

then cooled, concentrated, extracted with methylene chloride and washed and the extract was chromatographed as noted previously. Elution with ether afforded 2.51 g. of 4,17(20)-pregnadiene-11 β ,20-diol-21-al-3-one (VI), m.p. 190–205°. Recrystallization from ether-hexane gave 1.066 g. of VI, m.p. 203–208°, and a second crop of 0.770 g., 197–203°, $[\alpha]_D^{25} + 161^\circ$ (dioxane); $\lambda_{\text{max}}^{\text{MeOH}}$ 242 m μ (ϵ 17,000), 285 m μ (ϵ 14,200); $\lambda_{\text{max}}^{\text{Nujol}}$ 2.95 and 3.03 (OH), 5.98 (3- and 21-carbonyl), 6.12 ($\Delta^{4,17(20)}$).

Anal. Calcd. for $\text{C}_{21}\text{H}_{32}\text{O}_4$: C, 73.22; H, 8.19. Found: C, 73.77; H, 8.34.

On one occasion the reaction mixture from the action of acetic acid on IV was acetylated with acetic anhydride in pyridine solution and the steroidal mixture was isolated in the conventional way. From chromatography of the mixture over Florisil there was obtained, in addition to VIII, a small yield of 4-androstene-11 β -ol-3,17-dione, which was identified by comparison of infrared spectrum with that from an authentic sample.

VI into VIII.—A solution of 0.500 g. of VI in 5.0 ml. of pyridine and 5.0 ml. of acetic anhydride was stored overnight at room temperature. The reaction mixture then was treated with ice and water and the precipitate which formed was separated by filtration. There resulted 0.50 g. of solid, m.p. 230–237°. Recrystallization from acetone-hexane afforded 0.360 g. of 4,17(20)-pregnadiene-11 β ,20-diol-21-al-3-one 20-acetate (VIII), m.p. 234–239° dec. The m.p. could be raised to 243–247° by repeated crystallization; $[\alpha]_D^{25} + 127.6^\circ$ (dioxane); $\lambda_{\text{max}}^{\text{MeOH}}$ 245 m μ (ϵ 28,600); $\lambda_{\text{max}}^{\text{Nujol}}$ 2.96 (OH), 5.68 (acetate carbonyl), 5.96, 6.06 (3- and 21-carbonyl), 6.12 and 6.18 ($\Delta^{4,17(20)}$), 8.28 μ (C–O–C of acetate).

Anal. Calcd. for $\text{C}_{23}\text{H}_{30}\text{O}_6$: C, 71.48; H, 7.82. Found: C, 71.13; H, 7.82.

Corticosterone from VI.—To a solution of 1.0 g. of VI in 25.0 ml. of acetic acid was added 25.0 ml. of water and 10.0 g. of granular zinc. The reaction mixture was agitated for 4 hours at 30–35°. The zinc was removed by filtration and washed with 50% aqueous acetic acid. The combined filtrates were concentrated partially in an air draft and excess water was then added. Extraction of the aqueous with methylene chloride, washing, drying and concentration of the extracts afforded a residue which was crystallized from acetone-hexane. There was isolated thereby 0.642 g. of corticosterone (XIV), m.p. 171–182°, and 0.105 g. of a second crop, m.p. 153–172°. The infrared spectra of both fractions were identical with that of corticosterone and both fractions were homogeneous as measured by paper chromatography in toluene-propylene glycol.

VIII into IX.—To a solution of 0.325 g. of VIII in 15.0 ml. of acetic acid was added 15.0 ml. of water and 3.0 g. of

zinc granules. The reaction mixture was agitated at 30–35° for 4 hours and the steroidal products were isolated as in the preceding experiment. The crude steroid mixture was dissolved in hexane containing a small amount of methylene chloride and chromatographed over 7 g. of Florisil. Recrystallization of solids collected in the 50% ether-hexane fractions afforded 0.113 g. of 4,17(20)-pregnadiene-11 β ,20-diol-3-one 20-acetate (IX), m.p. 155–157°, $[\alpha]_D^{25} + 124^\circ$ (dioxane); $\lambda_{\text{max}}^{\text{MeOH}}$ 242 m μ (ϵ 16,200); $\lambda_{\text{max}}^{\text{Nujol}}$ 2.98 (OH), 5.74 (enolic acetate carbonyl), 6.10 (3-carbonyl), 6.22 (Δ^4), 8.20 μ (C–O–C of acetate).

Anal. Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_4$: C, 74.16; H, 8.66. Found: C, 74.47; H, 8.73.

IX into X.—A solution of 0.090 g. of IX in 5.0 ml. of methanol and 1.0 ml. of 5% methanolic potassium hydroxide was stored at 27° for 1.5 hours. Thereupon the reaction mixture was made acid and diluted with water. Extraction of the aqueous with methylene chloride, and the usual washing and drying of the extracts, afforded, on concentration, a crystalline residue, which after recrystallization from acetone-hexane gave 0.068 g. of 11 β -hydroxyprogesterone (X), m.p. 184–187°, $[\alpha]_D^{25} + 200^\circ$ (dioxane); $\lambda_{\text{max}}^{\text{Nujol}}$ 2.95 (OH), 5.88 (20-carbonyl), 6.05 (3-carbonyl), 6.18 μ (Δ^4). Magerlein and Levin¹³ report m.p. 186–188°, $[\alpha]_D^{25} + 212^\circ$ (acetone).

X into XI.—To a solution of 0.050 g. of X in 2 ml. of acetic acid was added 0.011 g. of chromic acid in 0.5 ml. of water. After 3 hours storage at room temperature, the mixture was treated with excess water and then extracted with ether. The ethereal extracts were washed, dried, concentrated and crystallization was induced by the addition of hexane. There precipitated 0.035 g. of 11-ketoprogesterone (XI), m.p. 175–176°, $[\alpha]_D^{25} + 263^\circ$ (CHCl_3). An authentic sample of XI prepared from 11 α -hydroxyprogesterone (Upjohn) by chromic acid oxidation had m.p. 175–176°, $[\alpha]_D^{25} + 258^\circ$ (CHCl_3), did not depress the melting point of XI on admixture and had the identical infrared spectrum. Peterson and co-workers¹⁴ give m.p. 172–175°, $[\alpha]_D^{25} + 227^\circ$ (CHCl_3). Fried and co-workers¹⁵ give m.p. 170–172°, $[\alpha]_D^{25} + 276^\circ$ (CHCl_3). Mancera and co-workers¹⁶ give m.p. 170–172°, $[\alpha]_D^{25} + 238^\circ$ (CHCl_3). The reason for the lack of agreement among the rotations reported is not apparent. Our results have been carefully checked and we believe them to be reliable.

(13) B. J. Magerlein and R. Levin, *J. Am. Chem. Soc.*, **75**, 3654 (1953).

(14) D. H. Peterson, *et al.*, *ibid.*, **74**, 5936 (1952).

(15) J. Fried, *et al.*, *ibid.*, **74**, 3962 (1952).

(16) O. Mancera, *et al.*, *J. Org. Chem.*, **17**, 1066 (1952).

[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

A New Photochemical Reaction¹

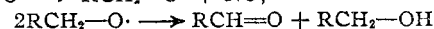
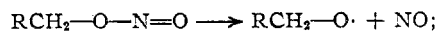
BY D. H. R. BARTON, J. M. BEATON, L. E. GELLER AND M. M. PECHET

RECEIVED MAY 4, 1961

The photolysis of suitably constituted organic nitrites provokes an intramolecular exchange of the NO of the nitrite residue with a hydrogen atom attached to a carbon atom in the γ -position. The C-nitroso compounds thus formed can be isolated as the corresponding nitroso-dimers or, after isomerization, as the oximes. Adequate structural proof has been provided for several examples of the reaction. The mechanism of the process has been discussed and an interpretation of all the relevant facts presented.

