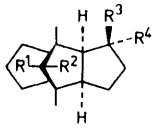
The Mechanism of the Barton Reaction

By **Derek H. R. Barton,* Robert H. Hesse, Maurice M. Pechet,** and **Leslie C. Smith,** Research Institute for Medicine and Chemistry, 49 Amherst Street, Cambridge, Mass. 02142, U.S.A.

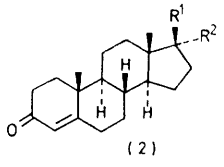
Photolysis of 6β-nitroso-oxy-5α-cholestan-3β-yl acetate gave the 19-oxime, 6β,19-oxide, 6-oxo-5α-cholestan-3β-yl acetate, and 6β-hydroxy-5α-cholestan-3β-yl acetate. The 6β,19-oxide was formed from the C-19 nitroso-dimer by a novel photochemical reaction involving nitric oxide and with subsequent displacement of the presumed 19-diazonium salt by the 6β-hydroxy-function. The formation of ketone was coupled with the appearance of hyponitrous acid. The alcohol was formed by intermolecular hydrogen atom abstraction by the intermediate C-19 alkyl radical in a reaction not related to ketone formation. Evidence for the intermediacy of peroxynitrites in the formation of nitrate esters by nitrite photolysis under oxygen is presented. Hydroperoxides and nitrosyl chloride gave the derived nitrates. Attention is drawn to the formation of androst-4-ene-3,17-dione (59%) from reaction of trifluoroacetic anhydride and 17α-hydroperoxyprogesterone.

THE functionalisation of a steroidal angular methyl group by generation of an alkoxyl radical 2—2.7 Å removed from and in a 1,3-diaxial relationship with that methyl has wide application.[1] An alkoxyl radical, conveniently generated by photolysis of the derived nitrite ester, abstracts in a *quasi*-chair transition state [2] a methyl hydrogen giving the oximino derivative *via* the nitroso-methyl intermediate. That the epimeric nitrites (1a and b) and the respective deuterio-derivatives (1c and d) gave the same oxime (1e) with the same kinetic isotope



(1)

(a) $R^1 = R^3 = R^4 = H$, $R^2 = ONO$
(b) $R^1 = ONO$, $R^2 = R^3 = R^4 = H$
(c) $R^1 = R^4 = H$, $R^2 = ONO$, $R^3 = D$
(d) $R^1 = ONO$, $R^2 = R^4 = H$, $R^3 = D$
(e) $R^1 = H$, $R^2 = OH$, $R^3 R^4 = NOH$

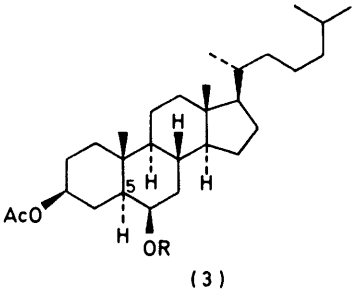


(2)

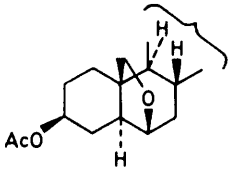
(a) $R^1 = COMe$, $R^2 = ONO$
(b) $R^1 R^2 = O$

effect is a proof that hydrogen abstraction is by the ground-state alkoxyl radical.[3] In the Barton reaction, oxime formation is accompanied by side reactions. α-Cleavage of the alkoxyl radical is a competing reaction but is only important with derivatives of cyclopentanol nitrite (see below) or with the nitrite (2a) which gave on photolysis androst-4-ene-3,17-dione (2b).[4] Alternatively, olefinic alkoxyl radicals may cyclise giving epoxy [5] or tetrahydrofuryl [6] oximes. The second intermediate, the alkyl radical, may undergo α-cleavage [7] or intramolecular addition to olefins.[8] All these side reactions require the presence of unusual structural features. In general, the parent alcohol, its derived ketone, and cyclic ether are the major by-products. Although the alcohol can be recycled, avoidance of all these by-products would improve the reaction and facilitate isolation of products. A more systematic mechanistic study of the Barton reaction here presented seeks to identify the origin of the side products and to suggest methods for their avoidance.

6β-Nitroso-oxy-5α-cholestan-3β-yl acetate (3c) was chosen for study since the only reactive function is the nitroso group and photolysis is known [9] to give the 6β,19-oxide (4), 6-ketone (5a), 6β-alcohol (3a), and oxime

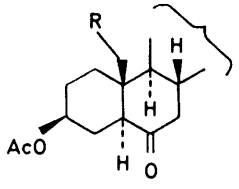


(3)



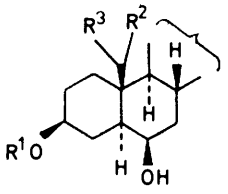
(4)

(a) R = H
(b) R = H, 5α-bromo
(c) R = NO

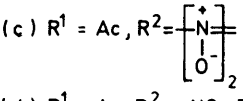


(5)

(a) R = H
(b) R = ONO_2
(c) R = OH



(6)

(a) R^1 = Ac, $R^2 R^3$ = NOH
(b) R^1 = Ac, R^2 = I, R^3 = H
(c) R^1 = Ac, R^2 =  , R^3 = H
(d) R^1 = Ac, R^2 = NO, R^3 = H
(e) R^1 = Ac, R^2 = N_2^+, R^3 = H
(f) R^1 = Ac, R^2 = OH, R^3 = H
(g) $R^1 = R^2$ = H, R^3 = OH
(h) R^1 = Ac, R^2 = ONO_2, R^3 = H
(i) R^1 = Ac, R^2 = OONO, R^3 = H

(6a). Nitrite (3c) was prepared from the bromohydrin (3b) by chromous acetate reduction in the presence of 2-mercaptoethanol [10] and subsequent reaction with nitrosyl chloride and pyridine. Photolysis in toluene

