of the oxime II. Later work[6] demonstrated that this nitrodiene VI is photochemically transformed to the oxime II in acetone, and we have found that the same conversion takes place in good yield in ethanol. This result affords further support for the role of 6-nitrocholesta-3,5-diene as an intermediate in the conversion of 6-nitrocholesteryl acetate into 3-oximinocholest-4-en-6-one (II).

The formation of the oxime from the nitrodiene is believed to take place via the intermediate nitrite VII. Similar transformations are postulated to occur in both nitroanthracenes and in nitrostyrenes.[3] A possible mechanism leading to the oxime would involve cleavage of the intermediate VII to give the NO radical followed by attack of this radical at $C_{(3)}$ and subsequent rearrangement of the product.

A further product of this irradiation is 3β-acetoxycholest-4-en-6-one (VIIIa), also isolated in low yield (6%) by chromatography on silica gel. Undoubtedly the first step in the formation of this product is the conversion of 6-nitrocholesteryl acetate to the nitrite IXa; cleavage of this intermediate could be expected to result in attack by the NO radical at $C_{(5)}$ but such a transformation was not observed and must therefore be assumed to be unfavourable.[11] The alternative, more favourable process, resulting in the formation of 3β-acetoxycholest-4-en-6-one would appear to involve cleavage of the nitrite IXa accompanied by loss of hydrogen at $C_{(4)}$.

In all irradiations of 6-nitrocholesteryl acetate in ethanol, we were unable to obtain any product arising from double bond migration from $C_{(5)}$ to $C_{(4)}$, although 3β-acetoxy-6-nitrocholest-4-ene (IIIa) was the major product of all previously reported studies in other solvents.

We have also studied the photolysis of 6-nitrocholesteryl acetate in cyclohexane and here, although there was conclusive evidence for the formation of some 3β-acetoxy-6-nitrocholest-4-ene (IIIa), it was not possible to obtain this product in a crystalline form. This product may well be a mixture of the 6α- and 6β-nitro isomers as reported in the photolysis of 6-nitrocholesteryl acetate in acetone.[6]

The major product of the irradiation in cyclohexane is, however, 3β-acetoxycholest-4-en-6-one (VIIIa). This is obtained in 40% yield, and constitutes a useful simple synthesis of VIIIa which is generally obtained from 6-nitrocholesteryl acetate by chemical methods.[12] The much increased yield of this product compared with the