The pyrolysis of organic nitrites is a reaction the mechanism of which has been thoroughly studied.² The primary step is the homolytic

fission of the —O—(N=O) bond followed by disproportionation (or alternative fission) of the alkoxy radicals thus derived.^{2,3} For example,



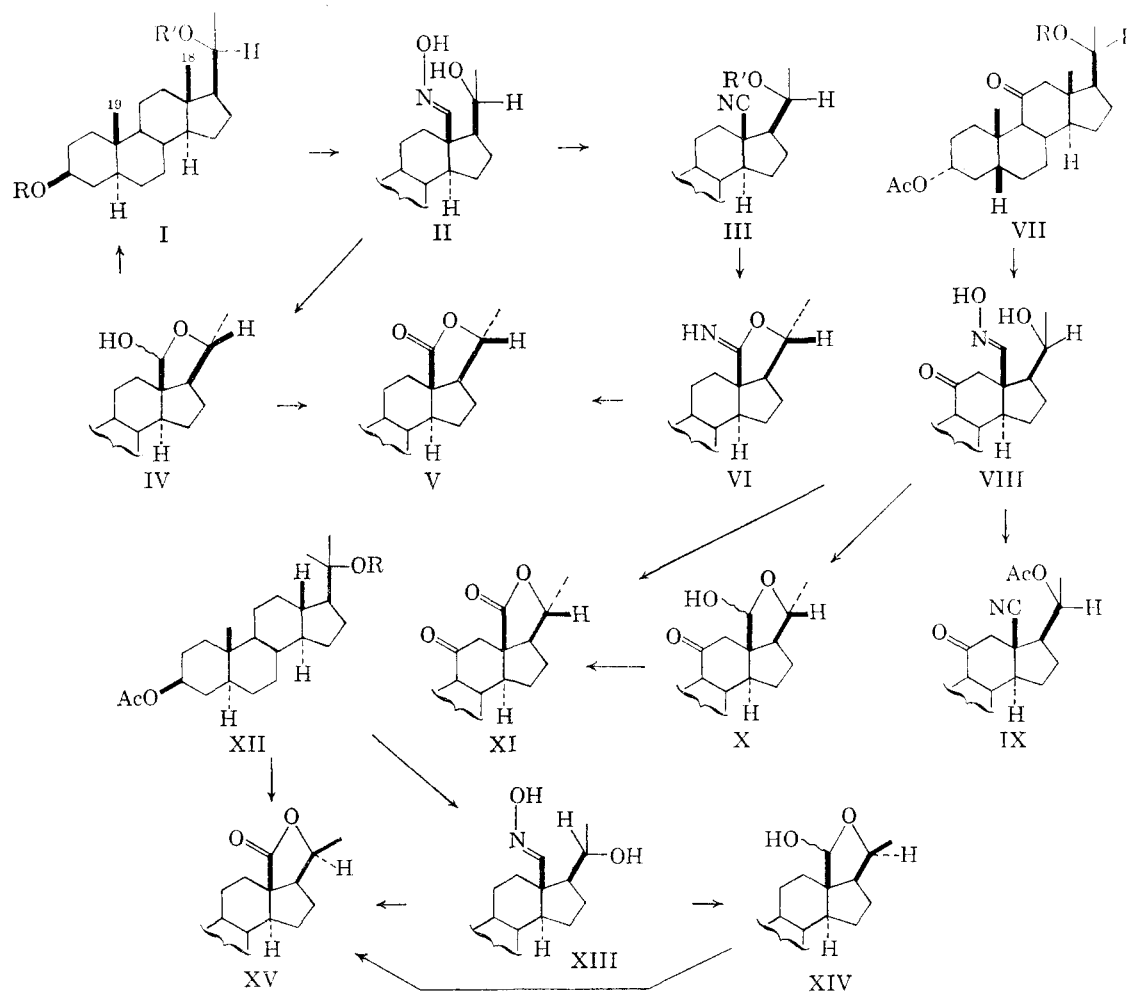
Although the corresponding photolysis of organic nitrites has not received the same attention,⁴

(3) F. O. Rice and E. L. Radowskas, *J. Am. Chem. Soc.*, **56**, 214 (1935).

(4) C. H. Purkis and H. W. Thompson, *Trans. Faraday Soc.*, **32**,

(1) This paper is Communication No. 11 from the Research Institute for Medicine and Chemistry. For a preliminary report see D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960).

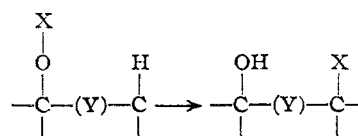
(2) E. W. R. Steacie and G. T. Shaw, *J. Chem. Phys.*, **2**, 345 (1934), and many later papers by E. W. R. Steacie. See E. W. R. Steacie, "Atomic and Free Radical Reactions," Vol. I, Reinhold Publ. Corp., New York, N. Y., 2nd Ed., 1954, p. 239; see also P. Gray, P. Rathbone and A. H. Williams, *J. Chem. Soc.*, 3932 (1960).



nevertheless the general consensus⁵ is that the photolytic and pyrolytic pathways are identical and lead to identical products. When nitroso-dimers (or their equivalent derived oximes) have been detected⁶ in earlier photolysis studies they have undoubtedly originated from fission of alkoxyl radicals into carbonyl compound and carbon radical followed by combination of the latter with NO.

Interest in this Institute in the general problem of preparing 18- and 19-substituted steroids by partial synthesis from compounds lacking substituents at these positions led one of us (D.H.R.B.) to the view that the photolysis of nitrites might furnish excited alkoxyl radicals with sufficient energy in excess of that found in thermally generated radicals to permit intramolecular hydrogen transfer according to the scheme below ($X = NO$; $Y =$ chain of atoms) with subsequent capture of NO by the carbon radical thereby generated. Of course X might, in principle, be halogen, NO_2 , OR or other substituent with ultraviolet absorption characteristics such as to permit homolytic

fission on photochemical activation. However, in the event, nitrites provide the most convenient method of effecting this transfer reaction as well



as affording functional groups ideally suited for aldosterone synthesis.⁷

The following examples are illustrative of our new reaction. 3β -Acetoxy- 5α -pregnan- 20β -ol (I, $R = Ac$, $R' = H$) was converted by treatment with nitrosyl chloride in pyridine⁸ into the corresponding nitrite I ($R = Ac$, $R' = NO$). Photolysis in dry benzene using a mercury arc lamp gave in 34% yield an isomeric oxime shown to be II ($R = Ac$) by the reactions outlined in the sequel. Mild alkaline hydrolysis gave the corresponding diol II ($R = H$). Treatment with pyridine-acetic anhydride and then with sodium acetate-acetic anhydride afforded the nitrilodiacetate III ($R = R' = Ac$). Similarly treatment of II ($R = Ac$) with pyridine-acetic anhydride and then with

(7) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, following paper.

(8) R. H. Pickard and H. Hunter, *J. Chem. Soc.*, 434 (1923); N. Kornblum and E. P. Oliveto, *J. Am. Chem. Soc.*, 71, 226 (1949).

1466 (1936); H. W. Thompson and F. S. Dainton, *ibid.*, 33, 1546 (1937); C. S. Coe and T. F. Doumani, *J. Am. Chem. Soc.*, 70, 1516 (1948); J. A. Gray and D. W. G. Style, *Trans. Faraday Soc.*, 48, 1137 (1952); P. Tarte, *Bull. soc. roy. sci. Liège*, 22, 226 (1953).

(5) P. Gray and A. Williams, *Chem. Revs.*, 59, 239 (1959).

(6) For example: B. G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 4190 (1955); 1670 (1956).

ethanolic potassium hydroxide furnished the corresponding diol III ($R = R' = H$). These experiments show that either the C_{18} - or the C_{19} -methyl group has been attacked. A distinction between the two possibilities was reached as follows. The oxime II ($R = Ac$), treated with acetone containing aqueous hydrochloric acid, gave the hemi-acetal IV ($R = Ac$), which on oxidation with pyridine-chromium trioxide gave the corresponding γ -lactone V ($R = Ac$).⁹ The formation of a γ -lactone is, of course, only possible if it is the C_{18} -methyl group which has been attacked in the photochemical reaction. The same γ -lactone V ($R = Ac$) was also obtained by an alternative route. The nitrile-diol III ($R = R' = H$), on brief treatment with ethanolic hydrochloric acid, gave the imino-lactone VI ($R = H$). More prolonged reaction with 2 *N* aqueous hydrochloric acid on the steam-bath then afforded the hydroxy-lactone V ($R = H$) which on acetylation gave the above described γ -lactone V ($R = Ac$). Oxidation of the lactone V ($R = H$) with chromic acid gave the corresponding keto-lactone. As a final proof that the photochemical reaction had not caused a rearrangement of the carbon skeleton, the masked aldehyde IV ($R = Ac$) was shown to give an almost quantitative yield of the diol I ($R = R' = H$) on Wolff-Kishner reduction.

In a similar series of experiments 3 α -acetoxy-11-oxopregnan-20 β -ol VII ($R = H$) was converted to the nitrite VII ($R = NO$) and photolyzed to give the isomeric oxime VIII in 18% yield. Acetylation-dehydration furnished the nitrile diacetate IX, whilst acid-catalyzed hydrolysis afforded the hemi-acetal X oxidized to the corresponding γ -lactone, also obtainable by direct chromic acid oxidation of the oxime VIII ($R = Ac$).

In a recent communication it was disclosed¹⁰ that the photolysis of a 20 α -nitrite gives a much higher yield of the corresponding 18-oxime than does a 20 β -nitrite. We have also studied the photolysis of a 20 α -nitrite, although uncertainty about the purity of our starting material prevents a statement of the true yield in the reaction. Reduction of 3 β -acetoxy-5 α -pregnan-20-one with sodium borohydride and separation of the 3 β -acetoxy-20 β -ol thereby formed as major product left a residue enriched in the 20 α -ol XII ($R = H$). This was converted to nitrite XII ($R = NO$) and photolyzed. Chromatography of the product furnished the desired 18-oxime XIII which with nitrous acid¹¹ gave the corresponding hemi-acetal XIV. Oxidation of the latter with chromic acid afforded the γ -lactone XV isomeric with that (V, $R = Ac$) described above.¹² The γ -lactone

was also available by direct chromic acid-acetone oxidation of the oxime XIII.

