The photosenzitized irradiation of I. A 3:1 mixture of benzene–95% ethanol was distilled twice in a vacuum system in order to remove dissolved oxygen. A third distillation was used to convey the solvents into the reaction vessel, which was then sealed under vacuum. The reaction vessel contained 101 mg. (0.219 mmole) of the diene I and 84 mg. (0.22 mmole) of Methylene Blue. The Pyrex tube was water-cooled and rotated during irradiation by a General Electric 275 watt, 110–125 v., 50–60 cycle AC sunlamp, which was *ca.* 6 in. from the vessel. After removal of the solvent the blue solid was chromatographed on an alumina column (2.1 cm. × 40 cm.), which was composed of 160 g. of alumina in hexane. The column was eluted with hexane-benzene (9:1) and the eluant was analyzed spectroscopically. In this manner, 63 mg. (62% yield) of a white solid was obtained, that gave colorless prisms, m.p. 163.0–163.4°, on recrystallization from benzene–95% ethanol. A mixed melting point depression was not observed from an admixture of this product with XIIb; m.p. 163.1–163.6°. The infrared spectra were also identical.

Further elution gave 3 mg. of a yellow solid that was not pentaphenylbenzene. Pentaphenylbenzene was not isolated from the chromatogram. No hydrocarbon other than the diene isomer XIIb was obtained and identified from the reaction mixture. The reason for the low yield of the diene isomer XIIb in this reaction was probably due to the room temperature extraction procedure of the initial blue solid by benzene.

The above reaction with an irradiation period of 243 hours was repeated. Of the four substances that were isolated from the alumina chromatogram, no pentaphenylbenzene, no diene I, nor diene isomer XIIb was found. Only 17 mg. of Compound A (see photo-oxidation of I in the absence of Methylene Blue) was identified by the four distinct fractions. Compound A was identified by melting point and infrared and ultraviolet spectra; the yield of Compound A was 17%.

The photodehydrogenation of I *by chloranil.* A solution of 2.03 g. (4.41 mmoles) of I and 6.12 g. (25.5 mmoles) of chloranil in 1.1 l. of distilled benzene, which was purged with nitrogen for 6 hours, was irradiated by the Hanovia mercury vapor lamp equipped with a Vycor filter, under a nitrogen atmosphere for 140 min. After removal of the solvent, the red solid was chromatographed on an alumina column (2.1 cm. × 52 cm.), which was composed of 200 g. of alumina in hexane-benzene (20/1). The column was eluted with this solvent ratio and the eluant was analyzed spectroscopically. In this manner, 2.01 g. of a colorless solid were obtained along with 15 mg. of a yellow solid as the only hydrocarbon fractions from the column.

The white solid, pentaphenylbenzene, was recrystallized from benzene-hexane; colorless prisms, m.p. 250.3–250.6°; a mixed melting point was determined with a synthetic sample of pentaphenyl melting point was determined with a synthetic sample of pentaphenylbenzene,[43] m.p. 250.3–250.8°C. The infrared spectra of the two samples were identical.

The yellow solid that was obtained from the column exhibited all the spectral properties of pentaphenylbenzene, and was assumed to be impure pentaphenylbenzene.

The yield of pentaphenylbenzene is 99%.

The photosensitized oxidation of II. A solution of 1.008 g. (2.05 moles) of II and 18 mg. (0.047 moles) of Methylene Blue in 850 ml. of benzene and 250 ml. of 95% ethanol was irradiated by the Hanovia mercury vapor lamp, which was equipped with a Pyrex filter, for 130 min., while the solution was saturated with oxygen. After removal of the solvent, the blue solid was chromatographed on an alumina column (2.1 cm. × 50 cm.), which was composed of 200 g. of alumina in hexane. The column was eluted with hexane-benzene (7:5) and the eluant was analyzed spectroscopically. In this manner 17 mg. of a colorless solid was obtained. This was recrystallized from benzene-hexane and identified by its melting point and infrared spectrum as pentaphenylbenzene, 2% yield.

The next fraction was obtained from the hexane-benzene (1:4) eluants, from which 590 mg. of a yellow solid was obtained. This material upon recrystallization from benzene-hexane gave colorless prisms, which were identified as starting material II by the infrared spectrum; 59% recovery of II.