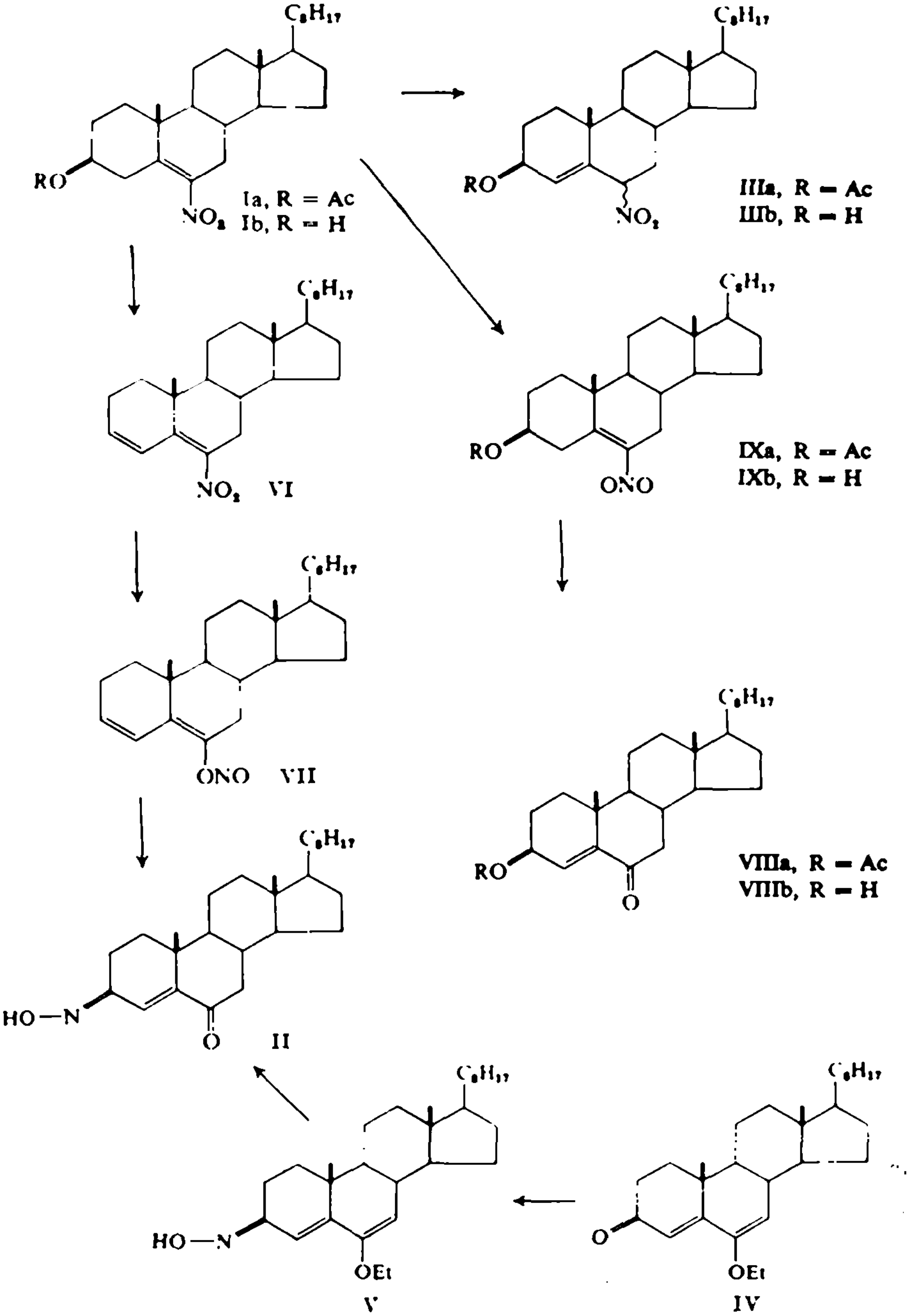
[8] J. Décombe, R. Jacquemain and J. Rabinovitch, *Bull. Soc. Chim. Fr* 447 (1948).

[9] K. Preis and B. Raymann, *Chem. Ber.* 12, 224 (1879).

[10] Personal communication from J. T. Pinhey, University of Sydney, Australia.

[11] A transformation of this type has been reported[8] in the conversion of β-methyl-β-nitrostyrene into 1-phenyl-1-oximinopropan-2-one on irradiation in acetone.

[12] I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.* 801 (1937); I. M. Heilbron, H. Jackson, E. R. H. Jones and F. S. Spring, *Ibid.* 102 (1938).


C8H17
RO
NO2
Ia, R = Ac
Ib, R = H
IIIa, R = Ac
IIIb, R = H
VI
ONO
IXa, R = Ac
IXb, R = H
VII
VIIIa, R = Ac
VIIIb, R = H
O
HO—N
II
OEt
V
IV

yield reported from the irradiation in hexane is most likely a consequence of the use of light of a different wavelength.[13] Δ^4-6-Oxo-steroids are also obtained by photolysis of 3,5α-cyclo-6-oxo-steroids.[14,15]

The influence of the $C_{(3)}$ substituent upon the formation of the oxime II by photolysis of the 6-nitrocholest-5-ene system has also been studied. The oxime II was obtained by photolyses in ethanol of both 3β-chloro-6-nitrocholest-5-ene and of the trifluoroacetate of 6-nitrocholesterol in yields of the same order as that obtained by the irradiation of 6-nitrocholesteryl acetate in ethanol. We believe that the nitrodiene VI is again an intermediate in these transformations.