We expected to find that the intramolecular rearrangement of nitrites would be facilitated by placing the nitrite grouping and the C-H bond to be attacked in 1:3-diaxial relationship. An example in the cholestane series confirmed this. 3 β -Acetoxycholestan-6 β -ol (XVII, $R = H$) was smoothly nitrosated to the derivative XVII ($R = NO$) which on photolysis in toluene solution gave a 67% yield of the nitroso-dimer XVIII (dimeric formula), identified by its characteristic ultraviolet absorption.¹³ We believe that the formation of a nitroso-dimer or oxime in the photochemical reaction is delicately balanced by the equilibrium position between monomer and dimer, the relative solubility of nitroso-dimer, as well as by the presence of adventitious traces of hydroxylic materials which catalyze the isomerization of nitroso-monomer to oxime. Since the latter is a thermal reaction it is facilitated by increase of temperature which has, of course, little effect upon the photochemical reaction proper. It is always possible to reflux the product of the photochemical reaction with (say) isopropyl alcohol which converts any nitrosomonomer, derived from thermal dissociation of dimer, to oxime. The course of the reaction can be followed by color change since the nitroso-monomer is the only colored species present. In the particular case here under comment the dimer XVIII (dimeric formula) was smoothly converted to oxime XIX, ($R = Ac$, $R' = R'' = H$) by refluxing isopropyl alcohol. Treatment of this oxime (XIX, $R = Ac$, $R' = R'' = H$) with sodium acetate-acetic anhydride gave the nitrile-diacetate XXII, thus showing that a methyl group had been attacked. With nitrous acid the above-mentioned oxime afforded the hemi-acetal XXI ($R = Ac$), characterized by hydrolysis to the corresponding alcohol XXI ($R = H$) and by oxidation to the γ -lactone XX. These facts prove that it is the C_{19} -methyl group which is involved in the reaction. That no rearrangement of the carbon skeleton was occurring was shown by Wolff-Kishner reduction of XXI ($R = Ac$) which afforded the diol corresponding to XVII.

On treatment with acid the oxime XIX ($R = Ac$, $R' = R'' = H$) was hydrolyzed and dehydrated to the interesting acetal XXIII in which ring A must have assumed a boat conformation. In another reaction lithium aluminum hydride reduction of the acetate XXI ($R = Ac$) afforded the triol XXIV. Treatment of the oxime XIX ($R = Ac$, $R' = R'' = H$) with methanesulfonyl chloride in pyridine and further processing furnished the unsaturated nitrile XXV ($R = Ac$), characterized by hydrolysis to the alcohol XXV ($R = H$). In order to avoid nitrile formation the protection of the oximino group by O-methylation was investigated. With ethereal diazomethane the oxime gave, after chromatography, four new products. The most easily eluted was the dimethylated compound XIX ($R = Ac$, $R' = R'' = Me$).

Arigoni and Jeger (*Helv. Chim. Acta*, **43**, 347 (1960)). The two sets of physical constants are in good agreement.

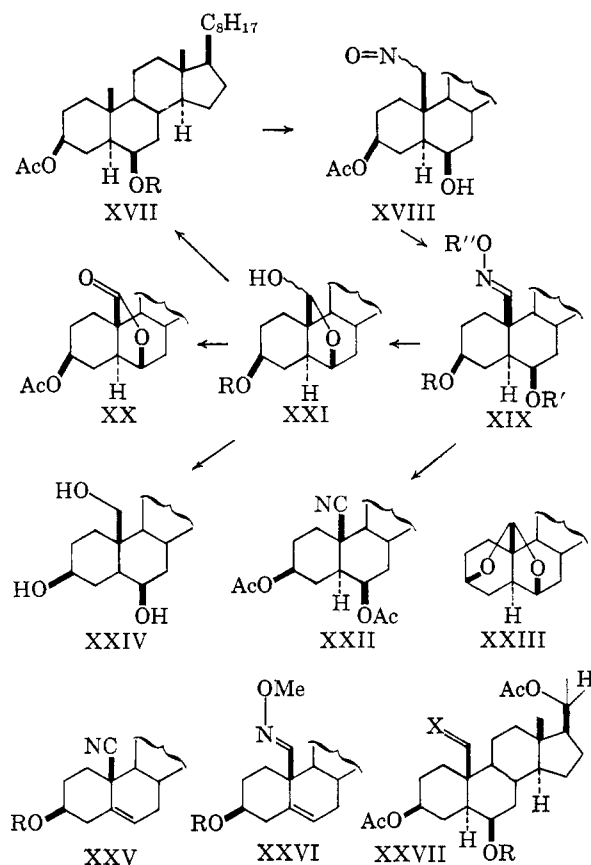
(13) See H. T. J. Chilton and B. G. Gowenlock, *J. Chem. Soc.*, 3232 (1953); L. Batt, B. G. Gowenlock and J. Trotman, *ibid.*, 2222 (1960).

(9) This lactone has also been prepared by Labler and Šorm (*Coll. Czech. Chem. Comm.*, **25**, 2855 (1960)) from degradation of the alkaloid holarrhimine. An exchange of specimens has confirmed the identity of the two materials.

(10) A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian and D. H. R. Barton, *J. Am. Chem. Soc.*, **82**, 2973 (1960).

(11) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958); see also H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershsberg, *J. Am. Chem. Soc.*, **77**, 4781 (1955).

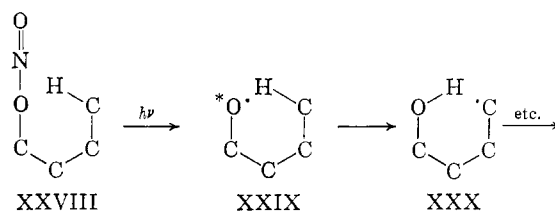
(12) The lactone XV has also been prepared by Kamber, Cainelli,



Next came the singly methylated compound XIX ($R = \text{Ac}$, $R' = \text{H}$, $R'' = \text{Me}$), then the corresponding diol XIX ($R = R' = \text{H}$, $R'' = \text{Me}$), and finally the non-methylated product XIX ($R = R' = R'' = \text{H}$). Treatment of the monomethylated compound XIX ($R = \text{Ac}$, $R' = \text{H}$, $R'' = \text{Me}$) with methanesulfonyl chloride and tertiary base then gave the olefin XXVI ($R = \text{Ac}$), characterized by hydrolysis to the alcohol XXVI ($R = \text{H}$).

In a similar series of experiments $3\beta,20\beta$ -diacetoxy- 5α -pregnan- 6β -ol (XXVII, $R = \text{H}$, $X = \text{H}_2$), prepared by a standard series of reactions from $3\beta,20\beta$ -diacetoxy- 5α -pregn- 5 -ene, was converted to the nitrite XXVII ($R = \text{NO}$, $X = \text{H}_2$) and photolyzed. After refluxing the product with isopropyl alcohol, chromatography over Florisil gave the desired 19-oxime diacetate XXVII ($R = \text{H}$, $X = \text{N-OH}$).

A brief study has been made of some of the variables controlling the yield of the oxime II ($R = \text{Ac}$) resulting from photolysis of the nitrite II ($R = \text{Ac}$, $R' = \text{NO}$). All experiments given in the table were conducted under oxygen-free nitrogen at 10–20° (water cooling). A typical procedure is given in detail in the Experimental section. Benzene and toluene were both good solvents for the reaction. Carbon disulfide was not satisfactory. The solvent $\text{CF}_2\text{Cl}-\text{CCl}_2\text{F}$ was satisfactory for the formation of oxime (II, $R = \text{Ac}$) only if the initial reaction product was heated in isopropyl alcohol. The addition of NO gas in controlled amounts reduced the yield appreciably.



In principle, the intramolecular exchange of NO and H resulting from the photolysis reaction could also be brought about by pyrolysis (see above). However, in fact, pyrolysis of either I ($R = \text{Ac}$, $R' = \text{NO}$) or XVII ($R = \text{NO}$) gave none of the oxime or nitroso-dimer normally obtained by photolysis. In the case of XVII ($R = \text{NO}$) a special nitrogen determination was run on the pyrolysate which indicated no detectable residual nitrogen.