Photolysis of nitrite (3c) in the presence of additives

Nitrite (3c)/mg	Solvent (ml)	Additive	Lamp	Time/min	Isolated products (chromatography or h.p.l.c. [%])
205	PhCl (120)	NO, 1 equiv.	I	120	Oxide (4) [25], oxime (6a) [11]
65	$CHCl_3$ (15)	Pr^i_2NH, 200 μl; NO, large excess	I	110	Oxide (4) [61], ketone (5a) [18]
220	PhCl (200)	None	I	70	Oxime (6a) [33]
201	PhCl (200)	Pyridine, 1 ml	I	70	Oxime (6a) [54]
200	PhCl (250)	1,5-diazabicyclo[4.3.0]non-5-ene, 1 ml	I	80	Ketone (5a) [22], Alcohol (3a) [17]
200	PhCl (250)	1,4-diazabicyclo[2.2.2]octane, 1 ml	I	80	Ketone (5a) [16], Alcohol (3a) [14]
200	PhCl (250)	1,5-diazabicyclo[2.4.0]undec-5-ene, 1 ml	I	80	Ketone (5a) [26], Alcohol (3a) [18]
200	PhCl (250)	2,2,6,6-tetramethylpiperidine, 1 ml	I	80	Ketone (5a) [19], Alcohol (3a) [12]
1.2	CH_2Cl_2 (750)	Bu^tNH_2, 1 ml	I	60	Ketone (5a) [15], Alcohol (3a) [60] (t.l.c.)
120	CH_2Cl_2 (750)	Bu^tNH_2, 1 ml	I	60	Ketone (5a) [14], Alcohol (3a) [40]
200	CH_2Cl_2 (20)	Bu^tNH_2, 200 μl	II	60	Ketone (5a) [15], Alcohol (3a) [10]
950	CH_2Cl_2 (20)	Bu^tNH_2, 200 μl	II	60	Ketone (5a) [17], Alcohol (3a) [11]
110	CH_2Cl_2 (20)	Ph_3P, 1.1 g	II	60	Ketone (5a) [8], Alcohol (3a) [61], Oxime (6a) [17]
350	CH_2Cl_2 (120)	Bu^tNH_2, 1 ml	I	80 (−78 °C)	Ketone (5a) [15], Oxime (6a) [80]
160	CH_2Cl_2 (20)	Bu^tNH_2, 1 ml hydroquinone, 50 mg	II	80	Ketone (5a) [15—20] (t.l.c.)
130	CH_2Cl_2 (20)	Bu^tNH_2, 200 μl; androstanone (7a) 125 mg	II	60	Alcohol (3a) [15], no 3,17-dione (7b) formed
60	CH_2Cl_2 (10)	Bu^tNH_2, 100 μl O_2–Argon 1 : 0.1, 1 : 1, or 0 : 1	II	60	Ketone (5a) [15—20]
80	PhH (10)	Pr^i_2NH, 100 μl	III	300 (0 °C)	No reaction
160	PyMe (20)	Pr^i_2NH or Bu^tNH_2, 200 μl	II	60	Oxime (6a) [65]
160	PhCl (20)		II	60	Oxime (6a) [62]
160	PhH (20)		II	60	Oxime (6a) [60]
160	DMF (20)		II	60	Oxime (6a) [52]
160	$CHCl_3$ (20)		II	60	Oxime (6a) [68]
160	CH_2Cl_2 (20)		II	60	Oxime (6a) [70], Alcohol (3a) [9], Ketone (5a) [15]
160	$CHCl_2CHCl_2$ (20)		II	60	Oxime (6a) [62]
160	$CCl_2{=}CCl_2$ (20)		II	60	Oxime (6a) [66]
160	EtOAc (20)		II	60	Oxime (6a) [64]
270	PhCl (150)	Pyridine 1 ml	I *	80	Oxime (6a) [60]
100	CH_2Cl_2 (15)	bisdimethylaminobenzophenone (60 mg)	II	80	Ketone (5a) [15], Alcohol (3a) [50], Oxime (6a) (t.l.c.)

* External MeOH–CS_2 9 : 1 filter.

gave only ketone (5a), alcohol (3a), and oxime (6a) (see Experimental). The yield of oxime (6a) was dependent on concentration giving highest yields with 0.04M-solutions; this has precedent [11] although it is in contrast to earlier [12] work. At high concentration (0.1M) the oxide (4) was also formed (22%). Photolysis in the presence of an excess of nitric oxide (Experimental section and Table) gave the oxide (4) as the major (61%) product and no oxime (6a). Suppression of oxime (6a) formation by nitric oxide has previously been reported [9] and suggested to result from the scavenging of reforming nitrite by alkoxyl radicals.[13] That iodide (6b) readily formed the oxide (4) [14] suggested formation of the oxide (4) *via* the intermediacy of a C-19 electrophilic intermediate. The oxime (6a) was inert to nitric oxide with or without irradiation. The nitroso dimer (6c) and nitric oxide in the dark slowly gave a complex mixture containing oxide (4). Irradiation, however, cleanly gave the oxide (4) (37%) and oxime (6a) (23%). That the nitroso dimer (6c) only reacted slowly with nitric oxide in the dark but on photolysis alone, rapidly gave the oxime (6a), suggested that the oxide (4) was formed from the nitroso-compound (6d) and nitric oxide. Since nitroso-compounds are known to react with nitric oxide to give diazonium nitrates [15] the oxide (4) was probably formed *via* intermediate (6e) and intramolecular S_{N2} displacement of N_2. Formation of the oxide (4) was eliminated at lower concentration. The photochemical cleavage of nitroso-dimers appears to be a new photochemical reaction.[16]

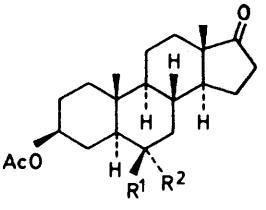
The alcohol (3a) could conceivably arise *via* hydrolysis of the nitrite. Nitrite esters are acid labile and, consistent with this, improved yields of oxime (6a) were obtained on photolysis in the presence of amines (ref. 17 and Table). Since formation of both the ketone (5a) (20%) and the alcohol (3a) (10—20%) were not avoided even in the presence of non-nucleophilic bases {1,5-diazabicyclo[5.4.0]undec-5-ene, etc. (Table)} their formation must involve either the primary photochemical process or radical reactions.

