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SOME RECENT DEVELOPMENTS IN THE PREPARATIVE PHOTOLYSIS OF ORGANIC NITRITES

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INTRODUCTION

THE use of photochemical reactions in preparative organic chemistry[1] has increased considerably during the last twenty years. Many structures accessible only with difficulty by more conventional means have been made available by the agency of radiant energy.

One of the most common primary photochemical processes is the homolytic dissociation of an appropriate bond to give rise to two fragments each containing an unpaired electron. The subsequent fate of these free radicals determines the synthetic usefulness of such photochemical processes.

It would appear that the nitrogen-oxygen bond in organic nitrite esters is particularly susceptible to homolysis. The latter process does not necessarily have to result from photochemical activation: on the contrary, most of the literature on the decomposition of nitrites describes pyrolytic procedures. In the present review, however, special emphasis will be given to photolysis, since the fragments thereby produced are endowed with sufficient energy[2] to result in subsequent behavior not otherwise attainable.

In fact, a very recent development in the field is the photolytic decomposition of nitrites to alkoxy radicals, followed by a stereoselective intramolecular hydrogen abstraction by the latter and recombination of the resulting carbon radicals with NO to form nitrose-monomers, dimers or oximes. This novel course we shall designate the *Barton Reaction*, in honor of the inventor, and experiments central and peripheral to its nature will form the core of this review.

EARLY WORK

The photochemistry of organic nitrites seems to have been investigated first by Thompson and his colleagues. Preliminary studies were reported[3] by Purkis and Thompson in 1936, and in the following year Thompson and Dainton described[4] the vapour-phase irradiation of primary, secondary, and tertiary alkyl nitrites, using both

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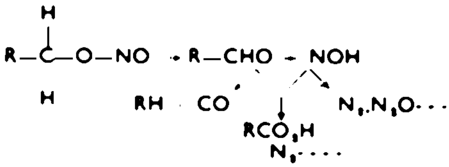
[1] For an elegant review of the entire subject, see A. Schonberg, *Präparative Organische Photochemie*, a monograph of the series *Organische Chemie in Einzeldarstellungen* (Edited by H. Bredereck and E. Müller). Springer Verlag, Berlin, Gottingen, Heidelberg, (1958). More of a bird's eye view exists in English. A chapter entitled "Photochemical Reactions" by C. R. Masson, V. Boekelheide and W. Albert Noyes appears in *Technique of Organic Chemistry* (2nd Ed., Edited by A. Weissberger) Vol. II. Interscience, New York (1956).

[2] See a recent article entitled "Optical Pumping" by A. L. Bloom, *Sci. Amer.* 203, 72 (1960).

[3] C. H. Purkis and H. W. Thompson, *Trans. Faraday Soc.* 32, 1466 (1936).

[4] H. W. Thompson and F. S. Dainton, *Trans. Faraday Soc.* 33, 1546 (1937).

the full mercury arc and filtered radiation.[5] Their qualitative data were interpreted on the basis of decomposition to the NOH radical, together with an aldehyde, ketone or unsaturated hydrocarbon (or a combination of these):



This interpretation of nitrite photolysis differed from the mechanism which had already been proposed[6,7] for gas-phase *pyrolysis* of organic nitrites, namely O—NO fission (as the primary step) giving an alkoxy radical and NO, followed by the formation[8] of carbonyl compounds and alcohols (disproportionation)

e.g.
$$RCH_2O{-}NO \rightarrow RCH_2O\cdot + NO$$
$$2RCH_2O\cdot \rightarrow RCHO + RCH_2OH$$

The Thompson-Dainton mechanism for nitrite photolysis remained untested for eleven years until Coe and Doumani[9] re-investigated the vapor phase photolysis of t-butyl nitrite, using a mass spectrometer for analysis of the gaseous products. The initial decomposition products, acetone and nitrosomethane,[10] were accounted for by a primary dissociation as shown:

$$(CH_3)_3C{-}ONO \rightarrow (CH_3)_2CO + CH_3NO$$

Not only is the production of acetone and nitrosomethane at variance with the mechanism originally[4] proposed for nitrite photolysis, but the products required by that mechanism were shown to be absent by mass spectrometric analysis.

In 1952, Gray and Style[11] examined the photolysis of methyl nitrite over a wide temperature range, using filtered mercury vapor radiation, and proposed, as the primary step, O—NO fission analogous with the Steacie mechanism for nitrite pyrolysis.