The facts described in this and the following paper can be interpreted in terms of the simple mechanism for the photolysis now outlined. Absorption of light by nitrite ester XXVIII affords an activated alkoxy radical XXIX and NO. The activated radical abstracts hydrogen to furnish a carbon radical (XXX) which is then captured by NO in the normal way. The whole process is conceived to take place within a solvent "cage" because solvent does not readily participate in the reaction even when it is a good radical reactant like

TABLE I

Solvent ^a	Quantity (g.) of nitrite I ($R = \text{Ac}$, $R' = \text{NO}$)	Subsequent treatment	Yield, %, of oxime II ($R = \text{Ac}$)
Benzene	10.0	None	34.2
Toluene	10.0	None	35.5
Carbon disulfide	2.0	$\Delta + \text{Me}_2\text{CHOH}$	12.1
$\text{CF}_2\text{Cl}-\text{CCl}_2\text{F}$	2.0	None	9.9
$\text{CF}_2\text{Cl}-\text{CCl}_2\text{F}$	2.0	$\Delta + \text{Me}_2\text{CHOH}$	35.9
Toluene	2.0 ^b	$\Delta + \text{Me}_2\text{CHOH}$	3.0
Toluene	2.0 ^c	$\Delta + \text{toluene}$	17.9

^a All experiments conducted in 200 ml. of solvent.

^b Addition of 2 mol. of NO. ^c Addition of $1/2$ mol. of NO.

toluene. We have made an additional experiment which underlines this point. The yield of nitroso-dimer in the photolysis of XVII ($R = \text{NO}$) in benzene solution is not influenced by addition of 5% of cumene. Clearly long-lived alkoxy or carbon radicals are not involved and the process certainly is not a chain reaction.

Now, an extensive survey of the photolysis of aliphatic and aralkyl nitrites^{14,15} has shown that the exchange process of XXVIII \rightarrow XXIX \rightarrow XXX only occurs if a six-membered transition state be involved as illustrated in XXIX \rightarrow XXX. Such discrimination would be consistent with a mechanism for the exchange in which there was a continuous switch of bond character from nitrite ester to final C-nitroso-compound without development of radical character. In the limit the "cage"

(14) Experiments by Dr. P. Kabasakian and his colleagues of the Schering Corp., Bloomfield, N. J., now in the course of publication. We thank Dr. Kabasakian for his kindness in informing us of his results in advance of publication.

(15) See A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, in press (1961). We thank Drs. Nussbaum and Robinson for a copy of their manuscript.

radical mechanism and the "continuous switch" mechanism merge. However, a number of cases are now known¹⁵ where the carbon radical XXX first formed in the reaction undergoes an alternative process to capture by NO. We shall discuss one example in the following paper. We feel therefore that the original conception of the reaction in terms of the mechanism XXVIII \rightarrow XXIX \rightarrow XXX etc. receives good support.

Acknowledgment.—It is a pleasure to acknowledge skillful technical assistance provided by Mrs. M. A. Golub, Misses L. T. Gendron, R. A. Holland, M. A. Kennedy and Mr. P. C. Ludwig. We also thank Dr. M. Akhtar for his helpful contributions to certain aspects of the work described in this paper.

Experimental

Melting points were determined on a hot-stage. Infrared spectra were measured in the media indicated by means of a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were determined in methanol using a Cary model 11 recording spectrophotometer. All rotations were determined in CHCl₃ except where noted.

3 β -Acetoxy-5 α -pregnan-20 β -yl Nitrite (I, R = Ac, R' = NO). (A).—A solution of 5 α -pregnane-3 β ,20 β -diol 3-acetate (I, R = Ac, R' = H; 1.40 g.) in dry pyridine (20 ml.) was kept in a cooling bath at -20 to -30° and stirred continuously while nitrosyl chloride (0.28 g., 1.1 mol.) was allowed to distill into the reaction flask. The red or yellow color of the nitrosyl chloride was rapidly discharged until near the end of the addition, when it persisted. Immediately thereafter water was added, the crystalline precipitate was filtered off and washed with water, then crystallized from methylene chloride-hexane, or from methanol, to give the nitrite I (R = Ac, R' = NO) as almost colorless blades or needles (1.42 g., 94%), m.p. 162 – 164.5° , $[\alpha]_D^{25} -16^\circ$, -18° (c 1.1, 1.0); $\nu_{\text{C-Cl}}^{\text{max}}$ 1745 and 1240 (acetate), 1650 and 1610 (nitrite) cm^{-1} ; λ_{max} 2290, 3370, 3470, 3580, 3700 and 3830 Å. (ϵ 1870, 27, 40, 54, 57 and 39, resp.).

Anal. Calcd. for C₂₇H₄₇O₄N: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.71; H, 9.53; N, 3.81.

(B).—It was later found that accurate measurement of nitrosyl chloride was unnecessary in this preparation. A solution of 5 α -pregnane-3 β ,20 β -diol 3-acetate (I, R = Ac, R' = H; 5.2 g.) in dry pyridine (50 ml.) at -20° was treated with nitrosyl chloride until a yellow color persisted in the solution. Isolation of the product as described in (A) gave a first crop (4.9 g., 87%) of the same nitrite.

Photolysis of 3 β -Acetoxy-5 α -pregnan-20 β -yl Nitrite (I, R = Ac, R' = NO) in Benzene.—The apparatus consisted of a Pyrex vessel with a gas inlet tube at the bottom, a water-cooled Vycor immersion well and a 200 watt Hanovia high pressure mercury arc lamp with a Pyrex filter sleeve. While a slow stream of pure dry nitrogen was passed into the vessel, a solution of 3 β -acetoxy-5 α -pregnan-20 β -yl nitrite (I, R = Ac, R' = NO; 10.00 g.) in dry benzene (200 ml.) was irradiated at $ca.$ 10° for 2.5 hr. during which time the characteristic nitrite bands disappeared from the infrared spectra of aliquots of the solution. After standing overnight, the orange or brown reaction solution was chromatographed on Florisil (300 g.). Methylene chloride containing small, increasing amounts of methanol eluted two main products. Several of the less polar fractions (2.47 g.) were crystallized with difficulty from methylene chloride-hexane to yield 5 α -pregnane-3 β ,20 β -diol 3-acetate (I, R = Ac, R' = H; 0.27 g.) as needles, m.p. 169 – 172° , identical in the infrared with an authentic specimen. A second, more polar, group of fractions (5.09 g.) crystallized from acetone-hexane to give 18-oximino-5 α -pregnane-3 β ,20 β -diol 3-acetate (II, R = Ac; 3.42 g.; 34.2%) as needles, m.p. 192 – 195° , $[\alpha]_D^{25} +19$, $+21^\circ$ (c 0.7, 0.7); $\nu_{\text{C=O}}^{\text{max}}$ 3700, 3400 and 3150 (hydroxyl), 1745 and 1240 (acetate) and (in KBr) 1635 (oxime) cm^{-1} , ϵ at 208 μ 2700.

Anal. Calcd. for C₂₇H₄₇O₄N: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.55; H, 9.44; N, 3.48.

18-Oximino-5 α -pregnane-3 β ,20 β -diol (II, R = H).—A solution of 18-oximino-5 α -pregnane-3 β ,20 β -diol 3-acetate

(II, R = Ac; 245 mg.) in 0.5 *N* methanolic sodium hydroxide (25 ml.) was refluxed for 5 min., then concentrated under reduced pressure. The needles obtained by the addition of water were recrystallized from acetone-hexane to give 18-oximino-5 α -pregnane-3 β ,20 β -diol (II, R = H) as needles (210 mg.), m.p. 231 – 234° , $[\alpha]_D^{25} +16$, $+14^\circ$ (c 1.1, 1.0 in dioxane); $\nu_{\text{max}}^{\text{KBr}}$ 3600 and 3300 (hydroxyl) and 1640 cm^{-1} (weak oxime), ϵ at 208 μ 3000.

Anal. Calcd. for C₂₇H₄₇O₃N: C, 72.16; H, 10.09; N, 4.01. Found: C, 71.87; H, 10.21; N, 4.18.

3 β ,20 β -Diacetoxy-5 α -pregnane-18-nitrile (III, R = R' = Ac).—A solution of 18-oximino-5 α -pregnane-3 β ,20 β -diol 3-acetate (II, R = Ac; 195 mg.) in pyridine (10 ml.) and acetic anhydride (5 ml.) was heated on the steam-bath for 15 min. Removal of solvent under reduced pressure gave a gum, the infrared spectrum of which showed bands at 1785, 1740 and 1630 cm^{-1} suggestive of the triacetate. Further treatment of the product with acetic anhydride (5 ml.) and sodium acetate (50 mg.) at reflux temperature for 30 min. followed by chromatography of the crude product on Florisil (6 g.) yielded fractions which crystallized from hexane to give 3 β ,20 β -diacetoxy-5 α -pregnane-18-nitrile (III, R = R' = Ac) as needles (66 mg.), m.p. 131 – 132° , $[\alpha]_D^{25} +5^\circ$ (c 1.0); $\nu_{\text{max}}^{\text{KBr}}$ 2250 (nitrile), 1740 and 1250 (acetate) cm^{-1} , no high intensity ultraviolet absorption above 210 μ .

Anal. Calcd. for C₂₈H₄₇O₄N: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.29; H, 9.09; N, 3.55.