Although exothermic,[18] formation of ketone (5a) and alcohol (3a) by disportionation of alkoxyl radicals is inconceivable at the concentrations employed in the photolysis. Photolysis at very low concentration increased the yield of alcohol (3a); the yield of ketone (5a) was invariant. This is inconsistent with radical disproportionation or a bimolecular reaction between nitrite (3c) and the alkoxyl or alkyl radical. The ketone (5a) and alcohol (3a) must arise by separate pathways.

Formation of the alcohol (3a) could arise by intermolecular abstraction of a hydrogen atom by either the alkoxyl or alkyl radical. That nitrite photolysis in the presence of *S*-deuteriothiophenol gave the *C*-monodeuteriated parent alcohol [14] excluded the former.

Photolysis of nitrite (3c) in the presence of an excess of triphenylphosphine, a scavenger of nitric oxide, gave less oxime (6a) and more alcohol (3a). Photolysis with argon being passed through the solution resulted in little loss of nitrogen to the atmosphere (microanalysis of the crude reaction mixture). Since alkyl nitrites have been used in intermolecular photonitrosation [19] the nitric oxide was presumably partially scavenged by the chlorobenzene solvent. Alternative solvents were examined (Table); dichloromethane gave the highest yield of oxime (6a). In contrast to the work of Suginome [20] and Kabasakalian [12] photolysis in ethanol gave only the alcohol (3a), but good yields of oxime (6a) were obtained in hydrogen atom donors as solvents. No alcohol (3a) was formed on photolysis in the presence of an excess of nitric oxide. Consistent with these results, in the absence of nitric oxide, the alkyl radical must abstract hydrogen presumably from the solvent giving the alcohol (3a). At −78 °C alcohol (3a) formation was suppressed presumably by decreasing the loss of nitric oxide; oxime (6a) (80%) and ketone (5a) (15%) were isolated.

The ketone (5a) was formed even in the presence of an amine and thus could not involve the known [21] nitrosonium ion oxidation of the nitrite (3c). Formation of ketone (5a) was not varied by photolysis in the presence of hydroquinone, oxygen, or the alcohol (7a). In the last experiment no 6,17-dioxo-5α-androstan-3β-yl acetate



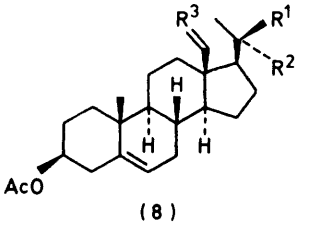
(7)

(a) R^1 = OH, R^2 = H

(b) R^1R^2 = O

(7b) was produced. Clearly, ketone (5a) did not arise by oxidation of the alcohol (3a) formed as a by-product. If ketone (5a) was derived directly from the nitrite (3c), the by-product would be hyponitrous acid. Photolysis without base or in the presence of tetramethylguanidine gave, respectively, hyponitrous acid and its dianion identified by the u.v. spectrum of the dianion [22,23] with a hypsochromic shift at pH 6 giving the unstable monoanion. The amount of bis-tetramethylguanidinium hyponitrite formed was comparable (u.v.) with the yield of ketone (5a). Formation of hyponitrous acid from photolysis of nitrites has previously been demonstrated only in an argon matrix at 20 K [23] and in the gas phase.[24] Since the formation of ketone (5a) was neither dependent upon concentration nor addition of nitric oxide, a ' cage radical ' or a concerted mechanism must be operating. In any case, we consider that ketone formation occurs in the primary photochemical act before transfer of a hydrogen atom.

Functionalisation of the 18-methyl group by a 20-alkoxyl radical is known [25] to be dependent on the configuration at C-20. Consistent with this, the epimeric nitrites (8a and b) gave different yields of both oxime (8f or g) and alcohol (8c or d) but identical yields of ketone (8e). This is good evidence for a concerted [26,27] or a ' cage radical ' photochemical elimination mechanism for formation of the ketone.



(8)

(a) R^1 = ONO, R^2 = H, R^3 = H_2

(b) R^1 = H, R^2 = ONO, R^3 = H_2

(c) R^1 = OH, R^2 = H, R^3 = H_2

(d) R^1 = H, R^2 = OH, R^3 = H_2

(e) R^1R^2 = O, R^3 = H_2

(f) R^1 = OH, R^2 = H, R^3 = NOH

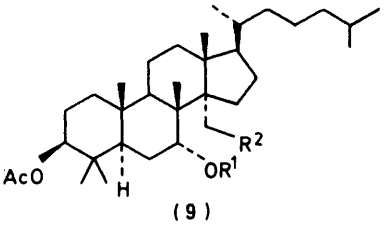
(g) R^1 = H, R^2 = OH, R^3 = NOH

The spin multiplicity of the nitrite ester in the N–O homolysis has not been determined. For convenience the photolysis of cyclopentyl nitrite was investigated. Photolysis gave the known 5-oximinopentanal [28] which was converted into the crystalline 1,5-dioximinopentane.[28] The photolysis was repeated following the disappearance of cyclopentyl nitrite. The reaction proceeded at a comparable rate with or without the triplet sensitisers benzophenone or 4,4'-bisdimethylaminobenzophenone. Addition of nitrobenzene or an external nitrobenzene filter considerably retarded the reaction. Cyclopentyl nitrite was stable to photolysis in the presence of benzophenone and the triplet quencher [29] (3*E*)-penta-1,3-diene. These results clearly demonstrated homolysis *via* the triplet nitrite. 9-Anthraldehyde had, however, too low a triplet energy level (167 kJ mol^{-1}) to sensitise the reaction. Photolysis of the 6β-nitrite (3c) in the presence of 4,4'-bisdimethylaminobenzophenone still gave ketone (5a), discounting a different electronic state in its formation.

