

Photolysis of Organic Nitrites. VIII. Intramolecular Addition to a Double Bond

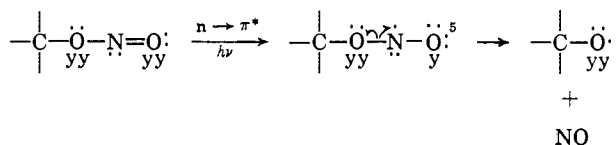
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Contribution from the Natural Products Research Department, Schering Corporation, Bloomfield, New Jersey. Received February 11, 1965

Irradiation of 20 β -hydroxy-4,16-pregnadien-3-one nitrite in benzene solution gave 17 ξ ,20 ξ -oxido-16-oximino-4-pregnen-3-one. Its formation by way of intramolecular addition of an alkoxy free radical to a double bond is discussed.

The photochemistry of organic nitrites has been extensively investigated.² It is convenient to regard the primary photochemical act as the excitation of a non-bonding 2p electron on the distal oxygen to the anti-bonding orbital, in analogy with the $n \rightarrow \pi^*$ situation postulated by Kasha³ for ketonic carbonyl. The electron promotion is followed by generation of NO and an alkoxy radical, as in Scheme I.⁴

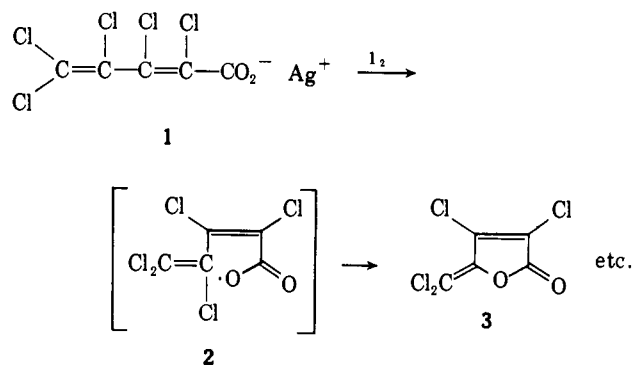
Scheme I



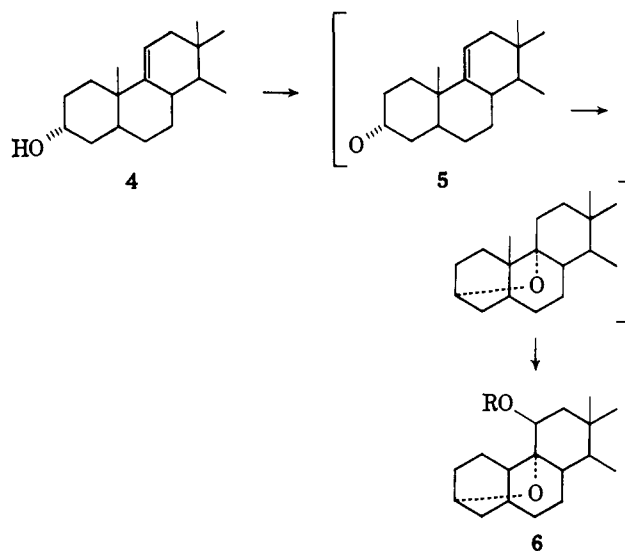
One would expect a "hot" species, here represented as an alkoxy radical, to decay in a variety of ways, depending upon its detailed structure, the nature of surrounding solvent molecules, and the presence of other species capable of acting as trapping agents.⁶ One such mode of decay would be addition to double bonds. This is generally of minor importance,^{7a,b} although certain alkoxy radicals possessing strongly electrophilic properties react easily with olefinic systems of high electron density.⁸ One would expect its occurrence also when favored by steric factors. For instance, the entropy factor would be especially favorable when the double bond is located in the same molecule, in a sterically accessible location; this would avoid the necessity for diffusion and collision processes.⁹

A number of such cases have been documented in the recent literature. Thus, acid **1** cyclizes to **3** in the

manner shown, presumably via acyloxy radical **2**,¹⁰ generated in the course of a Prévost reaction.¹¹ Immer, *et al.*,¹² reported the addition of the presumed



alkoxy radical **5**, generated from **4** with Pb(OAc)₄, to the double bond to give **6** upon termination.



In our own work, already briefly reported,¹³ a case of intramolecular addition to a double bond of a species generated by nitrite photolysis has been encountered. Our original aim had been to arrive at structures incorporating the features of **7**, since the steroidal lactones **8**¹⁴ had shown anti-aldosterone activity in ani-

(1) Research Division, Hoffmann-La Roche, Nutley, N. J.

(2) The subject has been reviewed: see M. Akhtar, *Advan. Photochem.*, **2**, 263 (1964); A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

(3) M. Kasha, *Discussions Faraday Soc.*, **9**, 14 (1950); J. W. Sidman, *Chem. Rev.*, **58**, 689 (1958).

(4) For symbolism, we have followed the conventions of H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **84**, 4527 (1962).