Further elution gave 216 mg. (22% by weight) of a mixture of II and a carbonyl derivative, which had been previously isolated from the photosensitized oxidation of I, and which arises from the photorearrangement of II.

NEW HAVEN, CONN.

[JOINT CONTRIBUTION FROM THE NATURAL PRODUCTS RESEARCH DEPARTMENT, SCHERING CORPORATION, AND THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY]

The Photolysis of Organic Nitrites. VII. Fragmentation of the Steroidal Side Chain

A. L. NUSSBAUM,[1a] E. P. YUAN,[1b] C. H. ROBINSON,[1b] A. MITCHELL,[1b]
E. P. OLIVETO,[1b] J. M. BEATON,[1c] AND D. H. R. BARTON[1c]

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Certain steroidal nitrite esters substituted vicinally by several oxygen-bearing moieties undergo oxidative carbon-carbon fission upon irradiation.

Various ramifications of the photochemical reactions of nitrile esters have recently been made the subject of a number of investigations.[1d] It would appear that structural features very much determine the outcome of such reactions. In general, it has been convenient to treat nitrite photolysis as proceeding by way of alkoxide radicals; the various pathways by which such radicals react further to give rise to more stable structures have been reviewed.[2] They include internal hydrogen abstraction, rearrangement, disproportiona-

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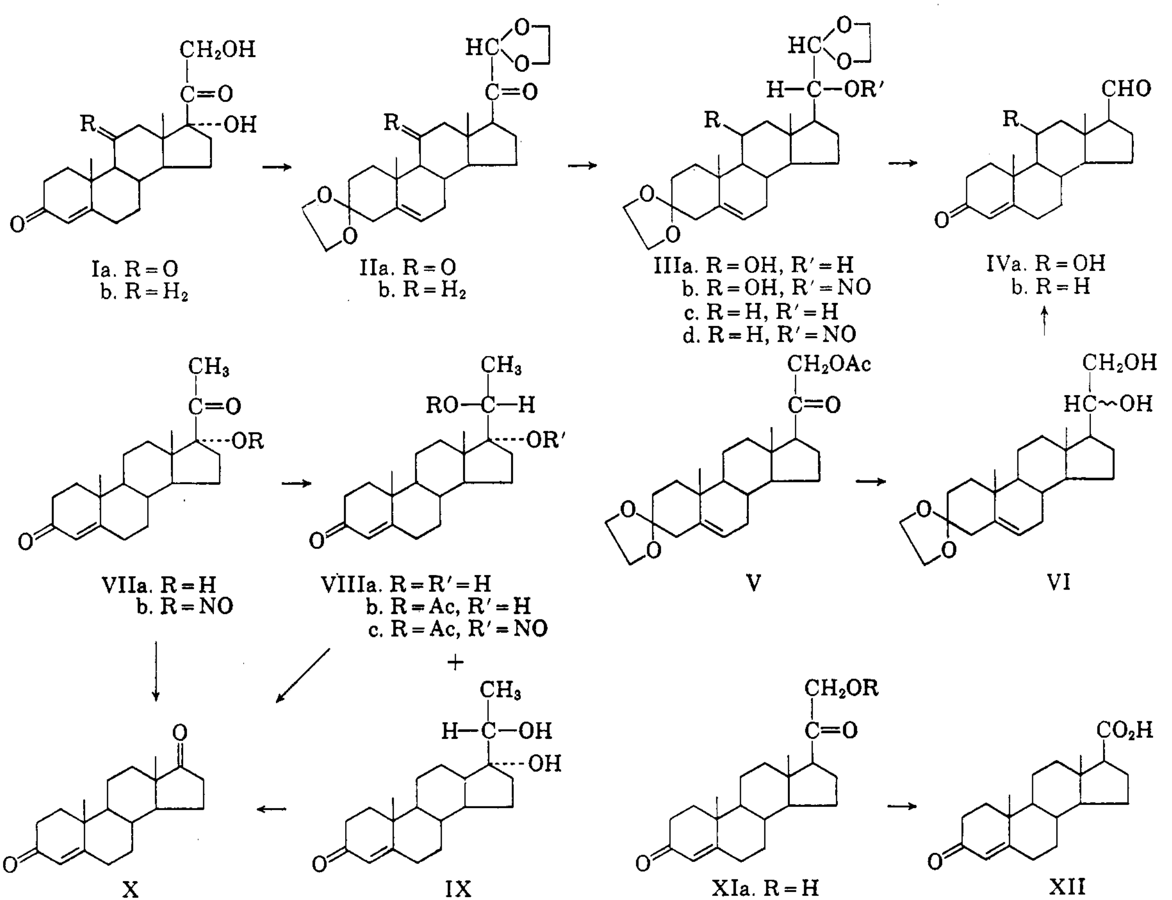
(1) (a) Current address: Department of Biochemistry, Stanford University Medical School, Palo Alto, Calif. (b) Schering Corporation. (c) Research Institute for Medicine and Chemistry. (d) Reviewed by A. L. Nussbaum and C. H. Robinson, *Tetrahedron, in press.*