Nitrite (3c) was inert to irradiation by a tungsten filament lamp but gave oxime (6a) on filtered (carbon disulphide–methanol >318 nm) irradiation (mercury arc).

Photolysis of steroid nitrite esters in the presence of oxygen gives nitrate esters.[30] For example,[30] the lanostane derivative (9a) afforded the 32-nitrate (9b). The reaction was suggested [30] to proceed *via* capture of the alkyl radical with oxygen and subsequent rapid rearrangement of the derived peroxynitrite. Irradiation of the 6β-nitrite (3c) under oxygen at −78 °C (to increase solubility of oxygen) gave a little oxime (6a), the oxide (4), and a major unstable product. Although this could not be obtained pure, oxidation gave the oxo-

nitrate (5b) which on zinc dust–ammonium acetate [31] reduction gave the 19-alcohol (5c). Zinc dust–ammonium acetate reduction of the unstable photo-product (6h) and subsequent hydrolysis gave the known [9]



(9)

(a) $R^1 = NO$, $R^2 = H$
(b) $R^1 = H$, $R^2 = ONO_2$

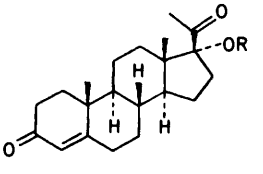
3β,6β,19-triol (6g). The photolysis product was unstable to sodium hydrogen carbonate; addition of this to the crude photolysate gave an increased yield of oxide (4). Clearly, the new photo-product was the nitrate (6h) which readily eliminated nitric acid giving the oxide (4).

Since some alkyl nitroso-compounds are reported [32] to give, on photolysis under oxygen, the derived nitrate photo-oxygenation of the nitroso-dimer (6c) was investigated. Only the oxime (6a) was formed, we consider, by the photochemical reaction to give nitroso-monomer already mentioned above. The intermediate peroxyalkyl radical was not intercepted with triethyl phosphite presumably due to more rapid reaction with nitric oxide.

In support of the intermediacy of alkyl peroxynitrites, an alternative synthesis of these compounds was investigated. Although peroxynitrous acid is known, it rapidly isomerises to nitric acid.[33] Nitrates are known to be formed, but in poor yield, from hydroperoxides and nitric oxide [34] or nitrous acid.[35]

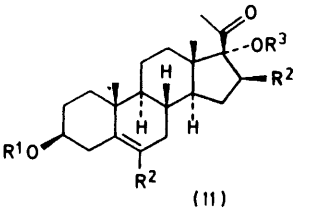
Reaction of t-butyl hydroperoxide with nitrosyl chloride in pyridine at −78 °C gave only the known t-butyl nitrate.[36] The intermediate t-butyl peroxynitrite could not be detected. 17α-Hydroperoxyprogesterone (10a) [37] and nitrosyl chloride in pyridine also gave, in an improved synthesis, the known [38] nitrate (10b). Reaction of the hydroperoxide (10a) with other electrophiles was also investigated. Hydroperoxide (10a) and chlorodiphenylphosphine gave the novel 17α-diphenylphosphonate (10c). This reaction has a precedent with t-butyl hydroperoxide.[39] Formulation as diphenylphosphonate (10c) followed from analysis, spectral data, and its inertness to triethyl phosphite. Acetylation of the 17-hydroperoxide (11a) was reported [40] to give the oxa-D-homo-derivatives (12a and b) whilst the pregnane derivative (11b) gave, in low yield, the alcohol (11c) and the androstane derivative (13a). A more electrophilic 17-peroxy-ester should give a higher yield of the androstane derivative (13). Consistent with this hypothesis, hydroperoxide (10a) and trifluoroacetic anhydride gave the derivative (13b) in 59% yield. Alternatively, reaction of the hydroperoxide (10a) with benzenesulphinyl chloride gave a complex mixture probably containing alcohol (10d) and ketone (13b).

In conclusion, the oxime (4), alcohol (3a), and ketone (5a) by-products in the photolysis of the 6β-nitrite (3c) were derived, respectively, from (i) the nitroso-derivative (6d) by a novel photochemical reaction to give monomer which by reaction with nitric oxide gave the diazonium nitrate (6e) which by S_{N2} displacement by the 6β-hydroxy gave (4), (ii) hydrogen atom abstraction by the intermediate alkyl radical probably from the solvent to give (3a), and (iii) a concerted or possible ' cage radical ' reaction between the alkoxyl radical and nitric oxide (also giving hyponitrous acid) to afford (5a). The intermediacy of peroxynitrite (6i) in the preparation of nitrate (6h) from nitrite (3c) by photolysis under oxygen was supported by formation of nitrate esters from hydroperoxides and nitrosyl chloride.[41]



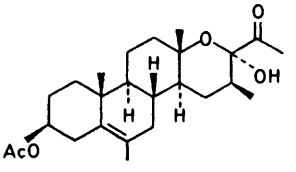
(10)

(a) R = OH
(b) R = NO_2
(c) R = $Ph_2P{=}O$
(d) R = H

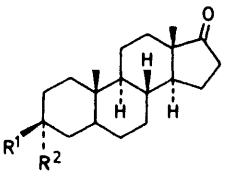


(11)

(a) R^1 = Ac, R^2 = Me, R^3 = OH
(b) $R^1 = R^2$ = H, R^3 = OH
(c) R^1 = Ac, $R^2 = R^3$ = H



(12a)
(12b) α,β-enone



(13)
(a) R^1 = OAc, R^2 = H, 5,6-didehydro
(b) R^1R^2 = O, 4,5-didehydro

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage. Optical rotations and i.r. spectra were recorded in chloroform and n.m.r. spectra in deuteriochloroform. Both preparative (p.l.c.) and analytical (t.l.c.) thin layer chromatography were carried out on GF_{254} silica gel. High pressure liquid chromatography (h.p.l.c.) and g.l.c. were carried out, respectively, on Porisil A using a Water's Associates ALC 201 unit and using a Perkin-Elmer 811 instrument. Unless stated to the contrary, photolyses were carried out at room temperature under argon using (I) a medium pressure lamp (Hanovia Chemical and Manufacturing Co.), (II) a ' black light ' lamp (2 × 4 W, General Electric), or (III) with a 150 W tungsten ' Photoflood ' lamp. Chloroform was purified by filtration through neutral alumina and redistillation from phosphorus pentaoxide under argon. Organic extracts were dried over sodium sulphate.