(5) The use of the single-headed arrow ("fishhook") to denote a one-electron shift, analogous to that of the conventional arrow used in depicting the movement of electron parts in classical resonance, follows the suggestion in H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p. xii.

(6) See P. Gray and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

(7) (a) J. R. Shelton and J. N. Henderson, *J. Org. Chem.*, **26**, 2185 (1961); (b) C. Walling and W. Thaler, *J. Am. Chem. Soc.*, **83**, 3877 (1961).

(8) F. Minisci and R. Galli, *Tetrahedron Letters*, No. 12, 533 (1962).

(9) Intramolecular free-radical reactions have been reviewed recently by K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964).

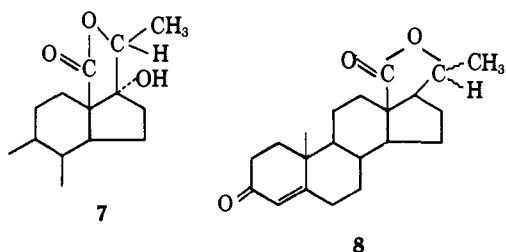
(10) A. Roedig, G. Märkl, and M. Schlosser, *Chem. Ber.*, **95**, 2243 (1962).

(11) Acyloxy radicals are known to initiate intermolecular attack on double bonds; see C. V. Wilson, *Org. Reactions*, **9**, 350 (1957).

(12) H. Immer, M. Lj. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 753 (1962).

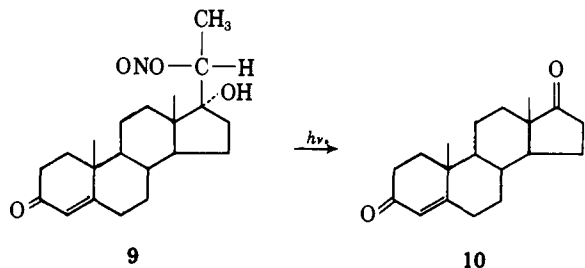
(13) A. L. Nussbaum, R. Wayne, E. Yuan, O. Zagneetko, and E. P. Oliveto, *J. Am. Chem. Soc.*, **84**, 1070 (1962). These data were also presented at the Second International Symposium on the Chemistry of Natural Products, IUPAC, Prague, Czechoslovakia, Aug. 27–Sept. 2, 1962, Abstracts, p. 116.

(14) A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian, and D. H. R. Barton, *Tetrahedron*, **18**, 373 (1962).



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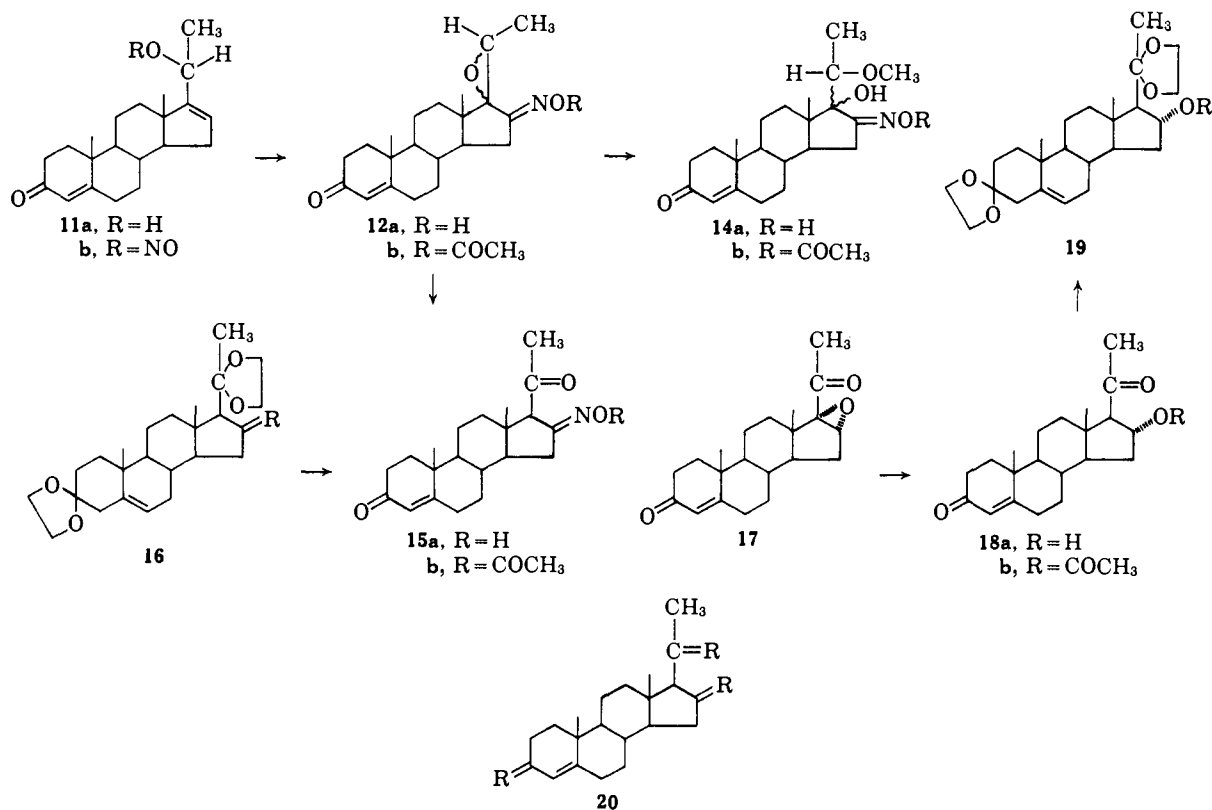
mals,¹⁵ and some structural variation seemed desirable. Our attempt to obtain this structure *via* a Barton reaction¹⁶ starting from **9** resulted, instead, in carbon-carbon fission¹⁷ to give **10**. A more indirect approach