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



Ia. R = O
b. R = H_2

IIa. R = O
b. R = H_2

IIIa. R = OH, R′ = H
b. R = OH, R′ = NO
c. R = H, R′ = H
d. R = H, R′ = NO

IVa. R = OH
b. R = H

VIIa. R = H
b. R = NO

VIIIa. R = R′ = H
b. R = Ac, R′ = H
c. R = Ac, R′ = NO

V

VI

X

IX

XIa. R = H
b. R = NO

XII

tion, and elimination of an appropriate fragment. In the present paper we wish to present the details of such fragmentations in the steroid series: the elimination of carbon atoms in the side chain resulting from carbon-carbon fission.

During the preliminary experiments which eventually led to a convenient synthesis of aldosterone,[3] it was considered advantageous to attempt attack on the angular methyl from C-20.[4] A particularly attractive starting material appeared to be 3,3:21,21 - bisethylenedioxy - 5 - pregnene - 11β,20β-diol (IIIa), a compound synthesized in the manner of Tsuda *et al.*,[5] who had prepared the corresponding 11-deoxy compound (IIIc) by means of a Mattox-Kendall rearrangement of Compound S (Ib), followed by reduction of the 20-carbonyl (IIb to IIIc). An analogous reaction series, starting with cortisone (Ia), gave the 11β-hydroxy derivative IIIa. The latter, upon conversion to the nitrite IIIb and irradiation, seemed to have undergone oxidative fission to the aldehyde IVa, as judged from its elementary composition and a weak but distinct band at 3.65 μ in the infrared. We decided to investigate this reaction in the more easily accessible 11-deoxy-series[6] and adumbrate its scope.

3,3:21,21-Bis-(ethylenedioxy)-5-pregnen-20β-ol (IIIc),[5] was converted to its nitrite IIId and the latter photolyzed, without purification, in benzene solution by a 200 watt mercury lamp at 20°, under nitrogen. The principal product again was clearly an aldehyde, as indicated by infrared bands at 3.69 and 5.83 μ. Elementary analysis indicated the loss of $C_3H_5O_3N$, *i.e.*, a fragment corresponding to an ethylenedioxy group, the nitrite portion, and an additional carbon atom. As the isolated product did not itself contain any nitrogen, structure IVb seemed reasonable. It was confirmed by an independent synthesis: 3,3-ethylenedioxy-21-acetoxy-5-pregnen-20-one (V),[7] a known compound was converted to the mixture of 20,21-diols (VI) by reduction with lithium aluminum hydride, and the diols cleaved to the authentic aldehyde IVb by periodate oxidation. This material proved to be identical with the nitrite photolysis product, thus verifying the assigned structure. The correspond-

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(3) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **82**, 2641 (1960).

(4) There is now in existence a number of reactions which do this; see the excellent review by K. Schaffner, D. Arigoni, and O. Jeger, *Experientia*, **16**, 169 (1960); also see D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960).

(5) K. Tsuda, N. Ikekawa, and S. Nozoe, *Chem. Pharm. Bull. (Japan)*, **7**, 519 (1959).

(6) For a preliminary account of this work, see A. L. Nussbaum, C. H. Robinson, E. P. Oliveto, and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 2400 (1961).

(7) R. Antonucci, S. Bernstein, R. Lenhard, N. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

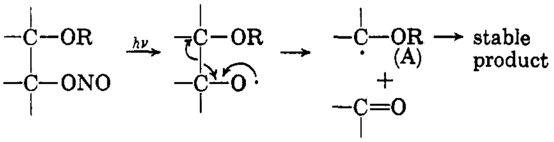
ing structure IVa in the 11-oxygenated series is assigned by analogy.