6β-*Hydroxy*-5α-*cholestan*-3β-*yl Acetate* (3a).—2-Mercaptoethanol (2 ml) and chromous acetate (5 g) in DMSO (50 ml)

were added in sequence to 5α-bromo-6β-hydroxycholestan-3β-yl acetate (3b) (3.8 g) in THF (20 ml) whilst degassing with carbon dioxide. After 3 h, water was added and the precipitate filtered off (15 min later), washed with water, and crystallised from methanol to give the acetate (3a) (2.6 g, 80%), m.p. 148—150° (lit.,[9] 141—142°), $[\alpha]_D$ −6° (*c* 0.8) (lit.,[9] −6°).

Photolysis of the Nitrite (3c).—The nitrite (3c) (900 mg) and pyridine (1 ml) in toluene (200 ml) were photolysed [42] (I) for 3 h at 0 °C. The solution was concentrated and refluxed in propan-2-ol overnight. Evaporation and repeated HPLC (acetonitrile–benzene 3 : 7; ethyl acetate–benzene 1 : 9) gave 3β-acetoxy-5α-cholestan-6-one (5a) [43] (175 mg, 21%), 6β-hydroxy-5α-cholestan-3β-yl acetate (3a) (150 mg, 18%), and 6β-hydroxy-19-oximino-5α-cholestan-3β-yl acetate (6a) [9] (477 mg, 53%), all identical (m.p., $[\alpha]_D$, and spectral data) with authentic materials. Variation in concentration of the nitrite (3c) gave the following yields of oxime (6a): 950 mg, 0.1M, 41%; 470 mg, 0.05M, 58%; 380 mg, 0.04M, 65%; and 95 mg, 0.01M, 52%. Reaction of the 0.1M-solution gave, in addition to oxime (6a), ketone (5a), and alcohol (3a), 3β-acetoxy-6β,19-oxy-5α-cholestane (4) (200 mg, 22%), m.p. 110—111° (from methanol) (lit.,[14] 105—110°), $[\alpha]_D$ +21° (*c* 0.8). Photolysis (I) of nitrite (3c) (700 mg) in chlorobenzene (150 ml) for 2 h gave on evaporation under high vacuum an oil (Found: N, 2.82. 100% Retention of nitrogen required 3.03%).

Reaction of Oxime (6a) *and Nitroso-dimer* (6c) *with Nitric Oxide*.—Nitric oxide was bubbled through the oxime (6a) (50 mg) and t-butylamine (100 μl) in chlorobenzene (10 ml). T.l.c. indicated no reaction in the dark or with irradiation (II) (10 min). Nitrite (3c) (150 mg) and t-butylamine (200 μl) in hexane (20 ml) was photolysed (II) for 15 min. The nitroso-dimer (6c) (54 mg, 36%) was filtered off, m.p. 176—179° (lit.,[9] 180—181°). Nitric oxide was bubbled through a slurry of the nitroso-dimer (6c) (50 mg) and t-butylamine (100 μl) in methanol (15 ml). Although the dark reaction was slow (t.l.c.) irradiation (II) rapidly (<5 min) gave the oxide (4). P.l.c. (ethyl acetate–benzene 1 : 2) gave oxime (6a) (16 mg, 23%) and oxide (4) (19 mg, 37%).

Detection of Hyponitrous Acid in the Photolysis of Nitrite (3c).—Nitrite (3c) (135 mg) and tetramethylguanidine (300 mg) in dichloromethane (20 ml) were photolysed (II) for 30 min. The solution was extracted with aqueous sodium hydroxide (0.1M, 10 ml) and an aliquot (2 ml) diluted with more alkali (0.1M, to 25 ml), to give the hyponitrous acid dianion (17%), $\lambda_{max.}$ 248 nm (absorbance 0.78) [lit.,[22] 248 nm (ε 3 980)]. Adjustment to pH 6 with hydrochloric acid gave a solution of the unstable hyponitrous acid monoanion, $\lambda_{max.}$ 233 nm with a half life of *ca.* 70 min (lit.,[22] 97 min). Although replacing tetramethylguanidine with t-butylamine was unsuccessful, photolysis without base gave hyponitrous acid extractable by alkali (u.v.).

Photolysis of 20β-*nitroso-oxypregn-5-en-3β-yl Acetate* (8a).—Photolysis (II) of nitrite (8a) (140 mg) and t-butylamine (200 μl) in dichloromethane (20 ml) for 90 min gave on evaporation and h.p.l.c. (benzene–ethyl acetate, 7 : 3) ketone (8e) (17 mg, 13%), alcohol (8c) (34 mg, 26%), and oxime (8f) (63 mg, 44%), identical with authentic materials.[44]

Photolysis of 20α-*nitroso-oxypregn-5-en-3β-yl Acetate* (8b).—An identical photolysis of nitrite (8b) [45] (139 mg) gave on evaporation, reflux in propan-2-ol (10 ml) overnight, and h.p.l.c. ketone (8e) (17 mg, 13%), alcohol (8d) (18 mg, 14%), and 20α-*hydroxy*-18-*hydroxyiminopregn-5-en-3β-yl acetate* (8g) (90 mg, 66%), m.p. 206—208° (from methanol), $[\alpha]_D$ −20° (*c* 0.2), $\nu_{max.}$ 3 500m, 3 000s, 1 720s, 1 640m, and 1 250s cm^{-1}, δ 0.9 (3 H, s, 10-Me), 1.15 (3 H, d, *J* 6 Hz, 20-Me), 2.0 (3 H, s, OAc), 3.6—4.2 (1 H, m, 20β-H), 4.2—5.0 (1 H, m, 3α-H), 5.4 (1 H, m, 6-H), and 7.46 (1 H, s, 18-H), *m/e* 389 (M^+) and 311 (100%) (Found: C, 70.8; H, 8.9; N, 3.6. $C_{23}H_{34}NO_4$ requires C, 71.1; H, 8.8; N, 3.6%).