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was then considered; the hydroxyl group was to be introduced, after generation of the lactone, by means of a pre-existing double bond at C-16. A suitable starting material would be the nitrite derived from 20-hydroxy-4,16-pregnadien-3-one. The actual nitrite subjected to photolysis had the 20 β -configuration **11b**.¹⁸

Chart I



(15) Personal communication, Dr. M. M. Pechet, Research Institute for Medicine and Chemistry.

(16) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960).

(17) A. L. Nussbaum, E. P. Yuan, C. H. Robinson, A. Mitchell, E. P. Oliveto, J. M. Beaton, and D. H. R. Barton, *J. Org. Chem.*, **27**, 20 (1962).

(18) The question of stereochemistry of the alcohols isomeric at C-20 has now been resolved (see W. R. Benn, R. Tiberi, and A. L. Nussbaum, *ibid.*, **29**, 3712 (1964)). It will be noted that, in our preliminary

communication,¹³ the opposite stereochemistry had been assigned. (19) It was noted that this nitrite was unusually unstable; mere solution in supposedly inert solvents like benzene caused rapid reappearance of the starting alcohol unless a drop of pyridine had been added. This behavior seems to be typical of allylic nitrites, or nitrites substituted by oxygen on the neighboring carbon. (20) By this time, the diphenylamine-hydrochloric acid test for nitrites had become negative. (21) F. Feigl, "Spot Tests in Organic Analysis," 6th Ed., Elsevier Publishing Co., Amsterdam, 1960, p. 162.

It was obtained in the usual manner by treatment of the alcohol **11a** (Chart I) with nitrosyl chloride in pyridine solution.¹⁹ Irradiation under nitrogen in benzene for a 1-hr. period,²⁰ using a 200-w. mercury source, supplying energy from 300 m μ upwards, gave a substance isomeric with the starting nitrite. The material had to be isolated by direct crystallization since chromatography of either the crude reaction mixture or, indeed, of the crystalline photoproduct itself did not permit the isolation of any solid material. Structure **12a** for the photoproduct follows from the data to be presented.

The material was more polar than either the nitrite or its precursor alcohol, as indicated by paper chromatographic mobility. Ultraviolet and infrared data indicated the survival of the original ring A unsaturated ketone, but the relatively negative optical rotation suggested a strong levorotatory influence, perhaps in ring D or the side chain. Titration in nonaqueous medium, as well as a specific color test,²¹ indicated that the nitrogen was now present in the form of an oxime. This was confirmed by generation of an infrared band typical for oxime acetate (5.67 μ) upon acetylation (see below).

The double bond at C-16 seemed to have disappeared: a positive tetranitromethane test present with starting material **11b** could no longer be observed. The compound was devoid of alcoholic hydroxyl; an acetylation

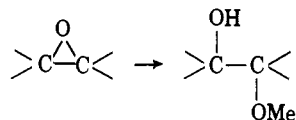
product (**12b**), clearly an oxime monoacetate by analysis, contained no hydroxyl band in the infrared, nor was ester acetate absorption discernible. In confirmation, the action of manganese dioxide²² on **12a** did not result in the regeneration of a 16-en-20-one, as concluded from a lack of the expected augmentation of the ultraviolet absorption intensity due to ring A unsaturation.²³

Oxime **12a** was unstable to acid treatment, fragmenting into a large number of products, none of which could be isolated from complex mixtures. Oxidative and reductive treatment likewise did not result in promising leads, but the material was converted into more recognizable transformation products by alkaline reagents (*vide infra*).

These data seem to exclude a simple parallel with the behavior of the corresponding analogs saturated at C-16,^{16,24} where a Barton reaction had resulted in functionalization of the angular methyl group at C-13 and regeneration of the alcoholic hydroxyl of the precursor nitrite. In confirmation, examination of the proton magnetic resonance spectrum of **12a** indicated that the angular methyl groups were untouched, and the double bond at C-16 was no longer present.²⁵

In the present situation, this is not entirely unexpected, since the postulated oxide radical at C-20 derived from the allylic nitrite is located at a greater distance from the angular methyl group (because of trigonal distortion) than in the corresponding analogs saturated at C-16, thus making internal hydrogen abstraction less probable.