A more extensive investigation,[12] reported by Tarte, involved the photolysis of primary, secondary and tertiary alkyl nitrites. Two decomposition mechanisms were considered. The first, like the proposal of Gray and Style, requires O—NO homolysis as the initiating step. Nitrosoalkanes can then be formed either through recombination or secondary reactions between radicals and other nitrite molecules.

The alternative pathway (preferred by Tarte) is identical to that suggested by Coe and Doumani and invokes molecular rearrangement leading *directly* to nitrosoalkanes

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[5] The filtered radiation consisted of the 3650, 3655 and 3663 Å triplet, which is absorbed by the nitrite group but should not lead to subsequent photolysis of ketonic and aldehydic reaction products.

[6] E. W. R. Steacie and G. T. Shaw, *J. Chem. Phys.* 2, 345 (1934) and subsequent papers. See also E. W. R. Steacie, *Atomic and Free Radical Reactions* (2nd Ed.) Vol. I, p. 239. Reinhold, New York (1954).

[7] F. O. Rice and F. L. Radowskas, *J. Amer. Chem. Soc.* 57, 350 (1935).

[8] These pyrolysis studies were confined to primary and secondary lower alkyl nitrites. Subsequent investigations have encompassed the pyrolysis of both tertiary and higher molecular weight alkyl nitrites, and it is now recognized that alkyl radicals and nitrosoalkanes also result from such pyrolyses. See P. Gray, P. Rathbone and A. Williams, *J. Chem. Soc.* 3932 (1960) for a summary of the recent literature on nitrite pyrolyses.

[9] C. S. Coe and T. F. Doumani, *J. Amer. Chem. Soc.* 70, 1516 (1948).

[10] Rapid dimerization of the nitrosomethane was observed.

[11] J. A. Gray and D. W. G. Style, *Trans. Faraday Soc.* 48, 1137 (1952).

[12] P. Tarte, *Bull. Soc. Roy. Sci. Liège* 22, 226 (1953).

and carbonyl compounds. The latter workers had objected to the existence of methyl free radicals in the photolysis of t-butyl nitrite because of the absence of detectable amounts of ethane.

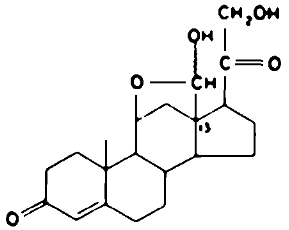
Gowenlock and Trotman[13] also scrutinized the gas phase photolytic decomposition of alkyl nitrites. Their product analysis was limited to ultraviolet absorption measurements which showed that nitrosoalkanes[14] were formed in low yield. Because these workers were particularly interested in the latter class of compounds and because of accompanying oxime formation their photolysis studies were not continued.

The photochemical investigations surveyed above have provided two reaction pathways. These two apparently distinct interpretations—i.e. intramolecular decomposition with direct generation of nitrosoalkane and a carbonyl compound vs. initial homolysis of the O—NO bond to give an alkoxy radical and NO may be reconciled by postulating the following state of affairs: the nitrite does indeed suffer homolysis, and the resulting alkoxy radical may undergo rapid decay to give a carbonyl fragment and an alkyl radical. The latter, however, immediately combines with NO which is in close proximity to it, in preference to the alternative recombination with a more distant second alkyl radical. At any rate, nitrite photolyses are now believed to involve alkoxy radicals, and a substantial body of recent work[15] supports this point of view.

THE ALDOSTERONE PROBLEM

The current interest in nitrite photolysis which occasioned this essay arose from the application of such a photolysis to an efficient partial synthesis of aldosterone. This is not the first time that a preparative method of organic chemistry has found a fruitful area of development in the field of steroids: the use of N-bromosuccinimide[16] and of manganese dioxide[17] are notable examples of a similar nature; the importance of the steroids in biology and the advanced development of physical and chemical methods in structure correlation have made this class of compounds a favored proving ground for a variety of novel, or heretofore obscure, chemical transformations.

The powerful salt-retaining hormone of the adrenal cortex, aldosterone (I), differs from the great majority of steroids found in nature by virtue of oxygenation of the angular methyl group at C-13. This substituent exists in the form of a masked aldehyde.



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[13] B. G. Gowenlock and J. Trotman, *J. Chem. Soc.* 4190 (1955); 1670 (1956).

[14] The nitrosoalkanes produced by photolysis were assumed to be the same (on the basis of ultraviolet absorption maxima) as those formed by pyrolysis of the same nitrites.

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

[16] C. Djerassi, *Chem. Rev.* 43, 271 (1948).

[17] R. M. Evans, *Quart. Rev.* 13, 61 (1957).