3 β ,20 β -Dihydroxy-5 α -pregnane-18-nitrile (III, R = R' = H).—A solution of 18-oximino-5 α -pregnane-3 β ,20 β -diol 3-acetate (III, R = Ac, R' = H; 1.00 g.) in pyridine (10 ml.) and acetic anhydride (10 ml.) was heated on the steam-bath for 30 min. The solvent was evaporated under reduced pressure and the gum thus obtained (presumably the triacetate) was dissolved in 0.5 *N* ethanolic potassium ethoxide (50 ml.) and refluxed for 15 min. After concentration to $ca.$ 10 ml., the solution was diluted with water. The needles which separated were recrystallized from methylene chloride-hexane to give 3 β ,20 β -dihydroxy-5 α -pregnane-18-nitrile (III, R = R' = H) as needles or plates (0.73 g., 86%), m.p. 229.5 – 231.5° , $[\alpha]_D^{25} -2^\circ$ (c 1.0), $+2^\circ$ (c 1.0 in acetone), $\nu_{\text{max}}^{\text{CHCl}_3}$ 3700 (hydroxyl) and 2250 (nitrile) cm^{-1} , no absorption in the ultraviolet above 200 μ .

Anal. Calcd. for C₂₇H₄₇O₃N: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.87; H, 10.01; N, 4.29.

The nitrile diol III (R = R' = H) was recovered unchanged after 30 min. from a refluxing solution of diethylene glycol (25 ml.) containing potassium hydroxide (0.6 g.).

Treatment of the nitrile diol III (R = R' = H) with pyridine and acetic anhydride on the steam-bath for 15 min. gave the nitrile diacetate III (R = R' = Ac), m.p. 131 – 132° , $[\alpha]_D^{25} +6^\circ$ (c 1.0), identical in the infrared with the specimen described above.

18-Oxo-5 α -pregnane-3 β ,20 β -diol 3-Acetate 18,20-Hemiacetal (IV, R = Ac).—A solution of 18-oximino-5 α -pregnane-3 β ,20 β -diol 3-acetate (II, R = Ac; 500 mg.) in acetone (25 ml.) containing water (5 ml.) and concentrated hydrochloric acid (0.5 ml.) was kept at room temperature for 18 hr. Water was gradually added until crystallization was complete. The product was recrystallized from methylene chloride-hexane to give 18-oxo-5 α -pregnane-3 β ,20 β -diol 3-acetate 18,20-hemiacetal (IV, R = Ac) as needles (373 mg., 78%), m.p. 174 – 176° . Recrystallization from methylene chloride-methanol yielded needles, m.p. 171 – 179° , $[\alpha]_D^{25} +17$, $+18^\circ$ (c 1.1, 1.0); $\nu_{\text{max}}^{\text{COI}}$ 3700 and 3450 (hydroxyl), 1740 and 1240 (acetate) cm^{-1} ; no absorption in the ultraviolet above 200 μ .

Anal. Calcd. for C₂₇H₄₇O₄: C, 73.36; H, 9.64. Found: C, 73.18; H, 9.53.

Wolff-Kishner Reduction of the Hemiacetal (IV, R = Ac).—A mixture of 18-oxo-5 α -pregnane-3 β ,20 β -diol 3-acetate 18,20-hemiacetal (IV, R = Ac; 48 mg.), diethylene glycol (25 ml.), hydrazine hydrate (100%, 5 ml.) and potassium hydroxide (2.5 g.) was refluxed for 15 min., then slowly distilled so that the temperature of the solution rose from 140 to 210° during 40 min. After refluxing for an additional 40 min. at 210° , the solution was cooled, poured into water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried (Na₂SO₄) and evaporated. The solid residue was crystallized from acetone-hexane to give 5 α -pregnane-3 β ,20 β -

diol (I, R = R' = H) as needles (38 mg., 93%), m.p. 197–198°, $[\alpha]_D^{20} + 2^\circ$ (c 1.1), identical in the infrared and having the same m.p. when admixed with an authentic specimen.

Rearrangement of the Nitrile Diol (III, R = R' = H) to the Iminolactone (VI, R = H).—A solution of the nitrile diol III (R = R' = H; 500 mg.) in ethanol (40 ml.) and concentrated hydrochloric acid (10 ml.) was refluxed for 15 min. After concentration under reduced pressure, water and methylene chloride were added. The aqueous layer was made alkaline with sodium bicarbonate and the precipitated solid was isolated by extraction with methylene chloride. Crystallization from acetone–hexane yielded the iminolactone VI (R = H) as prisms (447 mg., 89%), m.p. 171–174°, $[\alpha]_D^{20} + 3^\circ$ (c 1.0), $\nu_{\text{max}}^{\text{CHCl}_3}$ 3700 (hydroxyl) and 1670 (C=N) cm^{-1} .

Anal. Calcd. for $\text{C}_{21}\text{H}_{33}\text{O}_5\text{N}$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.92; H, 10.01; N, 4.10.

Occasionally the iminolactone separated from acetone–hexane as needles, m.p. 145–148°, but the high melting form could be regenerated by recrystallization and suitable seeding. A mixture of the two forms had m.p. 171–174°.

3 β ,20 β -Dihydroxy-5 α -pregnan-18-oic 18,20-Lactone (V, R = H).—A solution of the iminolactone (VI, R = H, 205 mg.) in 2 N hydrochloric acid (50 ml.) was heated on the steam-bath for 24 hr. The cooled mixture was filtered and the needles (180 mg.) crystallized from ethyl acetate to give 3 β ,20 β -dihydroxy-5 α -pregnan-18-oic 18,20-lactone (V, R = H) as prisms (45 mg.), m.p. 217–218°, $[\alpha]_D^{20} + 12, +11^\circ$ (c 1.0, 1.1 in acetone), $\nu_{\text{max}}^{\text{CHCl}_3}$ 3700 (hydroxyl) and 1750 (lactone carbonyl) cm^{-1} .

Anal. Calcd. for $\text{C}_{21}\text{H}_{32}\text{O}_7$: C, 75.86; H, 9.70. Found: C, 75.99; H, 9.78.

3 β -Acetoxy-20 β -hydroxy-5 α -pregnan-18-oic 18,20-Lactone (V, R = Ac). (A).—A solution of 3 β ,20 β -dihydroxy-5 α -pregnan-18-oic 18,20-lactone (V, R = H; 35 mg.) in pyridine (1 ml.) and acetic anhydride (1 ml.) was heated for 15 min. on the steam-bath. The acetate (V, R = Ac), isolated in the usual manner, crystallized from acetone–hexane as prisms (19 mg.), m.p. 207–209°, $[\alpha]_D^{20} - 9^\circ, -10^\circ$ (c 1.0, 1.5); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1765 (lactone), 1745 and 1240 (acetate) cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{34}\text{O}_7$: C, 73.76; H, 9.15. Found: C, 73.53; H, 8.83.

(B).—A solution of the hemiacetal (IV, R = Ac; 50 mg.) in pyridine (2 ml.) was added to the chromium trioxide–pyridine complex [prepared from chromium trioxide (200 mg.) and pyridine (2 ml.)] and the mixture allowed to stand at room temperature for 18 hr. The product, isolated by extraction with benzene, crystallized from acetone–hexane as prisms (37 mg.), m.p. 208–209°, $\nu_{\text{max}}^{\text{CHCl}_3}$ 1760 (lactone), 1740 and 1240 (acetate) cm^{-1} . The identity of the two specimens of the lactone acetate V (R = Ac) obtained from A and B was proved by the infrared spectra and mixture m.p.

3 α -Acetoxy-11-oxo-5 β -pregnan-20 β -yl Nitrite (VII, R = NO).—A solution of 3 α -acetoxy-11-oxo-5 β -pregnan-20 α -ol (VII, R = H; 1.0 g.) in dry pyridine (100 ml.) was treated at room temperature with nitrosyl chloride until a brown color showed that excess had been added. Addition of water gave a crystalline solid which was recrystallized from aqueous methanol containing a trace of pyridine and then from methylene chloride–hexane to give the nitrite VII (R = NO) as blades, m.p. 140–141°, $[\alpha]_D^{20} + 42^\circ$ (c 1.0); $\lambda_{\text{max}}^{\text{MeOH}}$ 225, 337, 347, 359, 371 and 384 $\text{m}\mu$ (ϵ 1890, 28, 41, 55, 57 and 38, resp.); $\nu_{\text{max}}^{\text{KBr}}$ 1740, 1700, 1640, 1605, 1260 and 780 cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{35}\text{O}_6\text{N}$: C, 68.12; H, 8.70; O, 19.73; N, 3.45. Found: C, 68.35; H, 8.68; O, 19.98; N, 3.50.