Concurrent with these experiments, we desired to extend the scope of a reaction series leading to 18-nitriloprogesterone and related structures[8] to 17-hydroxylated pregnane derivatives. Both 17α,-20β(VIIIa)[9] and 17α,20α-dihydroxy-4-pregnen-3-one (IX)[10] were converted to ill-defined mixtures of nitrites. Irradiation gave rise, in either case, to the same product, considerably less polar than the starting glycols, free of nitrogen, and possessing the infrared absorption of a 5-membered ring ketone. This material proved to be 4-androstene-3,17-dione (X). Again, an oxidative cleavage of a carbon-carbon bond had occurred.[11]

Further attempts to expand the scope of this reaction delineated its limits. 17α-Hydroxy-4-pregnene-3,20-dione (VIIa) was converted to the tertiary nitrite (VIIb) and irradiated as usual. Again, the predominating product was androstenedione (X). On the other hand, the glycol monoacetate VIIIb, 17α,20β-dihydroxy-4-pregnen-3-one 20-acetate, gave a nitrite (VIIIc) which did not, upon irradiation, give rise to androstenedione; instead, starting material VIIIb was recovered.

We next turned our attention to the behavior of 21-nitrites. 11-Desoxycorticosterone (XIa), a representative primary ketol, was converted to its nitrite XIb and irradiated. More than one product was observed by paper chromatography. However, it was possible to isolate the known 3-keto-4-etiocholenic acid XII.[12]

The irradiation of certain nitrites substituted vicinally by a number of oxygen-containing functions thus leads to carbon-carbon fission. It is thus another degradative method duplicating, and to some extent supplementing, such procedures as the use of periodate, bismuthate, and lead tetraacetate. It is attractive to ascribe the course of such reactions to the disruptive influence of the lone electron on an oxide free radical generated by the photolysis:



The driving force of the reaction is considered to be the ability of the other product of fission (A) to stabilize itself by coupling with one of the oxygen electrons.

We are presently investigating the effect of other structural features in the α-position of nitrite esters upon the course of their photolysis. This will be the subject of forthcoming publications from these laboratories.

EXPERIMENTAL[13]

17β-Formyl-5-androsten-3-one ethylene ketal (IVb). *A. From 3,3:21,21-bisethylenedioxy-5-pregnen-20β-ol* (IIIc).[4] The 20β-ol (IIIc, 300 mg.) in pyridine, 7.5 ml., was treated at −30° with a pyridine solution of nitrosyl chloride, until a color change was observed. The reaction was quenched and the product filtered off (m.p. 190–195°). After drying at room temperature *in vacuo*, it was dissolved in 170 ml. of benzene, and irradiated with a 200-watt mercury lamp at 20°, under nitrogen, for one hour. The resulting crude material was crystallized from methylene chloride–ether to give 81.6 mg., mp. 166–173°, of 17β-formyl-5-androsten-3-one 3-ethylene ketal (IVb). Recrystallization from the same solvent gave an analytical sample, m.p. unchanged, λ^{Nujol} 3.73, 5.84, 9.10 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.60; H, 9.17.

B. From 21-Acetoxy-3-ethylenedioxy-5-pregnen-20-one (V). 21-Acetoxy-3-ethylenedioxy-5-pregnen-20-one[7] (2.5 g.) was dissolved in 225 ml. of ethanol and treated with 4.1 g. of sodium borohydride and 25 ml. of 2.5% sodium hydroxide. The solution was refluxed for 6 hours, 200 ml. of water was added, and concentrated to half volume. Cooling and filtration gave 2.48 g. of crude diol VI, m.p. 210–225, λ^{Nujol} at 3.05 μ (very broad).

Of this crude, a portion of 203 mg. was dissolved in 20 ml. of dioxan, and 70 ml. of a solution of potassium periodate (1.1 g. in 200 ml. of water) was added, and the resulting suspension was kept in the dark, under nitrogen, for 20 hours. Extraction with ether, washing the extract with bicarbonate and water, drying, and concentration followed by crystallization from methylene chloride–ether, gave 75 mg. of the desired aldehyde IVb, identical in melting point and infrared spectrum to the material obtained via nitrite irradiation.