Photolysis of Cyclopentyl Nitrite.—Photolysis (II) of cyclopentyl nitrite [46] and di-isopropylamine (200 μl) in chloroform (20 ml) for 80 min gave a yellow oil, $\nu_{max.}$ 1 730 cm^{-1}, δ 9.8 (s). Hydroxyammonium chloride (71 mg) and the oil in aqueous ethanolic (2.2 : 1) sodium hydroxide (3%; 3.2 ml) were heated to reflux under argon for 30 min. Evaporation of ethanol gave 1,5-dioximinopentane (60 mg, 35%), m.p. 170—171° (lit.,[28] 171°). The photolysis proceeded at a comparable rate in the presence of 4,4′-bis-(dimethylamino)benzophenone (0.2—0.3 equiv.) with or without an internal or an external nitrobenzene (2—4 equiv.) filter or in the presence of benzophenone (1.2 equiv.) (g.l.c., cyclopentyl nitrite retention time 23 s). The reaction was retarded by nitrobenzene (1.9 equiv.) or a benzophenone (2.3 equiv.) filter. Cyclopentyl nitrite was stable to photolysis in the presence of benzophenone (1.1 equiv.) with (3*E*)-penta-1,3-diene (1.8 equiv.) or 9-anthraldehyde (1 equiv.) with a nitrobenzene (4.8 equiv.) filter. Cyclopentanone was not formed (retention time 43 s) nor was hyponitrous acid trapped with tetramethylguanidine.

Photolysis of Nitrite (3c) *under Oxygen*.—Oxygen was bubbled through the nitrite (3c) (225 mg) and triethylamine (1 ml) in chloroform (200 ml) at −78 °C whilst irradiating (I) for 40 min. Evaporation and h.p.l.c. (acetonitrile–benzene 3 : 7; ethyl acetate–benzene 2 : 23) gave the oxide (4) (34 mg, 16%), the unstable nitrate (6h) (72 mg, 32%), m.p. 79—83°, $[\alpha]_D$ +28° (*c* 0.3), $\nu_{max.}$ 3 550w, 1 720s, 1 645s, 1 280s, 1 240s, and 865m cm^{-1}; δ 0.67 (3 H, s, 13-Me), 0.85 (6 H, d, *J* 8 Hz, 25-Me_2), 2.0 (3 H, s, OAc), 3.58—3.9 (1 H, m, 6α-H), 4.88 (2 H, s, 19-H_2), and 4.36—5.17 (1 H, m, 3α-H), and the oxime (6a) (12 mg, 5%). Photolysis (I) of nitrite (3c) (175 mg) and triethylamine (1 ml) in toluene (150 ml) under oxygen at −78 °C for 75 min gave on evaporation an oil. Jones' reagent (2 ml) was added to the oil in acetone (50 ml). After 10 and 30 min, respectively, ethyl acetate (150 ml) and water (200 ml) were added. After filtration through Hi-flo the organic phase was washed with water, saturated aqueous sodium hydrogen carbonate, water, and brine, and dried. Evaporation, p.l.c. (ethyl acetate–benzene 1 : 9) and h.p.l.c. (ethyl acetate–benzene 3 : 17) gave ketone (5a) (100 mg, 58%) and 6-*oxo*-19-*nitro-oxy*-5α-*cholestan*-3β-*yl acetate* (5b) (53 mg, 30%), m.p. 103—107°, $[\alpha]_D$ +32° (*c* 0.5), $\nu_{max.}$ 1 725s, 1 645s, 1 255s, and 850m cm^{-1}, δ 0.66 (3 H, s, 13-Me), 0.85 (6 H, d, *J* 8 Hz, 25-Me_2), 2.0 (3 H, s, OAc), 4.13—5.0 (1 H, m, 3α-H), and 4.45 (2 H, s, 19-H_2), *m/e* 505 (M^+), 459, 399, 370, and 368 (Found: C, 69.2; H, 9.4; N, 2.6. $C_{29}H_{47}NO_6$ requires C, 68.9; H, 9.4; N, 2.8%). Alternatively, reaction of the crude photolysate with sodium hydrogen carbonate (1 g) in methanol (10 ml) overnight gave on work-up an oil. H.p.l.c. (ethyl acetate–benzene 2 : 23) gave the oxide (4) (35%).

6,19-*Dihydroxy*-5α-*cholestan*-3β-*yl Acetate* (6f).—Photolysis (I) of nitrite (3c) (250 mg) and di-isopropylamine (1 ml) in chloroform (200 ml) at −78 °C under oxygen for 75 min and evaporation gave a solid. An excess of zinc dust with ammonium acetate (1 g) was added to the solid in methanol (30 ml) at 0 °C. After 40 min, ethyl acetate (150 ml) was added, the mixture filtered through Hi-flo and the solution washed with water and brine and dried. Evapor-