Photolysis to give 18-Oximino-3 α -acetoxy-11-oxo-5 β -pregnan-20 β -ol (VIII).—A solution of 3 α -acetoxy-11-oxo-5 β -pregnan-20 β -yl nitrite (VII, R = NO; 4.81 g.) in benzene (200 ml.) was irradiated in a Pyrex vessel under nitrogen using a 200-watt Hanovia high pressure mercury arc lamp at ca. 20° for 2.5 hr. Chromatography on Florisil (115 g.) and elution with methylene chloride containing increasing amounts of methanol gave two distinct crystalline products. The less polar solid (crude weight 1.36 g.) was recrystallized from acetone–hexane to give 3 α -acetoxy-11-oxo-5 β -pregnan-20 β -ol (VII, R = H) as needles, m.p. 198–200°, identical in the infrared with an authentic specimen. The more

polar solid (crude weight 2.16 g.) was recrystallized from methylene chloride–hexane to give 18-oximino-3 α -acetoxy-11-oxo-5 β -pregnan-20 β -ol (VIII) as fine needles (0.86 g.), m.p. 120–129°, $[\alpha]_D^{20} + 70^\circ$ (c 1.2), end absorption (ϵ at 207 $\text{m}\mu$ 2900); $\nu_{\text{max}}^{\text{KBr}}$ 3400, 1740, 1700 and 1240 cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{35}\text{O}_6\text{N}$: C, 68.12; H, 8.70; N, 3.45. Found: C, 68.34; H, 8.83; N, 3.24.

3 α -Acetoxy-20 β -hydroxy-11-oxo-5 β -pregnan-18-oic 18,20-Lactone (XI). (A).—A solution of the 18-oxime VIII (1.23 g.) in acetone (148 ml.) was treated at room temperature with 8 N chromic acid (3 ml.). At the end of the addition, a yellow-brown color persisted in the solution. Addition of methanol and excess water, followed by extraction with methylene chloride and chromatography on alumina gave the 18,20-lactone XI as prisms (0.43 g.), m.p. 242–243°, $[\alpha]_D^{20} + 136^\circ$ (c 1.0), no significant ultraviolet absorption above 210 $\text{m}\mu$; $\nu_{\text{max}}^{\text{KBr}}$ 1760, 1740, 1710 and 1250 cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_8$: C, 71.10; H, 8.30; O, 20.59. Found: C, 71.10; H, 8.03; O, 20.58.

(B).—Treatment of the 18-oxime VIII with hydrochloric acid in aqueous acetone or with sodium nitrite in aqueous acetic acid gave a non-crystalline hemiacetal (X) which on subsequent oxidation in acetone with 8 N chromic acid gave the lactone XI (27%), m.p. 240–241°, identical in the infrared with the specimen described above.

18-Nitrilo-3 α ,20 β -diacetoxy-5 β -pregnan-11-one (IX).—A mixture of the 18-oxime VIII (203 mg.), potassium acetate (200 mg.) and acetic anhydride (50 ml.) was refluxed for 1 hr. and then evaporated to dryness under reduced pressure. The crude product was chromatographed on Florisil and the least polar solids recrystallized from methylene chloride–hexane to give the 18-nitrile IX as plates, m.p. 194.5–195.5°, $[\alpha]_D^{20} + 63^\circ$ (c 1.0); $\nu_{\text{max}}^{\text{KBr}}$ 2240, 1740, 1710 and 1250 cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_5\text{N}$: C, 69.90; H, 8.21; O, 18.62; N, 3.26. Found: C, 69.86; H, 8.30; O, 18.39; N, 3.48.

18-Oximino-5 α -pregnane-3 β ,20 α -diol 3-Acetate (XIII).—Reduction of 3 β -acetoxy-5 α -pregnan-20-one with sodium borohydride in aqueous methanol gave the corresponding 20 β -alcohol as the major product. Chromatography of the mother liquors and fractional crystallization gave needles, m.p. 145–147°, believed to be mainly 5 α -pregnane-3 β ,20 α -diol 3-acetate. It was not possible to prepare a pure specimen of the 20 α -alcohol in this manner. Nitrosation of the impure 20 α -alcohol gave a crystalline product which was separated by fractional crystallization from methanol into the 20 β -nitrite previously prepared and a more soluble crystalline nitrite, m.p. 110–132°, $[\alpha]_D^{20} + 4^\circ$ (c 1.2 in CHCl_3), believed to be fairly pure 3 β -acetoxy-5 α -pregnan-20 α -yl nitrite. This material was photolyzed as follows.

A solution of this nitrite (1.50 g.) in 1,1,2-trichloro-1,2,2-trifluoroethane (200 ml.) was irradiated at 20° for 1.25 hr. by means of a 200-watt Hanovia lamp in a Pyrex vessel. After refluxing in isopropyl alcohol for 15 min., the product was chromatographed on alumina. The most polar component of the mixture was crystallized from ethyl acetate to give 18-oximino-5 α -pregnane-3 β ,20 α -diol 3-acetate (XIII) as prisms (230 mg.), m.p. 196–198.5°, $[\alpha]_D^{20} + 16^\circ$ (c 1.2); $\nu_{\text{max}}^{\text{KBr}}$ 3459(s), 1745(s), 1635(w) and 1250(s) cm^{-1} . A mixture of the 18-oximino-20 α -alcohol (m.p. 198–199.5°) with 18-oximino-5 α -pregnane-3 β ,20 β -diol 3-acetate (II, R = Ac) (m.p. 194–195°) had m.p. 173–185°.

Anal. Calcd. for $\text{C}_{23}\text{H}_{37}\text{O}_6\text{N}$: C, 70.55; H, 9.53; O, 16.34; N, 3.58. Found: C, 70.55; H, 9.43; O, 16.59; N, 3.76.

18-Oxo-5 α -pregnane-3 β ,20 α -diol 3-Acetate (XIV).—A solution of the 18-oximino-20 α -alcohol XIII (190 mg.) in acetic acid (20 ml.) was treated with 5% aqueous sodium nitrite (10 ml.) and kept at room temperature for 5 min. The product was isolated by addition of water and recrystallized from methylene chloride–hexane to give 18-oxo-5 α -pregnane-3 β ,20 α -diol 3-acetate (XIV) as prismatic needles (130 mg.), m.p. 164–179°, $[\alpha]_D^{20} - 2^\circ$ (c 1.0); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3700, 3500, 1730, 1250 cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{36}\text{O}_6$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.04; H, 9.44; O, 16.95.

3 β -Acetoxy-20 α -hydroxy-5 α -pregnan-18-oic 18,20-Lactone (XV).—A solution of the hemiacetal (45 mg.) in acetone (10 ml.) was treated with excess of 8 N chromic acid at

room temperature for 2 min., then with methanol and water. The crystalline precipitate was recrystallized from methylene chloride-hexane to give the 18,20-lactone (XV) as blades (38 mg.), m.p. 198–199°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1755, 1730 and 1260 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{44}\text{O}_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 73.94; H, 9.01; O, 16.98.

The same lactone, m.p. 198–202°, $[\alpha]_D -12^\circ$ (c 0.8), was obtained directly from the 18-oximino-20 α -alcohol by chromic acid-acetone oxidation.

Kamber, Cainelli, Arigoni and Jeger¹² gave m.p. 196–197°, $[\alpha]_D -14^\circ$; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1760, 1725 and 1250 cm^{-1} for this compound.

3 β -Acetoxycholestan-6 β -yl Nitrite (XVII, R = NO).—A solution of 3 β -acetoxycholestan-6 β -ol (7.85 g.) in dry pyridine (80 ml.) was treated with gaseous nitrosyl chloride at -20° until the color was a permanent orange-brown. Addition of water and filtration gave 3 β -acetoxycholestan-6 β -yl nitrite (XVII, R = NO). Recrystallized from methanol-methylene dichloride this (7.08 g.) had m.p. 152–153°, $[\alpha]_D -31^\circ$ (c 0.56); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1745, 1660 and 1625 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{O}_4\text{N}$: C, 73.21; H, 10.38; O, 13.45; N, 2.94. Found: C, 73.23; H, 10.36; O, 13.01; N, 2.74.

Photolysis of 3 β -Acetoxycholestan-6 β -yl Nitrite (XVII, R = NO).—The nitrite (7.08 g.) in toluene (200 ml.) was irradiated at room temperature as described above. After 45 minutes the nitroso-dimer was filtered off and washed well with toluene. The dimer (4.7 g.) had m.p. 180–181°, $\nu_{\text{max}}^{\text{KBr}}$ 3550 and 1740 cm^{-1} , λ_{max} 293 μ (in MeOH; only slightly soluble). The dimer (4.7 g.) was refluxed in isopropyl alcohol-tetrahydrofuran for 20 min. (disappearance of green color). Treatment with charcoal and removal of the solvent *in vacuo* gave 3 β -acetoxy-19-oximinocholestan-6 β -ol (XIX, R = Ac, R' = R'' = H). Recrystallized from acetonitrile this (4.3 g.) had m.p. 180–181°, $[\alpha]_D -17^\circ$ (c 0.71); $\nu_{\text{max}}^{\text{KBr}}$ 3300, 3200, 1740, 1660 and 1242 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{O}_4\text{N}$: C, 73.21; H, 10.38; N, 2.94. Found: C, 73.27; H, 10.41; N, 3.01.