3,3:21,21-Bisethylenedioxy-5-pregnene-11,20-dione (IIa). Cortisone (Ia, 2 g.) was dissolved in dioxan (25 ml.) and methyl ethyl ketone (25 ml.), p-toluenesulfonic acid (50 mg.) was added, and the solution was refluxed for five hours. Neutralization with pyridine and the usual workup gave 1.1 g. of the bisketal (IIa), m.p. 169–173°; $[\alpha]^{23}_{D}$ +43° ($CHCl_3$); λ^{Nujol} at 5.75, 5.85, and 5.96 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; O, 22.30. Found: C, 70.01; H, 7.99; O, 22.30.

Reduction of (IIa) *with lithium aluminum hydride.* 3,3:-21,21-Bisethylenedioxy-5-pregnen-11,20-dione (IIa, 1.0 g.) was reduced in tetrahydrofuran solution and worked up in the usual manner. Chromatography on alumina gave 3,3:-

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(8) 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), and later papers.

(9) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

(10) See, for instance, D. R. Idler, V. H. M. Fagerlund, and A. P. Roland, *Biochem. and Biophys. Res. Comm.*, **2**, 133 (1960) for an alternate preparation. This compound has been isolated from a number of biological sources: R. Neher and A. Wettstein, *Helv. Chim. Acta*, **43**, 1172, 1628 (1960); M. L. Sweat, D. L. Berliner, M. J. Beyson, C. Nabors, Jr., J. Haskell, and F. G. Holmstrom, *Biochem. and Biophys. Acta*, **40**, 289 (1960); T. Sandor and A. Lanthier, *Can. J. Biochem. and Physiol.*, **38**, 1167 (1960); **39**, 973 (1961). Preparation and structure proof are given in the Experimental.

(11) The related pyrolytic fission of simple aliphatic 1,2-glycol dinitrites to aldehydes and ketones has been observed: see L. P. Kuhn and L. DeAngelis, *J. Am. Chem. Soc.*, **76**, 328 (1954).

(12) G. M. Picha, F. J. Saunders, and D. M. Green, *Science*, **115**, 704 (1952).

(13) All melting points were taken on a Kofler block. Rotations were carried out in a 1-dm. tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

21,21-bisethylenedioxy-5-pregnene-11β,20β-diol (IIIa), m.p. 178.5–180°; $[\alpha]_D^{22}$ −49 ($CHCl_3$), devoid of carbonyl absorption in the infrared.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.44; H, 8.62.

From later fractions, the 20α-isomer was obtained: m.p. 240–242.5°, $[\alpha]_D^{22}$ −55° ($CHCl_3$); no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81; O, 22.09. Found: C, 68.74; H, 8.81; O, 22.13.

3,3:21,21-Bisethylenedioxy-5-pregnene-11β,20β-diol 20-nitrite (IIIb). Treatment of IIIa (850 mg.) in the usual manner with nitrosyl chloride (130 mg.) in pyridine (5 ml.) gave the nitrite (IIIb, 825 mg.). Recrystallization from ethyl ether gave an analytical sample, m.p. 183–184°; λ^{nujol} at 2.78 and 6.03 μ; λ_{max} 368 mμ (ϵ 77).

Anal. Calcd. for $C_{25}H_{37}O_7N$: C, 64.77; H, 8.05; N, 3.02; O, 24.16. Found: C, 64.70; H, 7.87; N, 2.97; O, 23.94.

3,3-Ethylenedioxy-17β-formyl-5-androsten-11β-ol (IVa). The foregoing product (IIIb, 400 mg.) was dissolved in 20 ml. of toluene and photolyzed for 30 minutes. The major product was isolated by chromatography on alumina. It had m.p. 152–154°, $[\alpha]_D^{22}$ −3° ($CHCl_3$), λ^{nujol} at 2.70, 3.65 (weak, but definite!), and 5.82 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.12; H, 8.74; O, 17.83.