In order to arrive at a synthesis of such a structure, the following approaches have been utilized:[18]

(A) Total synthesis from simple, non-steroidal starting materials. This requires resolution of a racemic mixture.

(B) Fission of ring D of a steroid precursor devoid of C-18 oxygenation, introduction of a desired substituent into an angular methyl group temporarily activated by adjacent substitution, followed by reconstitution of ring D. The latter operation has been beset by great difficulties.

(C) Utilization of naturally occuring steroidal structures already possessing functional substituents at the C-18 angular methyl group.

(D) Oxygenation of C-18 by enzymatic means.

(E) Novel chemical means duplicating this enzymatic selectivity for an isolated, non-activated angular methyl group.

For a variety of reasons, the last-named approach has proved to be the one by means of which a great portion of the available synthetic aldosterone has actually been synthesized. The problem, as stated in the review mentioned above,[18] was to find "neuartige partialsynthetische Methoden, die auf einer breiten Base eine direkte und selektive Substitution der reaktionsträgen Methylgruppe 18 von intakten Steroiden erlauben". A number of such methods have, in fact, been recently developed.

In general, means were chosen to generate a highly reactive species (free radical, diradical such as uncoupled carbonyl, carbene, or a cationic species such as RO$^+$) of high energy content, which was located close in space to the methyl group, thus permitting the desired direct and selective attack. These methods included the Hofmann-Löffler-Freytag reaction (transforming 20-amino compounds to conane derivatives), generation of carbene at C-21 via diazoketone with subsequent attack on C-18, photochemical cyclization by the irradiation of C-20 ketones and, most fruitfully, formation of 18,20-ether linkages by the action of lead tetraacetate on 20-hydroxy compounds. The more important factors which should be considered in reactions of the general type described are (1) availability of starting material, (2) specificity of the reaction for the desired site –i.e. the reaction should tolerate the presence of a variety of non-interfering functional groups in the molecule, thus permitting a short synthetic sequence, and (3) efficiency of the process selected to assure a high degree of conversion to the desired product.

These considerations led D. H. R. Barton to select nitrite photolysis as a potentially useful tool for the general end in view. As can be seen from the discussion above, nitrites are a good source of alkoxy radicals. Generation of such an alkoxy radical, suitably located within the framework of the relatively rigid steroid molecule, might result in intramolecular hydrogen abstraction from a preselected site. (The excited energy state of the alkoxide radical, as guaranteed by its photolytic origin, might make such abstraction predominate over the relatively trivial disproportionation to the ketone). The resulting carbon free radical would then decay in a characteristic manner and, depending which of the various possibilities were to predominate, might be useful in such special aims as aldosterone synthesis.

The experimental work, carried out at the Research Institute of Medicine and Chemistry (RIMAC) in Cambridge, Massachusetts, demonstrated that nitrite

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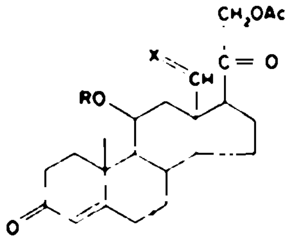
[18] This subject has been ably reviewed in a recent article by K. Schaffner, D. Arigoni and O. Jeger, *Experientia* 16, 169 (1960), which should be consulted for leading references.

photolysis did indeed result in intramolecular hydrogen abstraction from a desired site. Moreover, the resulting free radical underwent chain termination by recombination with NO, presumably the very NO generated by the original photolysis, to form the derived nitroso derivative isolated as the oxime. Thus, direct introduction of functionality into an unactivated position had been achieved; a functionality, moreover, which could be easily converted to an aldehyde or a variety of other chemical structures.

As applied specifically to the synthesis of aldosterone 21-acetate,[19] this involved the conversion of corticosterone acetate (2, $R = H$, $X = H_2$) to its nitrite (2, $R = NO$, $X = H_2$). Irradiation of the latter caused precipitation of aldosterone acetate oxime



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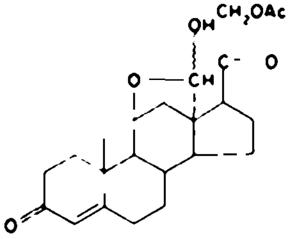

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(2, $R = H$, $X = NOH$) which was hydrolyzed to the desired aldosterone acetate (3) with nitrous acid.