In contrast to these observations, the oxime II is not formed from 6-nitrocholesterol (Ib) on irradiation in ethanol. The failure of this substance to yield oxime II is thought to be a direct result of the greater difficulty of elimination of the 3β-hydroxyl group as compared with the acetoxyl group. Without prior formation of 6-nitrocholesta-3,5-diene (VI), the formation of oxime II is excluded, and other photochemical processes therefore predominate. In fact, 3β-hydroxycholest-4-en-6-one (VIIIb) is obtained in good yield (37%) from the irradiation of 6-nitrocholesterol in ethanol, and separated by chromatography on neutral alumina. In addition, a crystalline substance is also obtained from the column which on repeated crystallisation affords pure 3β-hydroxy-6β-nitrocholest-4-ene (IIIb), identical with an authentic sample.[16] The nature of the other constituent contaminating this crystalline material was not discovered, but the possibility of it being the 6α-nitro isomer could not be excluded by infra-red evidence.

Consideration of the results presented in this paper suggests that there are three distinct pathways available to the photochemically excited molecule. These are;

(i) Elimination of the 3β-substituent to give the nitrodiene VI, followed by rearrangement of the diene to the oxime II. This process is favoured in ethanol or acetone,[6] and when the $C_{(3)}$ group is easily eliminated.

(ii) Photolysis to the nitrite IX followed by cleavage of the nitrite and rearrangement to the unsaturated ketone VIII. In our studies, this process is the preferred one in the absence of oxime formation.

(iii) Double bond migration to give the corresponding Δ^4-steroid. Rearrangement of this type is known to occur readily in the photolysis of α,β-unsaturated ketones.[17] The possibility that 3β-acetoxy-6-nitrocholest-4-ene (III) might be an intermediate in the formation of the nitrodiene VI and thus the oxime II was investigated; 3β-acetoxy-6β-nitrocholest-4-ene[5] decomposed slowly under the influence of UV light, but no oxime II was obtained.

The extent to which any one of these processes is preferred over the other two appears to depend on the solvent employed in the irradiation, the $C_{(3)}$ substituent, and possibly the wavelength of the radiation employed.

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[13] A quartz photochemical reactor was used in our work, whereas a pyrex filter was employed in the previously reported irradiation in hexane[6] in which a $n \rightarrow \pi^*$ transition is believed to be responsible for the transformations.

[14] C. H. Robinson, O. Gnoj and F. E. Carlon, *Tetrahedron* **21**, 2509 (1965).

[15] R. Beugelmans, *Bull. Soc. Chim. Fr* 3087 (1965).

[16] W. A. Harrison, Sir E. R. H. Jones, G. D. Meakins and P. A. Wilkinson, *J. Chem. Soc.* 3210 (1964); M. Davis, *Ibid.* 2830 (1964).

[17] See, for example, R. Y. Levina, V. N. Kostin and P. A. Gembitskii, *J. Gen. Chem. U.S.S.R.* **29**, 2421 (1959); H. Wehrli, R. Wenger, K. Schaffner and O. Jeger, *Helv. Chim. Acta* **46**, 678 (1963).

EXPERIMENTAL

Irradiation procedure. The irradiations were carried out in soln in a N atmosphere at a concentration of 3 mg/ml or less. A quartz Hanovia photochemical reactor fitted with a medium press Hg arc was employed. Adequate cooling was provided to maintain the soln at room temp. The reaction was followed by IR spectra, and the crude product isolated by the removal of the solvent under reduced press.

Irradiation of 6-nitrocholesteryl acetate (I) *in ethanol*

6-Nitrocholesteryl acetate (2·0 g) in EtOH (600 ml) was irradiated until the IR spectrum of a sample no longer contained a max at 1510 cm^{-1} due to the unsaturated nitro group. The crude product was dissolved in pet. ether from which a white crystalline ppt was deposited. This was recrystallized from EtOH to give 3-oximinocholest-4-en-6-one (0·67 g, 38%) with m.p. 221–222°; λ_{max} 286 mμ (ϵ 1·7 × 10^4); ν_{max} 3580, 3290, 1685, and 1600 cm^{-1}. The IR spectrum was identical to that of an authentic sample of 3-oximinocholest-4-en-6-one; no depression in m.p. was observed on admixture of the two samples. (Found C, 78·1; H, 10·5; N, 3·5. $C_{27}H_{43}NO_2$ requires: C, 78·4; H, 10·5; N, 3·4%.)