Chromatography of the photolysis mother liquors over Florisil afforded 3 β -acetoxycholestan-6-one and 3 β -acetoxycholestan-6 β -ol in a 5:1 ratio.

Pyrolysis of 3 β -Acetoxycholestan-6 β -yl Nitrite (XVII, R = NO).—The nitrite (1.0 g.) was heated at 160° under nitrogen until gas evolution was complete (1 min.) and then for a further 10 min. Chromatography of the product over Florisil gave only 3 β -acetoxycholestan-6-one and 3 β -acetoxy-6 β -hydroxycholestan-6-one.

In a separate experiment the nitrite (1.0 g.) was heated *in vacuo* at 160° as above. The whole residual product was submitted to a Kjeldahl nitrogen determination. No nitrogen was found.

3 β -Acetoxy-6 β -hydroxy-19-oxo-cholestan-6,19-Hemiacetal (XXI, R = Ac).—19-Oximino-3 β -acetoxycholestan-6 β -ol (XIX, R = Ac, R' = R'' = H; 500 mg.) in glacial acetic acid (20 ml.) was treated dropwise at room temperature with aqueous sodium nitrite (5%, 5 ml.). Dilution with water gave a product which was chromatographed over Florisil. First eluted was a substance (80 mg.) which on crystallization from ethyl acetate had m.p. 136–138°, $[\alpha]_D -38^\circ$ (c 0.74) and was not investigated further. The more polar fractions, recrystallized from methanol, gave 3 β -acetoxy-6 β -hydroxy-19-oxocholestan-6,19-hemiacetal (XXI, R = Ac; 400 mg.), m.p. 142–143°, $[\alpha]_D +30^\circ$ (c 0.96); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3450, 1748 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{O}_4$: C, 75.60; H, 10.50. Found: C, 75.64; H, 10.48.

This hemi-acetal (250 mg.) in diethylene glycol (15 ml.) and hydrazine hydrate (85%, 0.2 ml.) was refluxed for 1 hour. The condenser was removed, the temperature allowed to rise to 180°, and the refluxing continued for 3 hours more. Crystallization of the product from methanol gave 3 β ,6 β -dihydroxycholestan-6-one in nearly quantitative yield.

The acetoxy-hemi-acetal (XXI, R = Ac; 100 mg.) in ethanolic potassium hydroxide (5%, 5 ml.) was heated under reflux for 20 min. Crystallization of the product from aqueous methanol gave 3 β ,6 β -dihydroxy-19-oxocholestan-6,19-hemiacetal (XXI, R = H), m.p. 178–180°, $[\alpha]_D +4^\circ$ (c 0.94); $\nu_{\text{max}}^{\text{KBr}}$ 3400 cm^{-1} .

Anal. Calcd. for $\text{C}_{27}\text{H}_{46}\text{O}_3$: C, 77.84; H, 10.89. Found: C, 77.67; H, 10.84.

3 β -Acetoxy-6 β -hydroxycholestan-19-ol-6,19-Lactone (XX).—3 β -Acetoxy-6 β -hydroxy-19-oxocholestan-6,19-hemiacetal (XXI, R = Ac; 100 mg.) in acetone (5 ml.) was treated dropwise at room temperature with chromium trioxide reagent (0.1 ml.). Water was added and the lactone XX filtered off (98 mg.). Recrystallized from methanol this (87 mg.) had m.p. 180–181°, $[\alpha]_D +2^\circ$ (c 0.97); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1775 and 1725 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{O}_4$: C, 75.93; H, 10.10. Found: C, 75.96; H, 9.93.

3 β ,6 β ,19-Trihydroxycholestan-6,19-Hemiacetal (XXI).—3 β -Acetoxy-6 β -hydroxy-19-oxocholestan-6,19-hemiacetal (XXI, 1.2 g.) was stirred with a large excess of lithium aluminum hydride in ether at room temperature for 1 hour. Crystallization of the product from methanol gave 3 β ,6 β ,19-trihydroxycholestan-6,19-hemiacetal (XXI, 1.0 g.), m.p. 235–237°, $[\alpha]_D +18^\circ$ (c 0.475 in dioxane); $\nu_{\text{max}}^{\text{KBr}}$ 3500 and 3300 cm^{-1} .

Anal. Calcd. for $\text{C}_{27}\text{H}_{46}\text{O}_3$: C, 77.09; H, 11.50; O, 11.41. Found: C, 76.86; H, 11.35; O, 11.41.

3 β ,19-6 β ,19-Diepoxycholestan-6,19-Hemiacetal (XXII).—19-Oximino-3 β -acetoxy-6 β -hydroxycholestan-6,19-hemiacetal (XXI, R = Ac, R' = R'' = H; 500 mg.) in acetone (20 ml.), water (4 ml.) and concd. hydrochloric acid (2 ml.) was refluxed for 2.5 hours. The product, crystallized from methanol, gave 3 β ,19-6 β ,19-diepoxycholestan-6,19-hemiacetal (XXII, 310 mg.), m.p. 146–147°, $[\alpha]_D +50^\circ$ (c 0.70 in methanol), no infrared bands indicative of hydroxyl or carbonyl groups.

Anal. Calcd. for $\text{C}_{27}\text{H}_{44}\text{O}_2$: C, 81.22; H, 11.07. Found: C, 81.09; H, 11.23.

3 β ,6 β -Diacetoxy-19-nitrilocholestan-6,19-Hemiacetal (XXII).—3 β -Acetoxy-19-oximinocholestan-6 β -ol (XIX, R = Ac, R' = R'' = H; 1.5 g.) in acetic anhydride (200 ml.) containing sodium acetate (200 mg.) was refluxed for 3.5 hours and then left overnight. The product, crystallized from methanol, gave 3 β ,6 β -diacetoxy-19-nitrilocholestan-6,19-hemiacetal (XXII, 1.0 g.) as thick needles, m.p. 146–148°, $[\alpha]_D -17^\circ$ (c 0.76); $\nu_{\text{max}}^{\text{KBr}}$ 2260, 1750 and 1740 cm^{-1} .

Anal. Calcd. for $\text{C}_{31}\text{H}_{48}\text{O}_4\text{N}$: C, 74.51; H, 9.88; O, 12.81; N, 2.80. Found: C, 74.80; H, 9.71; O, 12.58; N, 3.16.

3 β -Acetoxy-19-nitrilocholestan-5-ene (XXV, R = Ac).—3 β -Acetoxy-19-oximinocholestan-6 β -ol (XIX, R = Ac, R' = R'' = H; 5.0 g.) in pyridine (20 ml.) and methanesulfonyl chloride (5 ml.) was left at room temperature for 24 hours. The non-crystalline product (5.51 g.), which showed cyano- and methanesulfonate bands in the infrared, was refluxed for 3 hours with collidine (100 ml.). The product crystallized from methanol to give 3 β -acetoxy-19-nitrilocholestan-5-ene (XXV, R = Ac, 82%), m.p. 129–130°, $[\alpha]_D -132^\circ$ (c 0.80); $\nu_{\text{max}}^{\text{KBr}}$ 2250 and 1750 cm^{-1} .

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{O}_2\text{N}$: C, 79.22; H, 10.32; O, 7.28; N, 3.19. Found: C, 79.26; H, 10.35; O, 7.56; N, 3.19.

The nitrilo-acetate (XXV, R = Ac; 4.2 g.), heated under reflux for 20 min. with 5% ethanolic potassium hydroxide, gave 3 β -hydroxy-19-nitrilocholestan-5-ene. Crystallized from methanol or acetonitrile this (3.5 g.) had m.p. 133–134°, $[\alpha]_D -127^\circ$ (c 0.93); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3700, 3500 and 2250 cm^{-1} .

Anal. Calcd. for $\text{C}_{27}\text{H}_{44}\text{ON}$: C, 81.53; H, 10.92; O, 4.02. Found: C, 81.74; H, 10.55; O, 4.19.

Methylation of 3 β -Acetoxy-19-oximinocholestan-6 β -ol (XIX, R = Ac, R' = R'' = H).—The steroidal oxime (3.22 g.) in ether (100 ml.) containing boron trifluoride etherate (190 mg.) was treated at 0° with stirring with an excess of ethereal diazomethane. The oily product (3.0 g.) was chromatographed over neutral alumina (90 g.). Besides unchanged starting material the following compounds were obtained. Elution with benzene-hexane 1:3 to 3:1 gave 3 β -acetoxy-6 β -methoxy-19-oximinocholestan-6,19-O-methyl ether (XIX, R = Ac, R' = R'' = Me; 20%) which, crystallized from methylene chloride-acetonitrile, had m.p. 97–99°, $[\alpha]_D -16^\circ$ (c 0.88); $\nu_{\text{max}}^{\text{KBr}}$ 1740, 1690 and 1060 cm^{-1} .

Anal. Calcd. for $\text{C}_{31}\text{H}_{48}\text{O}_4\text{N}$: C, 73.91; H, 10.60; O, 12.70; N, 2.78; OMe, 12.32. Found: C, 73.85; H, 10.62; O, 12.93; N, 2.79; OMe, 11.93.