RECENT DEVELOPMENTS

The remainder of this review will be devoted to a description of experiments which have been carried out at RIMAC and in the laboratories of the Schering Corporation with the aim of exploiting the Barton Reaction and delineating its scope. If nitrite photolysis does indeed give rise to alkoxide free radicals, then it would be useful to consider the following reactions from the point of view of alkoxide radical chemistry,[15] and we find it convenient to use the classification of Gray and Williams, as outlined in their excellent review. According to these authors, alkoxide radicals may react by any of the following pathways:

(1) Association with other radicals, including dimerization.
(2) Addition to unsaturated compounds.
(3) Hydrogen abstraction from another molecule.
(4) Disproportionation.
(5) Rearrangement, including internal hydrogen abstraction.
(6) Decomposition by carbon or hydrogen elimination.

Several of these pathways have been observed in nitrite photolysis and have already been described: we shall deal with others in due course.

The Barton Reaction is clearly an example of intramolecular hydrogen abstraction. Energetically, this is not a favored step, since "C—H bond fission is expected to play only a minor role in the decomposition of alkoxyl radicals."[20] However, the energy is not the only factor to be considered. McBay and Tucker[21] enumerate, in addition, a steric and a repulsion factor; clearly, the steric factor must play a very considerable role in the Barton Reaction, and in any case, the photolytic origin of the presumed

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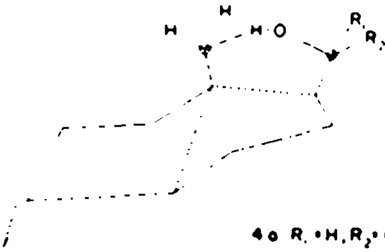
[19] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.* **82**, 2641 (1960).
[20] See ref. 15, p. 276.
[21] H. C. McBay and O. Tucker, *J. Org. Chem.* **19**, 869 (1954).

alkoxy radical, because of the high energy content of the latter, would be expected to facilitate pathways otherwise thermodynamically unfavorable.

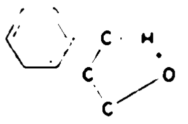
A more detailed consideration of the steric factors involved in intramolecular hydrogen abstraction suggest the existence of a six-membered transition state (4).



4 a $R_1 = H, R_2 = CH_3$
b $R_1 = CH_3, R_2 = H$

Structures of this type were first proposed by Davis and Noyes[22] in connection with the irradiation of ketones, and have recently been discussed by Yang[23] and the Swiss authors previously quoted.[18] Such a concept would predict attack on the hydrogen of a carbon atom removed by two from that holding the active abstractor, a course which is actually observed. Incidentally, a transition state as pictured in 4 would also help to explain the observation[24] that the yield of 18-oxime from a 20α-nitrite is much higher than from the corresponding 20β-isomer: examination of the model (4) shows that the proposed transition state of the former (a) is sterically preferable to the latter (b), since in 4a the bulkier methyl group points away from the rest of the molecule, whereas in 4b distinct hindrance with the rear of the steroid molecule, especially at C-12, is manifestly observed.[25]

Conclusive support for the formation of a six-membered transition state in the Barton Reaction comes from the work of Kabasakalian *et al.*[26] who studied the photolysis of aromatic alkyl nitrites in solution. 3-Phenyl-1-propyl nitrite did not give rise



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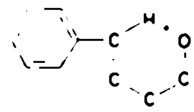

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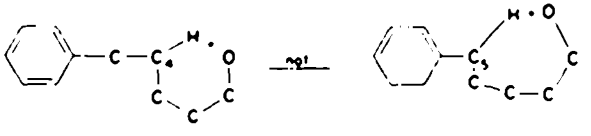

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[22] W. Davis, Jr. and W. A. Noyes, Jr., *J. Amer. Chem. Soc.* **69**, 2153 (1947).

[23] N. C. Yang and D. D. H. Yang, *J. Amer. Chem. Soc.* **80**, 2913 (1958).

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

[25] L. Velluz, G. Muller, R. Bardoneschi and A. Poittevin, *C. R. Acad. Sci., Paris* 725 (1960), in a reaction which generates a C18 → C20 ether bridge by means of lead tetraacetate and which must also involve conformational considerations of the kind here outlined, report considerably higher yields from the 20α- than from the 20β-isomer. *Note added in proof.* This has now been rationalized in a manner identical to ours. *Cf.* G. Cainello, B. Kamber, J. Keller, M. Lj. Mihailovic, D. Avigoni and O. Jeger, *Helv. Chim. Acta* **44**, 518 (1961).

[26] P. Kabasakalian, E. R. Townley and M. D. Yudis, in preparation.

to any nitroso dimer: the postulated 5-membered ring transition state (5) apparently did not form, in spite of the predicted ease of benzyl-hydrogen abstraction. 4-Phenyl-1-butyl nitrite can form a six-membered transition state (6) and isolation of the corresponding nitroso-dimer supports this view. A particularly intriguing instance is the next higher homologue, 5-phenyl-1 pentyl nitrite. This compound undergoes hydrogen abstraction at C-4 (7) rather than C-5 (8); apparently the advantages to be gained from a six-membered vs. a seven-membered complex outweigh the greater ease of benzyl-hydrogen abstraction.