17α,20α-(IX) *and 17α,20β-Dihydroxy-4-pregnen-3-one* (VIIIb). 17α-Hydroxyprogesterone (VIIIa, 10 g.), dissolved in 200 ml. of tetrahydrofuran, was added to 4 g. of lithium aluminum hydride in 400 ml. of the same solvent in the usual apparatus, with ice cooling. The solution was refluxed for 45 minutes, then cooled again to 5°. Excess reagent was destroyed with ethyl acetate, and the complex decomposed with saturated sodium sulfate solution (until clumpy). After drying with additional solid sodium sulfate, the organic solution was decanted and concentrated to dryness. The resulting steroidal mixture was redissolved in chloroform (1 l.), and 100 g. of active manganese dioxide was added. The resulting suspension was stirred for 23 hours at room temperature, then filtered and concentrated. The residual oil (10 g.) was crystallized once from acetone-hexane to give 4.73 g. of a mixture epimeric at C-20 (in benzene-formamide: R_f = 0.31 and 0.44).

Of this, 500 mg. were chromatographed on a partition column of chromosorb W (100 g.) made up with benzene-formamide. Resolution of this mixture was incomplete, but some pure material was obtained. From the early fractions, 82 mg. of 17α,20β-dihydroxy-4-pregnen-3-one m.p. 200–203 (lit. 201–204°).[9] After the bulk of the material came off the column as mixture, some 37 mg. of the more polar 17α,20α-dihydroxy-4-pregnen-3-one (IX) were eluted. One recrystallization gave 10 mg. m.p. 207–210°, λ^{Nujol} at 2.82, 3.05, 6.10, 6.22 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.74. Found: C, 76.15; H, 9.67.

4-Androstene-3,17-dione (X). *A. From 17α,20α-Dihydroxy-4-pregnen-3-one* (IX). The 20α-ol (300 mg.) was dissolved in 8 ml. of pyridine and treated with nitrosyl chloride–pyridine at −25° until a color change persisted. The reaction mixture was quenched in water, filtered, and dried *in vacuo* at room temperature. The 247 mg. thus obtained migrated with R_f = 0.85 (in benzene-formamide) and gave a positive color test with $(C_6H_5)_2NH \cdot HCl$. This material was irradiated in benzene solution with a 200-watt mercury lamp, through pyrex, under nitrogen, at 20°.

Chromatography gave 148 mg. of androstenedione (X), ascertained by m.p. and infrared spectrum.

B. From 17α,20β-Dihydroxy-4-pregnen-3-one (VIIIa). The 20β-ol (78 mg.) was similarly nitrosated and irradiated. Chromatography again gave 27 mg. of androstenedione.

C. From 17α-Hydroxyprogesterone (VII). 17α-Hydroxyprogesterone (1 g.) was dissolved in 10 ml. of pyridine and treated dropwise, at −20°C. with a solution of nitrosyl chloride in pyridine until a permanent blue color developed. The reaction was quenched with 500 ml. of ice water, and the resulting nitrite was filtered and dried at room temperature *in vacuo* for two hours. The material was dissolved in benzene and irradiated for one hour. Isolation in the manner described above gave 430 mg. of androstenedione.

Desoxycorticosterone 21-nitrite (XIb). A stirred solution of desoxycorticosterone 21-alcohol (1.0 g.) in pyridine (20 ml.) at −20° was treated with excess nitrosyl chloride in pyridine (5 ml.) and stirring was continued for 15 minutes. The reaction mixture was then poured into water (250 ml.), and the precipitated solid was filtered, washed with water, and dried at room temperature. The crude nitrite (876 mg.) had m.p. 126–127° (frothing), $[\alpha]_D$ 157°; $\lambda_{max.}^{MeOH}$ 241 mμ (17,200); $\lambda_{max.}^{nujol}$ 5.81, 6.02, 6.10, 6.19 μ.

3-Keto-4-Etiocholenic Acid (XII). The crude nitrite from the previous reaction (800 mg.) in benzene (200 .ml.) was irradiated by a 200 watt lamp for 1 hour, at 18°. The solution was then evaporated to dryness at room temperature. Paper chromatography showed the presence of three components, of polarity greater than, equal to, and less than desoxycorticosterone 21-alcohol (ligroin–toluene–propylene glycol system).

Partition chromatography on Chromosorb W, using the same solvent system, resulted in the isolation of the three components, each of which was apparently homogeneous, as judged by paper chromatography.

Product A 138 mg. (more polar than desoxycorticosterone; 36 mg. after crystallization from acetone) had m.p. 238–247°. This material was identical with genuine 3-keto-4-etiocholenic acid in every respect.

BLOOMFIELD, N. J.
CAMBRIDGE, MASS.