Elution with methylene chloride containing up to 0.5% methanol gave 3 β -acetoxy-19-oximinocholestan-6 β -ol 19-O-methyl ether (XIX, R = Ac, R' = H, R'' = Me; 30%). After crystallization from methanol or from acetonitrile this had m.p. 165–166°, $[\alpha]_D -10^\circ$ (c 0.76); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3700, 3400, 1745 and 1060 cm^{-1} .

Anal. Calcd. for $C_{30}H_{51}O_4N$: C, 73.57; H, 10.50; O, 13.07; N, 2.86. Found: C, 73.38; H, 10.40; O, 13.51; N, 3.17.

Elution with methylene dichloride containing 3–4% of methanol afforded 3 β ,6 β -dihydroxy-19-oximincholestan-19-O-methyl ether (XIX, R = R' = H, R'' = Me). Crystallized from methanol this had m.p. 198–200°, $[\alpha]_D^{25} - 15^\circ$ (c 0.86), γ_{max}^{KBr} 3500 and 1070 cm^{-1} . An authentic specimen was prepared by hydrolysis of the corresponding 3 β -acetate (see above) with 5% ethanolic potassium hydroxide.

Anal. Calcd. for $C_{28}H_{49}O_5N$: C, 75.12; H, 11.03; O, 10.72; N, 3.13; OMe, 6.32. Found: C, 74.98; H, 10.86; O, 11.24; N, 3.50; OMe, 6.18.

Elution with methylene dichloride containing 4–6% of methanol furnished 3 β ,6 β -dihydroxy-19-oximincholestan-19-O-methyl ether (XIX, R = R' = H), identical with a specimen obtained by alkaline hydrolysis of the corresponding 3 β -acetate (see above). Recrystallized from acetonitrile this had m.p. 194–195°, $[\alpha]_D^{25} - 7^\circ$ (c 0.875), γ_{max}^{KBr} 3400 and 3300 cm^{-1} .

Anal. Calcd. for $C_{27}H_{47}O_5N$: C, 74.78; H, 10.92; O, 11.07; N, 3.23. Found: C, 74.45; H, 10.89; O, 11.17; N, 3.35.

3 β -Acetoxy-19-oximincholest-5-ene 19-O-Methyl Ether (XXVI, R = Ac).—Treatment of 3 β -acetoxy-19-oximincholestan-6 β -ol 19-O-methyl ether (XIX, R = Ac, R' = H, R'' = Me) in pyridine with excess of methanesulfonyl chloride for 2 hours at room temperature followed by refluxing of the product with collidine for 2 hours gave 3 β -acetoxy-19-oximincholest-5-ene O-methyl ether (XXVI, R = Ac; 86%). Crystallized from methanol or acetonitrile this had m.p. 117–118°, $[\alpha]_D^{25} - 129^\circ$ (c 0.96), $\gamma_{max}^{CHCl_3}$ 1750 cm^{-1} .

Anal. Calcd. for $C_{30}H_{49}O_5N$: C, 76.38; H, 10.47; N, 2.97; OMe, 6.58. Found: C, 75.98; H, 10.23; N, 2.54; OMe, 6.44.

Alkaline hydrolysis with refluxing 5% ethanolic potassium hydroxide for 30 minutes gave the corresponding alcohol XXVI (R = H). Crystallized from methanol this had m.p. 114–115°, $[\alpha]_D^{25} - 127^\circ$ (c 0.94), $\gamma_{max}^{CHCl_3}$ 3700, 3500 and 1620 cm^{-1} .

Anal. Calcd. for $C_{28}H_{47}O_5N$: C, 78.32; H, 10.94; O, 7.45; OMe, 8.32. Found: C, 77.96; H, 11.24; O, 7.2; OMe, 7.05.

3 β ,20 β -Diacetoxy-6-nitropregn-5-ene.—Fuming nitric acid (75 ml.) was added dropwise during 1 hour with stirring to 3 β ,20 β -diacetoxy-6-nitropregn-5-ene (5 g.) in ether (100 ml.) at 0°. The stirred solution was kept at -10° for 2 hours

after which water (150 ml.) and ether (100 ml.) were added and the product separated in the usual way. Crystallization from methanol gave 3 β ,20 β -diacetoxy-6-nitropregn-5-ene (3.2 g.), m.p. 153–155°, $[\alpha]_D^{25} - 80^\circ$ (c 1.07), λ_{max} 263, 240 $m\mu$ (ϵ 1,200 and 236, resp.), γ_{max}^{Nujol} 1740 and 1520 cm^{-1} .

Anal. Calcd. for $C_{25}H_{37}O_6N$: C, 67.11; H, 8.27; N, 3.13. Found: C, 67.02; H, 8.40; N, 3.00.

3 β ,20 β -Diacetoxy-5 α -pregnan-6-one.—3 β ,20 β -Diacetoxy-6-nitropregn-5-ene (5 g.) in acetic acid (100 ml.) and water (10 ml.) was stirred with zinc dust (10 g.) under reflux for 4 hours. The product, crystallized from methanol, afforded 3 β ,20 β -diacetoxy-5 α -pregnan-6-one (almost quantitative yield), m.p. 183–185°, $[\alpha]_D^{25} - 14^\circ$ (c 0.93).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15; O, 19.11. Found: C, 71.78; H, 8.93; O, 18.84.

The diacetate (1.75 g.) in methanol (70 ml.) was left at 15° with sodium borohydride (500 mg.) in water (1.5 ml.) for 30 min. Crystallization of the product from acetone-hexane furnished 3 β ,20 β -diacetoxy-5 α -pregnan-6 β -ol (XXVII, R = H, X = H₂), m.p. 170–173°, $[\alpha]_D^{25} \pm 0^\circ$ (c 1.10), $\gamma_{max}^{CHCl_3}$ 3700, 3500 and 1735 cm^{-1} .

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.37; H, 9.59; O, 19.03. Found: C, 71.13; H, 9.42; O, 18.88.

3 β ,20 β -Diacetoxy-5 α -pregnan-6 β -yl Nitrite (XXVII, R = NO, X = H₂).—The above-mentioned diacetate alcohol (2.0 g.) in pyridine (10 ml.) was treated at -30° with excess of nitrosyl chloride. Addition of water, filtration and crystallization from hexane gave 3 β ,20 β -diacetoxy-5 α -pregnan-6 β -yl nitrite (XXVII, R = NO, X = H₂; approx. 2.0 g.), m.p. 156–157°, $[\alpha]_D^{25} - 36^\circ$ (c 0.73), γ_{max}^{Nujol} 1730 and 1653 cm^{-1} .

Anal. Calcd. for $C_{25}H_{40}O_6N$: C, 66.64; H, 8.95; O, 21.30; N, 3.11. Found: C, 66.94; H, 8.74; O, 21.27; N, 2.58.

Photolysis of 3 β ,20 β -Diacetoxy-5 α -pregnan-6 β -yl Nitrite (XXVII, R = NO, X = H₂).—The nitrite (2.0 g.) in toluene (70 ml.) was photolyzed at room temperature for 1 hour with a 200-watt mercury lamp. The solvent was removed *in vacuo* and the residue refluxed in isopropyl alcohol until the green color changed to orange-brown. The isopropyl alcohol was removed *in vacuo* and the residue chromatographed over Florisil (60 g.). After elution of 3 β ,20 β -diacetoxy-5 α -pregnan-6-one and 3 β ,20 β -diacetoxy-5 α -pregnan-6 β -ol, there was obtained the desired 3 β ,20 β -diacetoxy-19-oximino-5 α -pregnan-6 β -ol (XXVII, R = H, X = NOH; 1.08 g.). Recrystallized from ethyl acetate and then acetonitrile this had m.p. 219–220°, $[\alpha]_D^{25} - 25^\circ$ (c 0.90), γ_{max}^{KBr} 3600, 3450, 1740 and 1715 cm^{-1} .

Anal. Calcd. for $C_{25}H_{38}O_6N$: C, 66.94; H, 8.54; O, 21.40. Found: C, 66.91; H, 8.90; O, 20.96.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

A Synthesis of Aldosterone Acetate¹

By D. H. R. BARTON AND J. M. BEATON

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Photolysis of corticosterone acetate nitrite affords aldosterone acetate oxime which with nitrous acid gives aldosterone acetate. The over-all yield based on corticosterone acetate is about 15%. Products resulting from intramolecular attack of the activated C₁₁ alkoxyl radical involved in this reaction upon the methyl group at C₁₉ have been isolated and their structures determined. A novel rearrangement reaction is involved in the genesis of these compounds.

The elucidation of the constitution (V, R = H) of aldosterone² has presented organic chemists

with a challenging problem of synthesis. Several total syntheses have been effected³ but, at the time

(1) This paper is Communication No. 12 from the Research Institute for Medicine and Chemistry. For a preliminary report see D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **82**, 2641 (1960).

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