ation and h.p.l.c. (acetonitrile–benzene 6 : 19) gave the *diol* (6f) (116 mg, 52%), m.p. 179—179.5°, $[\alpha]_D$ +75° (*c* 0.3), $\nu_{max.}$ 3 450s, 3 000s, and 1 720s cm^{-1}, δ 0.72 (3 H, s, 13-Me), 0.85 (6 H, d, *J* 8 Hz, 25-Me_2), 2.02 (3 H, s, OAc), 3.25—4.1 (3 H, m, 6α-H, 19-H_2), and 4.11—5.1 (1 H, m, 3α-H), *m/e* 462 (M^+), 382, 371, and 353 (100%) (Found: C, 75.3; H, 10.9. $C_{29}H_{50}O_4$ requires C, 75.4; H, 10.9%). Oxidation with Jones reagent prior to the zinc–ammonium acetate reduction gave *19-hydroxy-6-oxo-5α-cholestan-3β-yl acetate* (5c) (50 mg, 25%), m.p. 111—116°, $[\alpha]_D$ +28° (*c* 0.3), $\nu_{max.}$ 3 550m, 3 000s, 1 720s, and 1 710s cm^{-1}, δ 0.7 (3 H, s, 13-Me), 0.85 (6 H, d, *J* 8 Hz, 25-Me_2), 2.01 (3 H, s, OAc), 3.46—4.08 (2 H, m, 19-H_2), and 4.25—5.03 (1 H, m, 3α-H), *m/e* 460 (M^+), 370, and 197 (100%) (Found: C, 75.3; H, 10.5. $C_{29}H_{48}O_4$ requires C, 75.6; H, 10.5%).

Hydrolysis of the Acetate (6f).—Hydrolysis of the acetate (6f) with methanol–potassium carbonate at reflux overnight gave on work-up 5α-cholestane-3β,6β,19-triol (6g) (55%), m.p. 228—232° (lit.,[9] 235—237°).

Photolysis of the Nitroso-dimer (6c).—Photolysis (II) of the nitroso-dimer (6c) in (50 mg) in methanol (15 ml) for 5 min gave only oxime (6a).

Reaction of t-Butyl Hydroperoxide with Nitrosyl Chloride.—Nitrosyl chloride was bubbled through t-butyl hydroperoxide (500 mg) and pyridine (1 ml) in dichloromethane (20 ml) at −78 °C until the solution remained permanently brown. After 10 min the solution was washed with water, dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine and dried. Evaporation gave t-butyl nitrate (480 mg, 73%), b.p. 26° at 10 mmHg (lit.,[36] 23° at 5 mmHg), $\nu_{max.}$ 1 645s, 1 375m, 1 300s, and 1 160s cm^{-1}, $\lambda_{max.}$ 272sh nm (ε 21) (lit.,[36] 270sh nm), δ 1.53 (s), *m/e* 119 (M^+) 104, 84, and 57 (100%). The intermediate peroxynitrite was not detected by n.m.r. at −40 °C.

Reaction of 17α-Hydroperoxyprogesterone (10a) *and Nitrosyl Chloride.*—Reaction of hydroperoxide (10a) [37] (190 mg) and nitrosyl chloride in pyridine (25 ml) at −40 °C gave the nitrate (10b) (145 mg, 71%), m.p. 173—174° (lit.,[37] 174—174.5°) (from MeOH–H_2O), $[\alpha]_D$ +59° (*c* 1.0), (lit.,[37] +54°) (Found: C, 65.6; H, 7.9; N, 3.6. Calc. for $C_{21}H_{29}NO_5 \cdot 0.5H_2O$: C, 65.6; H, 7.9; N, 3.6%). Zinc dust–ammonium acetate reduction gave 17α-hydroxyprogesterone (10d), m.p. 197—208° (lit.,[47] 200—208°) (Found: C, 76.1; H, 9.3 Calc. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.2%).

Reaction of 17α-Hydroperoxyprogesterone (10a) *with Other Electrophiles.*—(*a*). Reaction of chlorodiphenylphosphine (200 μl), hydroperoxide (10a) (100 mg), and dry pyridine (10 ml) at 50 °C for 1 h gave, on work-up, *3,20-dioxopregn-4-en-17α-yl diphenylphosphinate* (10c) (100 mg, 66%), m.p. 190—191° (from H_2O–MeOH), $[\alpha]_D$ +90° (*c* 0.9), $\nu_{max.}$ 1 720s, 1 680s, 1 601m, 1 240s, 1 130s, and 945s cm^{-1}, $\lambda_{max.}$ 241 nm (ε 12 900), δ 0.70 (3 H, s, 10-Me), 1.20 (3 H, s, 13-Me), 2.36 (3 H, s, 20-Me), 5.75 (1 H, s, 4-H), and 7.2—8.2 (10 H, m, aryl-H), *m/e* 530 (M^+), 487, and 269 (100%) (Found: C, 74.8; H, 7.4; P, 5.9. $C_{33}H_{39}O_4P$ requires C, 74.7; H, 7.4; P, 5.8%). The product (10c) was inert to triethyl phosphite (14 equiv.) in benzene for 1 h although the hydroperoxide (10a) gave the alcohol (10d) (60%). (*b*). Trifluoroacetic anhydride (210 μl) was added to the hydroperoxide (10a) (200 mg) in pyridine (15 ml) at −5 °C. After 15 min, work-up and h.p.l.c. (ethyl acetate–benzene 3 : 17) gave androst-4-ene-3,17-dione (13b) (59%) identical with authentic material. (*c*). 4-Methylbenzenesulphinyl chloride (200 μl) in dichloromethane (10 ml) was added to hydroperoxide (10a) (110 mg) and pyridine (1 ml) in dichloromethane (10 ml) at 0 °C. After 1 h, work-up and h.p.l.c. (acetonitrile–benzene 17 : 83) gave the dione (13b) (23 mg, 25%) and, possibly, the alcohol (10d) although this was not obtained pure.

We thank Dr. A. G. M. Barrett for his help in the preparation of this manuscript.