We shall now proceed to enumerate systematically the results so far obtained in an investigation of the Barton Reaction.

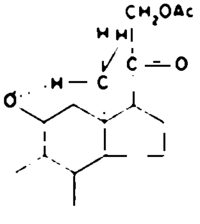
I. INTRAMOLECULAR HYDROGEN ABSTRACTION

A. *Termination with* NO

1. *Formation of oxime*

The recombination of a carbon radical with NO is not unprecedented: NO is a well-known radical trap.[27] The resulting monomeric nitroso compound may then dimerize (see next section) or rearrange to the oxime. Such recombinations have been observed for a large number of cases, the mode of alkyl radical generation ranging ranging anywhere from the thermal decomposition of peroxides[28] or alkyl mercury derivatives[29] to the direct irradiation of certain organic compounds by means of γ-rays.[30] The process in which alkyl free radicals are generated by irradiation of hydrocarbons in the presence of nitrosyl chloride to give oximes was first described by Lynn,[31] and this and related procedures have been investigated in great detail by Müller and his school;[32] eventually an economically important synthesis of cyclohexanone oxime resulted.

The Barton Reaction proper was first applied to steroids, as has already been discussed. In the aldosterone synthesis,[19] hydrogen at C-18 is abstracted by an alkoxy radical at C-11β: the six-membered transition state 9 appears convincing. The postulated intermediate nitroso-monomer 10 resulting from recombination of the C-18 radical with NO does not dimerize, presumably because steric factors prevent the convergence of two steroid molecules, but rearranges to the oxime (2, X = NOH) instead.



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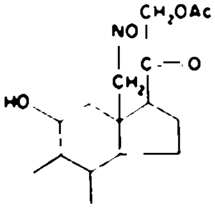

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[27] See N. N. Semenov, *Angew. Chem.* 69, 775 (1957). C. N. Hinshelwood, *Ibid* 69, 446 (1957).

[28] J. H. Raley, F. F. Rust and W. E. Vaughan *J. Amer. Chem. Soc.* 70, 88 (1948).

[29] W. A. Bryce and K. U. Ingold, *J. Chem. Phys.* 23, 1968 (1955).

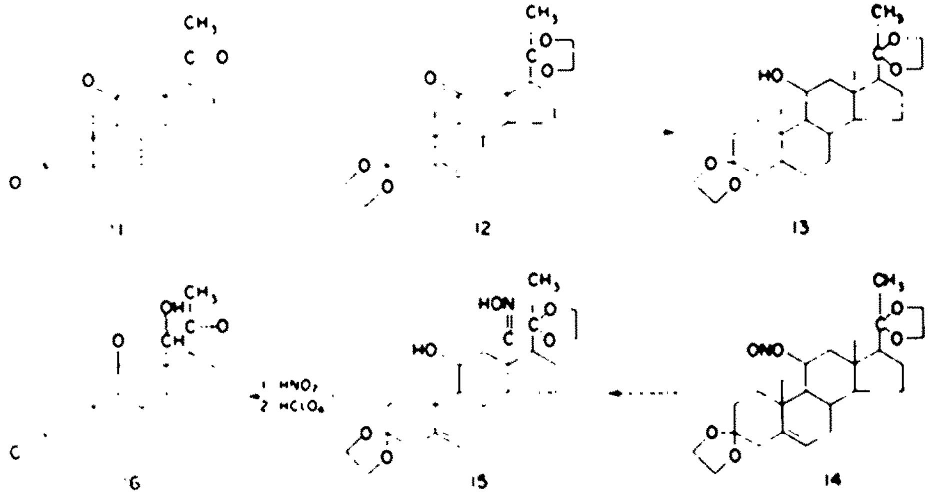
[30] A. Henglein, *Angew. Chem.* 72, 603 (1960).

[31] E. V. Lynn, *J. Amer. Chem. Soc.* 41, 368 (1919) and later publications.