The petroleum residues were chromatographed on silica gel. Elution with a 1:1 mixture of pet. ether and benzene gave 6-nitrocholesta-3,5-diene (0·046 g, 2·5%) after recrystallization from EtOH, m.p. 72–73·5° (Lit.,[6] m.p. 72–73°). ν_{max} 1500 and 1625 cm^{-1}. (Found: C, 78·2; H, 10·2. $C_{27}H_{43}NO_2$ requires: C, 78·4; H, 10·5%.) Elution with a 4:1 mixture of benzene and chf gave 3β-acetoxycholest-4-en-6-one (0·130 g, 6·9%) after crystallization from EtOH, m.p. 109°, identical with authentic material (Lit.,[18] m.p. 110°).

3-*Oximinocholest-4-en-6-one* (II)

(a) A soln of 6-ethoxycholesta-4,6-dien-3-one[7] (1·30 g) in EtOH (50 ml) was heated under reflux for 1 hr with hydroxylamine hydrochloride (0·25 g) and AcONa (0·30 g) in water (5 ml). After removal of EtOH at reduced press, water was added and the ppt filtered off, washed, and dried. Without further purification, the 6-ethoxy-3-oximinocholesta-4,6-diene thus obtained was heated under reflux for 5 min in 85% AcOH (10 ml). The crystalline ppt (cooling) was filtered off, washed with water, and recrystallized from EtOH to give 3 oximinocholest-4-en-6-one (0·72 g, 57%), m.p. 221–222°.

(b) Cholest-4-ene-3,6-dione (2·0 g) in EtOH (40 ml) was heated under reflux for 45 min with hydroxylamine hydrochloride (0·36 g) and anhyd AcONa (0·70 g) in water (10 ml). After removal of EtOH at reduced press, water was added and the ppt filtered off, washed with water, and recrystallized from EtOH to give 3-oximinocholest-4-en-6-one (0·90 g, 44%), m.p. 221–222°.

*Cholest-4-ene-*3,6*-dione*

3-Oximinocholest-4-en-6-one (0·15 g) was heated under reflux for 9 hr in glacial AcOH (8 ml) with AcONa (0·06 g) and pyruvic acid (0·25 ml) in water (2 ml). The crystalline ppt (cooling) was filtered off and recrystallized from MeOH to give cholest-4-en-3,6-dione (0·11 g, 79%), m.p. 122–125°. This material was identical with an authentic sample (Lit.,[18] m.p. 124–125°).

6-*Nitrocholesta-*3,5*-diene* (VI)

A soln of 3β-chloro-6-nitrocholest-5-ene[9] (0·300 g) in quinoline (10 ml) was heated under reflux for 15 min, poured into 4N HCl, and the product extracted with chf. The chf extract was washed with dil HCl, water, and then dried. The solvent was removed under reduced press, and the oily residue chromatographed on silica gel. Elution with a 4:1 mixture of benzene and pet. ether gave 6-nitrocholesta-3,5-diene (0·072 g, 27%) which was recrystallized from EtOH, m.p. 72–73°.

*Irradiation of 6-nitrocholesta-*3,5*-diene* (VI) *in ethanol*

6-Nitrocholesta-3,5-diene (0·17 g) was irradiated in EtOH (400 ml) until the IR spectrum no longer contained a max at 1500 cm^{-1} due to the unsaturated nitro group. The crude product was dissolved in pet. ether from which crystalline 3-oximinocholest-4-en-6-one (0·080 g, 47%) separated. After recrystallization from EtOH, the oxime had m.p. 221–222°.