[8/891 *Received*, 15*th May*, 1978]

REFERENCES

[1] R. H. Hesse, *Adv. Free Radical Chem.*, 1967, **3**, 83; K. Heusler and J. Kalvoda, *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.
[2] M. Akhtar, *Adv. Photochem.*, 1964, **2**, 263.
[3] A. Nickon, F. J. McGuire, J. R. Mahajan, B. Umezawa, and S. A. Narang, *J. Amer. Chem. Soc.*, 1964, **86**, 1437; A. Nickon, R. Ferguson, A. Bosch, and T. Iwadare, *ibid.*, 1977, **99**, 4518.
[4] A. L. Nussbaum, E. Yuan, C. H. Robinson, A. Mitchell, E. P. Oliveto, J. M. Beaton, and D. H. R. Barton, *J. Org. Chem.*, 1962, **27**, 20.
[5] A. L. Nussbaum, R. Wayne, E. Yuan, O. Zagneetko, and E. P. Oliveto, *J. Amer. Chem. Soc.*, 1962, **84**, 1070; 1965, **87**, 2451.
[6] J. M. Surzur, M. P. Bertrand, and R. Nouguier, *Tetrahedron Letters*, 1969, 4197.
[7] H. Reimann, A. S. Capomaggi, T. Strauss, E. P. Oliveto, and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1963, **83**, 4481.
[8] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, 1961, **83**, 4083.
[9] D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1961, **83**, 4076.
[10] D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1966, **88**, 3016.
[11] R. R. Rieke and N. A. Moore, *J. Org. Chem.*, 1972, **37**, 413.
[12] P. Kabasakalian and E. R. Townley, *J. Amer. Chem. Soc.*, 1962, **84**, 2711.
[13] M. Akhtar and M. M. Pechet, *J. Amer. Chem. Soc.*, 1964, **86**, 265.
[14] M. Akhtar, D. H. R. Barton, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1965, **87**, 4601.
[15] E. Robson and J. M. Tedder, *Proc. Chem. Soc.*, 1963, 344; J. F. Brown, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 2480; C. A. Burkhard and J. F. Brown, jun., *J. Org. Chem.*, 1964, **29**, 2235.
[16] B. G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 1955, 4190.
[17] D. H. R. Barton, N. K. Basu, M. J. Day, R. H. Hesse, M. M. Pechet, and A. N. Starrat, *J.C.S. Perkin I*, 1975, 2243.
[18] P. Gray and A. Williams, *Chem. Rev.*, 1959, **59**, 239.
[19] A. Mackor, Ph.D. Thesis, University of Amsterdam, 1969.
[20] H. Suginome, T. Mizuguchi, S. Honda, and T. Masamune, *J.C.S. Perkin I*, 1977, 927.
[21] D. H. R. Barton and C. P. Forbes, *J.C.S. Perkin I*, 1975, 1614; D. H. R. Barton, G. C. Ramsey, and D. Wege, *J. Chem. Soc.* (*C*), 1967, 1915.
[22] M. N. Hughes, *Quart. Rev.*, 1968, **22**, 1; P. N. Clough, B. A. Thrush, D. A. Ramsay, and J. C. Stamper, *Chem. Phys. Letters*, 1973, **23**, 155; M. N. Hughes and G. Stedman, *J. Chem. Soc.*, 1963, 1239; J. Buchholz and R. E. Powell, *J. Amer. Chem. Soc.*, 1963, **85**, 509.
[23] H. W. Brown and G. C. Pimentel, *J. Chem. Phys.*, 1958, **29**, 883.
[24] C. H. Purkis and H. W. Thompson, *Trans. Faraday Soc.*, 1936, **32**, 1466.
[25] H. Suginome, T. Kojima, K. Orito, and T. Masamune, *Tetrahedron*, 1971, **27**, 291.
[26] *cf.* B. E. Ludwig and G. R. McMillan, *J. Amer. Chem. Soc.*, 1969, **91**, 1085; H. W. Thompson and F. S. Dainton, *Trans. Faraday Soc.*, 1937, **33**, 1546.
[27] P. Gray and M. W. T. Pratt, *J. Chem. Soc.*, 1958, 3403.
[28] P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 1962, **27**, 2918.
[29] G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Amer. Chem. Soc.*, 1964, **86**, 3197.
[30] J. Allen, R. B. Boar, J. F. McGhie, and D. H. R. Barton, *J.C.S. Perkin I*, 1973, 2402, and references there cited.
[31] K. T. W. Alexander, M. Akhtar, R. B. Board, J. F. McGhie, and D. H. R. Barton, *J.C.S. Chem. Comm.*, 1971, 1479; 1972, 383.

[32] Y. L. Chow, T. Hayasaka, and J. N. S. Tam, *Canad. J. Chem.*, 1970, **48**, 508.
[33] M. N. Hughes and H. G. Nicklin, *J. Chem. Soc.* (*A*), 1968, 450.
[34] J. R. Shelton, and R. F. Kojima, *J. Org. Chem.*, 1967, **32**, 2908.
[35] A. Baeyer and V. Villiger, *Chem. Ber.*, 1901, **34**, 755.
[36] A. Michael and G. H. Carlson, *J. Amer. Chem. Soc.*, 1935, **57**, 1268.
[37] E. J. Bailey, D. H. R. Barton, J. Elks, and J. J. Templeton, *J. Chem. Soc.*, 1962, 1578.
[38] G. Snatzke, H. Laurent, and R. Wiechert, *Tetrahedron*, 1969, **25**, 761.
[39] G. Sosnovsky, D. J. Rawlinson, and E. H. Zaret, *Chem. Comm.*, 1966, 453.
[40] J. N. Gardner, F. E. Carlton, and G. Gnoj., *J. Org. Chem.*, 1968, **33**, 1566.
[41] Preliminary communication, D. H. R. Barton, R. H. Hesse, M. M. Pechet, and L. C. Smith, *J.C.S. Chem. Comm.*, 1977, 754.
[42] S. L. Murov, ' Handbook of Photochemistry,' Dekker, New York, 1973.
[43] R. M. Dodson and B. Riegel, *J. Org. Chem.*, 1948, **13**, 424.
[44] J. Hora, *Coll. Czech. Chem. Comm.*, 1967, **32**, 2820.
[45] D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J.C.S. Perkin I*, 1975, 2252.
[46] N. Kornblum and C. Tertelbaum, *J. Amer. Chem. Soc.*, 1952, **74**, 3076.
[47] P. L. Julian, E. W. Meyer, and I. Ryden, *J. Amer. Chem. Soc.*, 1950, **72**, 367.