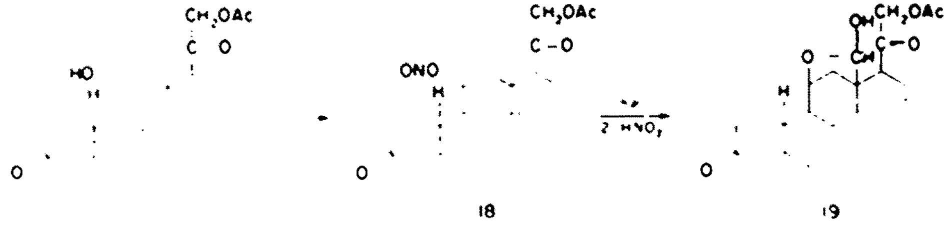
[32] E. Muller, H. Metzger, D. Fries, V. Heuschkel, K. Witte, E. Waidelich and G. Schmid, *Angew. Chem.* 71, 229 (1959).

Subsequently, this general procedure of attack at C-18 via the 11-nitrite was broadened and resulted in the synthesis of 21-desoxyaldosterone[33] (11-16) and 19-noraldosterone.[34] (17-19) Both syntheses are outlined in flow-sheet form.

21-Desoxyaldosterone



19-Noraldosterone



Incidentally, irradiation of steroidal 11β-nitrites does not necessarily result in exclusive attack at C-18: hydrogen abstraction from the other angular methyl group may result, as well; the 19-norcorticosterone used as a precursor (in form of its acetate) for 19-noraldosterone (17) arose from such a course.[34] Corticosterone 3,20-bisethyleneketal[35] was acetylated (20) and converted to the 11β-nitrite (21), which upon irradiation gave both the 18-oxime (22) and a non-crystalline 19-oxime (23). The latter, upon treatment with acid, gave the 19-isomer of aldosterone (24). Alkali treatment resulted in a retro-aldol elimination[36] to the known[37] 19-norcorticosterone (25).

Attack at C-18 is also possible from alkoxide radical at C-20. In their original

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[33] A. L. Nussbaum, G. Brabazon Topliss and E. P. Oliveto, unpublished data.

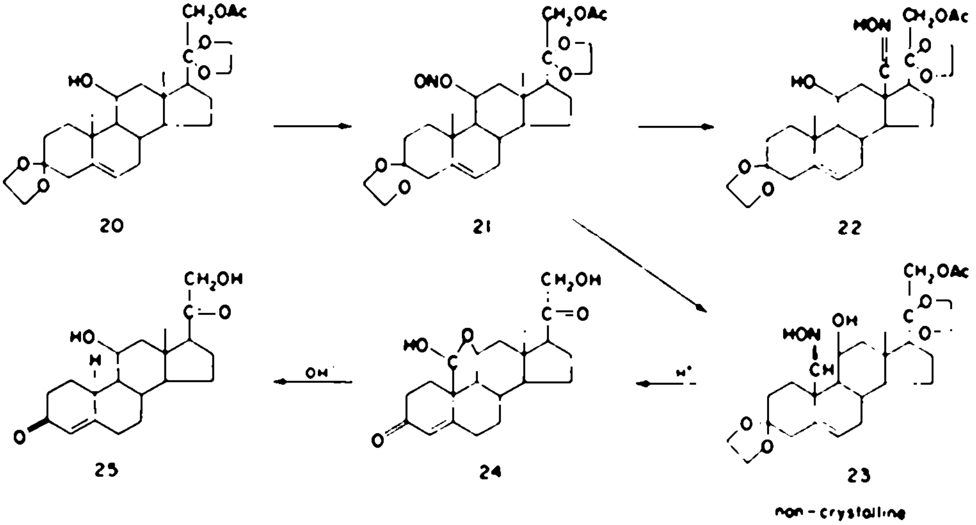
[34] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.* **83**, 750 (1961).

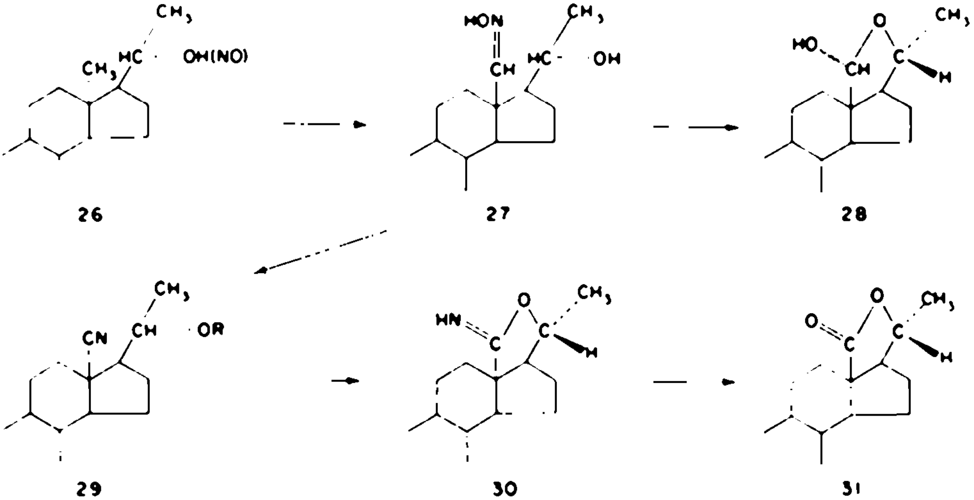
[35] S. Bernstein and R. H. Lenhard, *J. Amer. Chem. Soc.* **77**, 2331 (1955).