Two of the oxygen atoms present in **12** have been accounted for, as the carbonyl oxygen of the Δ^4 -3-ketone, and in the oxime; the third was not part of either a hydroxyl or carbonyl; hence, presence of an oxide grouping was considered. Subjection to alcoholic potassium hydroxide gave a product **14** which proved to be more polar than the starting material **12**. It was believed at first that an epoxide opening to a glycol had occurred. However, analysis indicated the addition of the elements of methanol, and a Zeisel determination confirmed the presence of one methoxyl group. Acetylation gave an oxime monoacetate still presenting hydroxyl in the infrared spectrum. The transformation could now be pictured as



the hydroxyl being tertiary, or otherwise resistant to acylation.

In order to avoid methoxylation, treatment with aqueous alkali was investigated. Two-phase exposure to aqueous potassium hydroxide-dioxane gave a

(22) For leading references, see R. M. Evans, *Proc. Chem. Soc.*, 47 (1958).

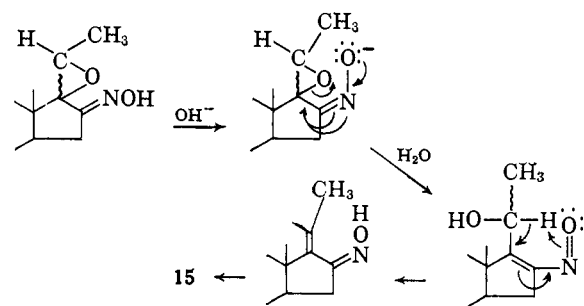
(23) The action of manganese dioxide on **12a**, however, gave rise to a new compound **13** in good yield. This latter material, described in detail in the Experimental section, misled us for some time as to the actual structure of its precursor. It had an analysis correct for loss of $\text{C}_2\text{H}_4\text{O}$ (the side chain?) and exhibited a band at 5.72μ in the infrared (five-membered ring ketone?). Its structure is still under investigation.

(24) 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).

(25) We wish to thank Dr. Leon Mandell of Emory University for carrying out this measurement.

product which was indeed somewhat more polar than the foregoing methoxy derivative **14** but possessed a new carbonyl absorption (5.87μ) in the infrared, strongly suggestive of a C-20 ketone. Formulation of this material as an oxime dione **15a** found support in an examination of the infrared spectrum of an acetyl derivative **15b**, which still showed the new carbonyl band, the expected oxime acetate absorption at 5.65μ , and neither an ordinary ester acetate nor free hydroxyl. Analysis confirmed this interpretation. The formation of **15** in terms of the structures depicted could be rationalized by the mechanistic stages shown in Scheme II.

Scheme II



The oxime proton is removed by the basic reagent, and the resulting negative charge is distributed to the oxide *via* a mesomeric shift with epoxide opening. Replacement of the proton on the oxygen with the greatest charge density leads to the nitrosoolefin depicted; an oxidooxime has undergone a tautomeric shift. The resulting structure then undergoes cyclic decay through a six-membered prototropic rearrangement to the enol form of the presumed final product.²⁶

This oxime dione **15a** was the first derivative of the original photolysis product **12a** which was amenable to structure proof by independent synthesis. A corresponding bisketal **16**, $\text{R} = \text{NOH}$, had already been described²⁷ by Bernstein's group, which had obtained this material by a series of transformations²⁸ utilizing functionalization at C-16 by a procedure previously described by Hirschmann.²⁹ We preferred the alternative approach of Cole and Julian³⁰ which had already been utilized in transforming **17** to **18**.³¹

The resulting 16α -hydroxyprogesterone **18a** was identical with a sample kindly provided by Dr. Bernstein. Since the Lederle workers observed dehydration during the ketalization of 16α -hydroxy-20-ones, the material was converted to the known acetate **18b**.²⁸ The latter, like the corresponding benzyl ether,²⁸ survived ketalization to give bisketal acetate (**19**, $\text{R} = \text{Ac}$) in good yield. Saponification followed by oxidation and oximation²⁷ gave the desired oxime bisketal **16** ($\text{R} = \text{NOH}$), as described.

The remaining problem was one of differential de-ketalization without effecting removal of the oxime.

(26) Similar rearrangements have been described by Huang-Minlon and Chung-Tungshun, *Tetrahedron Letters*, No. 19, 666 (1961), and P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).

(27) S. Bernstein, M. Heller, and S. M. Stolar, *J. Am. Chem. Soc.*, **77**, 5327 (1955).

(28) S. Bernstein, M. Heller, and S. M. Stolar, *ibid.*, **76**, 5674 (1954).

(29) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *ibid.*, **74**, 539 (1952).

(30) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(31) V. Schwarz, V. Černý, and F. Sorm, *Chem. Listy*, **51**, 1362 (1957).