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[18] L. F. Fieser, *J. Amer. Chem. Soc.* 75, 4386 (1953).

Irradiation of 6-nitrocholesteryl acetate (I) *in cyclohexane*

(a) 6-Nitrocholesteryl acetate (1·0 g) in cyclohexane (600 ml) was irradiated for 40 min when there was no evidence in the IR spectrum of any unsaturated nitro group. The product was chromatographed on neutral alumina (grade 4). Crystalline material (0·410 g, 44%) with ν_{max} 1735, 1690, 1635 cm^{-1} was eluted from the column with petroleum and had m.p. 109° after recrystallization from MeOH; this material was identical with authentic 3β-acetoxycholest-4-en-6-one (lit.,[18] m.p. 110°).

Other compounds containing saturated and unsaturated nitro groups (ν_{max} 1550, 1510 cm^{-1}) were shown to be present in the residues.

(b) 6-Nitrocholesteryl acetate (2·3 g) was again irradiated in cyclohexane (950 ml), and the crude product chromatographed on silica gel (45 g). A non-crystalline fraction (0·45 g) was eluted with a 4:1 mixture of benzene and petroleum, and had ν_{max} at 1725, 1640 and 1550 cm^{-1}. This material is believed to be a mixture of the 6α-nitro and 6β-nitro derivatives of 3β-acetoxycholest-5-ene.

3β-Acetoxycholest-4-en-6-one with m.p. 110° from MeOH (0·50 g, 24%) was eluted from this column with chf.

6-Nitrocholesteryl trifluoroacetate (6-nitro-3β-trifluoroacetoxycholest-5-ene)

6-Nitrocholesterol (2·0 g) was dissolved in trifluoroacetic anhydride (10 ml) and the soln heated gently under reflux for 90 min. On addition of this soln to water, a white ppt of 6-nitrocholesteryl trifluoroacetate was obtained (1·72 g, 70%) and recrystallized from EtOH, m.p. 117–118·5°; ν_{max} 1780, 1515, 1155 cm^{-1}. (Found: C, 66·0; H, 8·6. $C_{29}H_{44}F_3NO_4$ requires: C, 66·0; H, 8·4%.)

Irradiation of 6-nitrocholesteryl trifluoroacetate in ethanol

6-Nitrocholesteryl trifluoroacetate (1·0 g) was irradiated in EtOH (400 ml) as described for 6-nitrocholesteryl acetate. 3-Oximinocholest-4-en-6-one (0·31 g, 40%), m.p. 220–222° was obtained by crystallization from pet. ether.

Irradiation of 3β-chloro-6-nitrocholest-5-ene

3β-Chloro-6-nitrocholest-5-ene (0·65 g) was irradiated in EtOH (600 ml) for 45 min, and the oily product chromatographed on silica gel. Elution with a mixture of 3:1 chf and benzene gave 3-oximinocholest-4-en-6-one (0·13 g, 21%) which was recrystallized from EtOH, m.p. 221–222°.

Irradiation of 6-nitrocholesterol (Ib) *in ethanol*

6-Nitrocholesterol (2·0 g) in EtOH (650 ml) was irradiated as described for 6-nitrocholesteryl acetate. The crude product was chromatographed on silica gel (40 g). Crystalline material with ν_{max} 3590, 1545 cm^{-1} in the IR spectrum was eluted from the column with a 1:1 benzene and chf mixture. White needles having m.p. 152–153° were separated by repeated recrystallization using MeOH, and proved to be 6β-nitrocholest-4-en-3β-ol (Lit.,[16] m.p. 151–152°). There was no m.p. depression on admixture with an authentic sample, and the IR spectra of the two samples were identical.

Elution of the silica gel column with 4:1 chf–MeOH gave 3β-hydroxycholest-4-en-6-one (0·47 g, 37%) which had m.p. 151° after recrystallization from MeOH. This was identified by comparison with an authentic sample (lit.,[18] m.p. 151°).