[36] *Cf.* D. H. R. Barton and P. DeMayo, *J. Chem. Soc.* 887 (1953). See esp. A. S. Meyer, *Experientia* **11**, 99 (1955).

[37] A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 6110 (1958).

19-Norcorticosterone





communication, Barton and co-workers[38] report such an attack and subsequent transformations as outlined (26–31).

The especially strategic location of substituents at C-20 for attack on the C-18 angular methyl group has, of course, been noted with a variety of other reactions[18] (*vide supra*). It was pointed out recently, however, that slight changes in bond angles (brought about by a trigonal C-11, for instance) might result in sufficient deformation of the molecule to vitiate the desired hydrogen abstraction.[39]

Incidentally, when the approach outlined (26–31) was carried out in the progesterone series, it was possible to prepare a number of substances useful in correlating several

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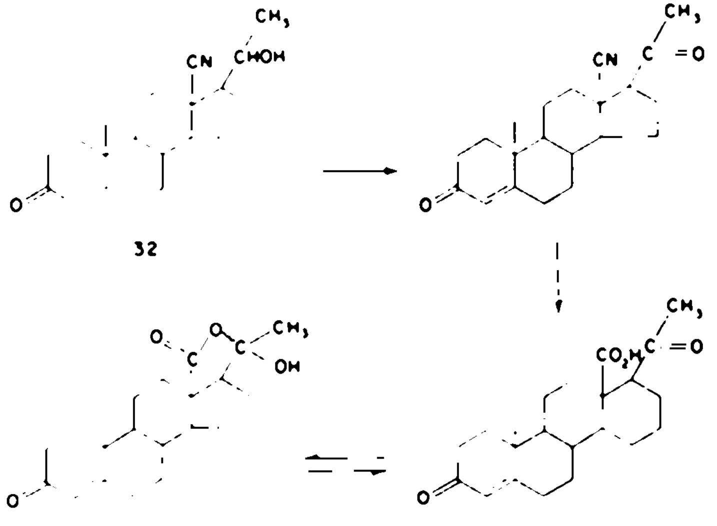
[38] D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Amer. Chem. Soc.* 82, 2640 (1960).

[38a] The photolysis products described in this review article are indeed the result of light-induced reactions rather than of thermal decomposition. thus was ascertained by performing the necessary controls.

[39] A. Bowers and E. Denot, *J. Amer. Chem. Soc.* 83, 4956 (1960)

independent lines of inquiry. Thus, oxidation and acid hydrolysis of the nitrile 32 (analogous to 29) gave rise to 3,20-diketo-4-pregnen-18-oic[24] acid 33 identical with a material derived from the steroidal alkaloid conessine.[40]



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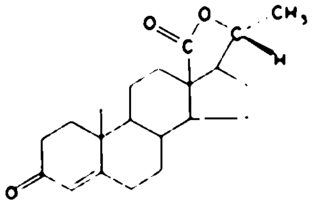
Similarly, hydrolysis and oxidation of the progesterone analogue of 27 (20β) gave the 20β-lactone 34, identical with a substance derived from holarrhimine.[41] Finally a corresponding hydrolytic oxidation of the isomeric 20α-oxime led to the 20α-lactone 35 also derived from paravallarine.[42,43]



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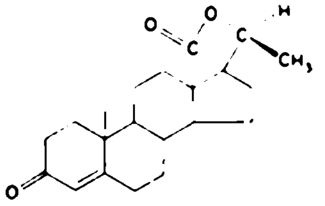

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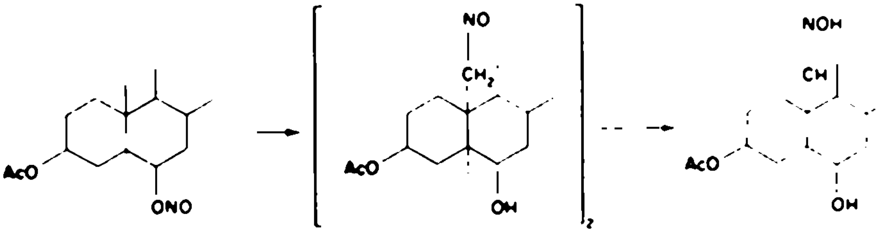
A third position in the steroid molecule investigated as to the course of nitrite



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[40] R. Pappo, *J. Amer. Chem. Soc.* **81**, 1011 (1959).