This proved necessary since the oxime dione **15**, the photolysis transformation product, could not be deoximated to the known trione **20** ($R = O$)³² without extensive decomposition. An alternative approach, conversion of both **15** and **16** ($R = O$) (kindly supplied by Dr. Fried) to a common trioxime (**20**, $R = NOH$), also failed because of the instability of such substances.³³

When the oxime bisketal **16** ($R = NOH$) was subjected to 90% aqueous acetic acid, a total of six different spots was perceived by paper chromatography. A control run on oxime dione **15** under the same conditions gave rise to an identical paper chromatographic pattern. More careful investigation showed that when the reaction was run for a 10-min. period, the oxime bisketal **16** ($R = NOH$) gave an optimum yield of a spot with an R_f identical with that of oxime dione **15**, the other components of the mixture being kept at lower levels. Finally, adsorption chromatography of this complex mixture resulted in the isolation of the desired oxime dione **15**, identical by the usual criteria with the corresponding transformation product from nitrite irradiation.

These data establish the structure of **12a**, the photoproduct. There remains the question of stereochemistry. It might be assumed that the C-21 methyl group of the original nitrite (and the resulting postulated alkoxy radical) would assume a less strained distal conformation (with respect to both C-12 and the angular methyl group at C-13³⁴). A further conformational requirement for the postulated alkoxide radical addition to the double bond could be the necessity of maximum orbital overlap of the single electron on the approaching radical moiety with the π -electron system of that same double bond. This would result in conformation **21** (Scheme III) as a species capable of addition. However, retention of configuration of an alkoxy radical cannot be taken for granted: there are some cases on record^{35,36} where inversion has been observed. Occurrence of such an event would lead to **22**, if the assumption of a relatively strainless conformation for the C-21 methyl group is still maintained. Addition to the double bond would then lead to **23** or **24**, respectively. Subsequent (or concerted) termination by combination with NO (presumably *trans* to the oxide attack) and tautomerization of the resulting nitroso derivative (**25** or **26**) would give the oxido-oxime **12a**. Of the two possibilities, **26** is preferred over **25** on the basis of the relatively pronounced levorotation of **12**, which suggests the presence of an iso side chain.³⁷ However, the experimental data do not permit stereochemical assignment at this point.

(32) J. Fried and R. Thoma, U. S. Patent 2,799,690 (July 16, 1957).

(33) 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).

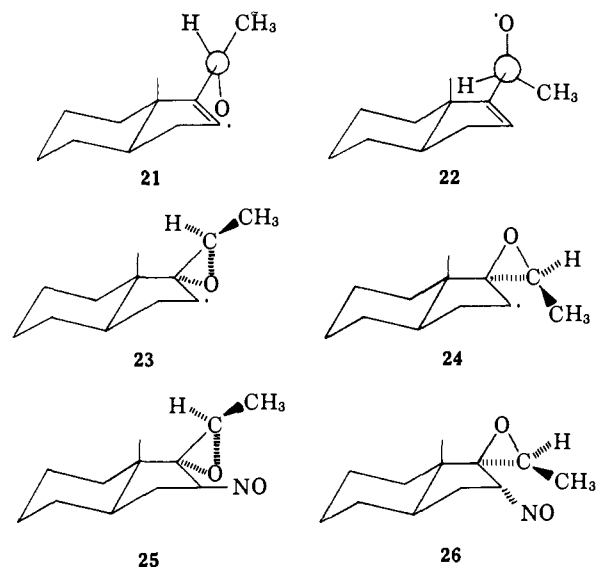
(34) Similar reasoning has been used to explain the greater yield during the radiation of 20 α - over 20 β -nitrites,²⁴ and has also been discussed for lead tetraacetate oxidations: cf. G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **44**, 518 (1961).

(35) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961).

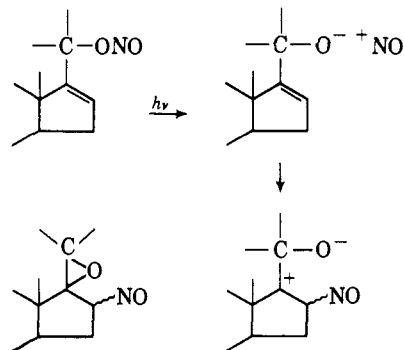
(36) K. Heusler, J. Kalvoda, G. Auner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).

(37) N. Danieli, Y. Mazur, and F. Somdheimer, *J. Am. Chem. Soc.*, **84**, 875 (1962), and references quoted therein. The argument is weakened by the fact that trigonal carbon C-16 itself has a levorotatory contribution, e.g., **20** ($R = O$) has $[\alpha]^{25D} = +37$ ($CHCl_3$).³² However, there is a distinct additional negative increment; **12a** has $[\alpha]^{25D} = -42.8$ ($CHCl_3$): see Experimental.

Scheme III



Whether these mechanistic ideas represent the actual state of affairs remains to be demonstrated by more direct criteria. Other possibilities exist. Thus, it might be assumed that an NO free radical generated during photolysis adds first at the least hindered end of the double bond. The resulting diradical could then easily collapse to form the epoxide.³⁸ Alternatively, a purely ionic addition of NO^+ (also of photolytic origin) to the double bond could similarly be postulated.³⁹



However, in view of the generally consistent picture of homolytic fission during nitrite photolyses,⁴⁰ we feel that an ionic mechanism is unlikely.

Experimental⁴¹

17 ξ ,20 ξ ,*-Oxido-16-oximino-4-pregnen-3-one (12a)*.

A. Nitrite Formation. 20 β -Hydroxy-4-16-pregnadien-3-one¹⁸ (**11b**, 4.09 g.) was dissolved in 40 ml. of dry pyridine and cooled to -25° . A freshly prepared solution of nitrosyl chloride in pyridine (about 1:5) was added dropwise, with stirring, moisture being excluded. The color of the reagent was immediately discharged until the appearance of a persistent powder

(38) Personal communication, Professor J. R. Shelton.

(39) Dr. A. Afonso of these Laboratories suggested this possibility. Such an ionic mechanism is closely related to the ideas expressed by R. M. Moriarty and K. Kapadia, *Tetrahedron Letters*, 1165 (1964).

(40) M. Akhtar and M. M. Pechet, *J. Am. Chem. Soc.*, **86**, 265 (1964).

(41) All melting points were taken on a Kofler Block, except where indicated, and are uncorrected. Rotations were carried out in a 1-dm. tube at a concentration of ca. 1% in the solvent specified. Analyses and spectral data were obtained by the microanalytical and physical chemistry departments of these laboratories.

blue tint indicated the end point. A few drops of excess reagent were added (the color turned orange, then brown) and the solution was allowed to stir for another 5 min. The reaction was then quenched with 800 ml. of ice water. The resulting white precipitate was filtered and dried at room temperature overnight, yielding 4.3 g. of the nitrite ester **11b**. It was less polar than the starting material ($R_f = 0.9$ in a ligroin-toluene (1:1)-propylene glycol system, **11a** having $R_f = 0.52$), and had a positive nitrite color reaction with the diphenylamine-hydrochloric acid reagent. The material could not be recrystallized without decomposition, and had $[\alpha]^{23D} +104^\circ$ (CHCl_3 , 1% pyridine). It was used in the next step without further purification.

B. Photolysis. The nitrite **11b** was dissolved in 190 ml. of benzene containing 1% pyridine, dried over sodium sulfate, and filtered into a photolysis vessel.⁴² It was then irradiated for 1 hr. under nitrogen, at 10° , by a 200-w. low-pressure mercury arc. A spot test indicated complete disappearance of the nitrite, and the solution was concentrated *in vacuo* at 50° . The oily residue was triturated with acetone, and the resulting oxidooxime (**12a**, 918 mg., homogeneous by paper chromatography) was removed by filtration. The filtrate was concentrated to dryness and dissolved in 200 ml. of methylene chloride, and the solution was washed with 5% hydrochloric acid, 5% sodium bicarbonate, and water, dried over sodium sulfate, and decolorized with charcoal. Crystallization from acetone gave another 161 mg. of the oxidooxime, total yield 1.079 g. Several recrystallizations from acetone or isopropyl ether gave an analytical sample, m.p. $211-225^\circ$; $E_{239.5} = 17,700$; $[\alpha]^{22D} -56.7^\circ$ (dioxane), -42.8° (CHCl_3); $\lambda^{\text{Nujol}} 3.09, 6.08, \text{ and } 6.24 \mu$; the material gave no color with tetranitromethane or ferric chloride; $R_f = 0.25$ (ligroin-toluene (1:1)-propylene glycol).

Anal. Calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_3$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.65; H, 8.19; N, 4.00.

An *acetate* (**12b**) of this oxime was prepared in the usual manner; 150 mg. of VII was dissolved in 6 ml. of pyridine, and 3 ml. of acetic anhydride was added. After standing for 2 hr. at room temperature the solution was precipitated in 200 ml. of ice water, and filtration gave 142 mg. of a product which appeared homogeneous ($R_f = 0.80$ in the ligroin-toluene (1:1)-propylene glycol system) by paper chromatography. Three recrystallization from acetone-hexane gave an analytical sample, m.p. $173-177^\circ$; $E_{237.5} = 18,500$; $\lambda^{\text{Nujol}} 5.67, 6.08, 6.24, 7.9, 8.08, 8.22, 8.38, \text{ and } 8.48 \mu$; $[\alpha]^{25D} -74.2^\circ$ (CHCl_3).

Anal. Calcd. for $\text{C}_{23}\text{H}_{31}\text{NO}_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.33; H, 7.94; N, 3.49.

Product 13 of the Reaction of 17 ξ ,20 ξ -Oxido-16-oximino-4-pregnen-3-one (12a) with Manganese Dioxide. Oxidooxime (**12a**, 301.9 mg.) was dissolved in 60 ml. of chloroform and 6.0 g. of manganese dioxide (Beacon Chemical Industries Inc., Cambridge, Mass.) was added. The suspension was stirred for 1 hr. at room temperature, filtered, concentrated to an oily residue,

and chromatographed on Florisil. Elution with benzene and benzene-ether gave 130 mg. of a new substance (**13**). Recrystallization from acetone-isopropyl ether gave an analytical sample; m.p. $199-204^\circ$; $E_{239.5} = 15,400$; $\lambda^{\text{Nujol}} 5.72, 5.99, \text{ and } 6.18 \mu$; $[\alpha]^{25D} -110.8^\circ$ (CHCl_3); $R_f = 0.53$ in ligroin-propylene glycol. (In this system, the starting material remains at the origin.) The ferric chloride, Zimmermann, and cupric acetate tests were all negative (thus eliminating a 16-oximino-17-one). The material, again unlike an oxime, was neutral in a nonaqueous titration study.⁴³

Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_2$: C, 76.41; H, 8.72; N, 4.57. Found: C, 76.22; H, 8.42; N, 4.68.

Treatment of this material with hydroxylamine hydrochloride in pyridine gave a product which did not retain either the band at 5.72μ (!) nor those assigned to the α, β -unsaturated ketone in the infrared.

17 ξ -Hydroxy-20 ξ -methoxy-16-oximino-4-pregnen-3-one (14a). 17 $\xi, 20\xi$ -Oxido-16-oximino-4-pregnen-3-one (**12a**, 100 mg.) was dissolved in 50 ml. of a methanolic solution of potassium hydroxide (5 g. of potassium hydroxide in 5 ml. of water made up to 100 ml. with methanol) and refluxed, under nitrogen, for 1 hr. The base was neutralized with acetic acid and 100 ml. of water was added. After vacuum concentration to remove most of the methanol, the aqueous suspension was extracted with methylene chloride, and the extract was washed with water, dried, and concentrated. The remaining oil showed four spots in the benzene-formamide system, $R_f = 0.40, 0.28, 0.19, \text{ and } 0.06$. (The starting material had $R_f = 0.59$ in this system). Chromatography over Florisil resulted in the isolation of the least polar constituent (**14a**, $R_f = 0.40$) from the benzene-ether eluates. Crystallization of the combined fractions from ethyl acetate gave 10.5 mg., m.p. $238-244^\circ$; $\lambda^{\text{Nujol}} 2.84, 3.12, 3.23, 6.03, \text{ and } 6.18 \mu$; $[\alpha]^{25D} -34.8^\circ$ (CHCl_3).

An *acetate* (**14b**), prepared in the usual manner, crystallized from acetone-isopropyl ether, had m.p. $161-163^\circ$; $\lambda^{\text{Nujol}} 2.96, 5.68, 6.02, 6.21, 8.11, \text{ and } 8.39 \mu$.

Anal. Calcd. for $\text{C}_{24}\text{H}_{35}\text{NO}_5$: C, 69.03; H, 8.45; N, 3.35; OCH_3 , 7.42. Found: C, 68.86; H, 9.00; N, 3.53; OCH_3 (Zeisel), 6.38.

16-Oximino- Δ^4 -pregnene-3,20-dione (15a). 17 $\xi, 20\xi$ -Oxido-16-oximino-4-pregnen-3-one (**12a**, 1.98 g.) was dissolved in 100 ml. of dioxane and 100 ml. of 10% aqueous potassium hydroxide was added. The two-phase system was allowed to reflux for 12 min. under nitrogen, with vigorous stirring, then cooled and neutralized with acetic acid. The layers were partitioned between water and methylene chloride and the organic phase was dried and concentrated. The residual oil was a mixture of at least six substances (paper chromatography showed spots at $R_f = 0.87, 0.70, 0.29$ (major), 0.16, 0.05, and 0.01 in the benzene-formamide system, where the starting material had $R_f = 0.59$, *vide supra*). Chromatography on Florisil allowed isolation of the major ($R_f = 0.29$) spot from the 40% ether-benzene eluates. Recrystallization from methylene chloride-isopropyl ether gave 307 mg. of **15**. An analytical sample had m.p. $244-248^\circ$; $E_{239.5} = 17,400$; $\lambda^{\text{Nujol}} 3.04, 5.87, 6.04, \text{ and } 6.20 \mu$.

(43) We wish to thank Mr. J. McGlotten for these measurements.

(42) A Hanovia ultraviolet lamp, Model 654-A-36, was utilized as an energy source. The Pyrex jacket on the immersion well limited the light entering the photolysis cell to wave lengths above $300 \mu\text{m}$. See P. Kabasakalian and E. R. Townley, *J. Am. Chem. Soc.*, **84**, 2711 (1962).

Anal. Calcd. for $C_{21}H_{29}NO_3$: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.35; H, 8.83; N, 3.53.

An acetate (**15b**), not further characterized, had λ^{CHBr_3} 5.65, 5.86, 6.03, and 6.19 μ .

16 α -Hydroxy-5-pregnene-3,20-dione Acetate Bisethylene Ketal (**19**, R = Ac). *16 α -Acetoxy-4-pregnene-3,20-dione*^{28,31} (**18**, R = Ac, 500 mg.) was dissolved in 45 ml. of benzene. Ethylene glycol (10 ml.) and *p*-toluenesulfonic acid monohydrate (30 mg.) were added, and the two-phase system was refluxed for 4 hr., water being continuously removed by means of a Dean-Stark trap. At the end of the reaction period, the mixture was cooled and neutralized with a saturated sodium bicarbonate solution and partitioned between water and methylene chloride. The organic layer was dried and concentrated. Crystallization from acetone-petroleum ether (b.p. 60–90°) gave 547 mg. of the bis-ketal acetate **19** (R = Ac),²⁷ m.p. 234–237°.

16 α -Hydroxy-5-pregnen-3,20-dione Bisethylene Ketal (**19**, R = H). The foregoing acetate (**19**, R = Ac, 490 mg.) was refluxed under nitrogen for 2 hr. in 40 ml. of a solution consisting of 5 g. of potassium hydroxide dissolved in 5 ml. of water made up to 100

ml. with methanol. After cooling, the pH of the solution was adjusted to 8 with acetic acid, the solution was concentrated to incipient crystallization under vacuum, and water was added. The resulting crystals were filtered and recrystallized from acetone-petroleum ether to give 246 mg. of **19** (R = H),²⁸ m.p. 197–202°.

Deketalization of 16-Oximino-5-pregnene-3,20-dione Bisethylene Ketal. 16-Oximino-5-pregnene-3,20-dione bisethylene ketal²⁷ (**16**, R = NOH, 85.5 mg.) was dissolved in 1 ml. of 90% acetic acid and heated to 100° for 12 min. The solution was cooled and carefully neutralized with sodium bicarbonate solution and extracted with methylene chloride, and the extract was washed with water, dried, and concentrated. The resulting mixture of substances was chromatographed on 1.5 g. of Florisil, using 10-ml. eluates. After removing an oil with benzene, the desired 16-oximino-4-pregnene-3,20-dione (**15**) was eluted with 30% ether-benzene. A crude yield of 9.5 mg. gave 5.9 mg. after recrystallization from methylene chloride-isopropyl ether, identical with the photolysis transformation product **15a** (*vide supra*) by melting and mixture melting points, R_f , and infrared spectrum.

The Methanolysis of Some D-Arabinofuranosyl Halides Having a Nonparticipating Group at Carbon 2

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The rates of methanolysis of three 2-O-nitro-3,5-di-O-p-nitrobenzoyl-D-arabinofuranosyl halides have been measured and the proportions of anomeric products formed have been analyzed by gas-liquid chromatography; the evidence adduced indicates that an S_N1 mechanism operates in these solvolyses, and that the stability of the intermediate ion pair has a strong influence on the configuration of the products. The possible role of participation by acyl groups at C-3 and C-5 in the nucleophilic displacement of the halogen in pentofuranosyl halides is discussed. The solvolysis of pentofuranosyl halides lacking a participating group at C-2 favors the 1,2-cis product in the cases examined; it is possible that this may be generally true irrespective of the configuration of the halide.

Owing to the central role which they play in a large variety of syntheses, the fully acylated glycosyl halides have been the subject of many investigations.² In recent years, particular attention has been given to the mechanism of the solvolysis of these halides,^{3–7} and it

appears established that an S_N1 type reaction is normally involved but that, with certain nucleophiles and with solvents of low polarity, some S_N2 character is manifest. Those halides bearing an acyloxy group at C-2 *cis* to the halogen at C-1 normally react with inversion while the corresponding *trans* halides react with predominant retention of configuration, the acyl group at C-2 participating in the nucleophilic displacement. Thus, from a practical synthetic point of view, aldose derivatives having a substituent at C-1 *trans* to that at C-2 are readily accessible whether the parent halide is *cis* or *trans*. On the other hand, the synthesis of the anomeric *cis* derivatives, many of which are of biochemical interest, often presents a difficult problem. One approach to the synthesis of such substances is through the use of glycosyl halides which are fully masked by nonparticipating groups or masked by such only at C-2, the remainder being masked by acyl groups. We have recently listed a number of halides of this latter type which have been reported in the literature.⁸

(1) Visiting Scientist in the Visiting Program of the National Institutes of Health, 1962–1965.

(2) L. J. Haynes and F. H. Newth, *Advan. Carbohydrate Chem.*, **10**, 207 (1955).

(3) F. H. Newth and G. O. Phillips, *J. Chem. Soc.*, 2896, 2900, 2904 (1953).

(4) R. U. Lemieux and G. Huber, *Can. J. Chem.*, **33**, 128 (1955).

(5) G. L. Mattok and G. O. Phillips, *J. Chem. Soc.*, 1836 (1956); G. L. Mattok and G. O. Phillips, *ibid.*, 268 (1957).

(6) R. U. Lemieux and A. R. Morgan, *J. Am. Chem. Soc.*, **85**, 1889 (1963).

(7) B. Capon, P. M. Collins, A. A. Levy, and W. G. Overend, *J. Chem. Soc.*, 3242 (1964).