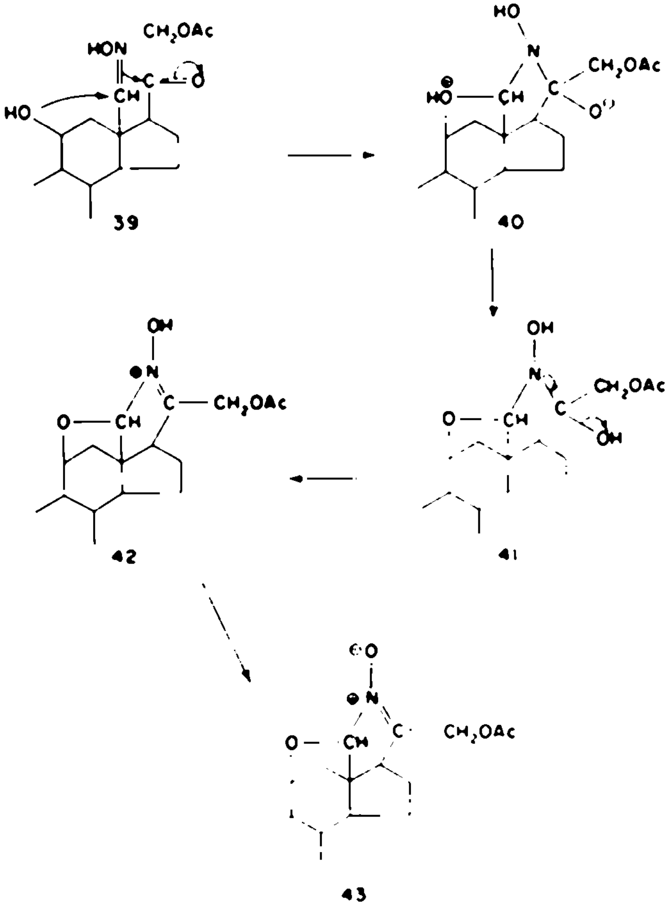
[41] L. Lábler and F. Šorm, *Chem. & Ind.* 935 (1960).

[42] J. LeMen, *Bull. Soc. Chim. (Fr.)* 860 (1960).

[43] Here, too, one of us (A.L.N.) wishes to thank Drs. Pappo and Lábler and Prof. LeMen for their kindness in either providing samples or carrying out the necessary comparison.

photolysis was C-6β.[38] The nitrite derived from cholestane-3β,6β-diol 3-acetate (partial 36) was irradiated,[38a] and the resulting nitroso dimer 37 (see below) was converted to the 19-oxime 38 by refluxing in 2-propanol. In this instance, as in all those preceding, a six-membered transition state would seem to be required for internal hydrogen abstraction.

As was stated earlier, the primary product of the Barton Reaction is considered to be a nitroso compound, which may either dimerize (see next section) or rearrange to the oxime. The latter substance, however, may itself react further under the proper circumstances. Thus, an examination[43a] of the mother liquors of the aldosterone 18-oxime obtained from the irradiation of corticosterone acetate 11-nitrite[19] (2, R = NO, X = H_2) showed the presence of nitrone; the latter was also obtained by thermal treatment or refluxing in methanol, of the oxime.[19] This transformation is pictured in 39–43.[43b]



[43a] J. M. Beaton, personal communication.

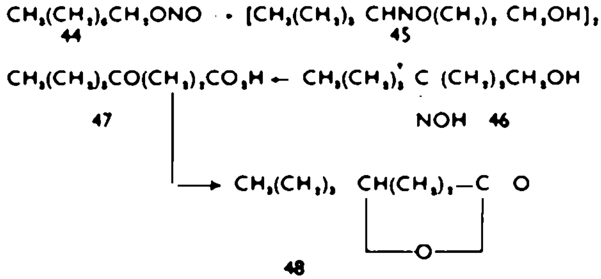
[43b] For nitrone formation from nitroso compounds, see W. J. Hickinbottom, *The Chemistry of Carbon Compounds* (Edited by E. H. Rodd) Vol IIIA, p 151 Elsevier, Amsterdam (1954).

2. *Formation of nitroso dimer*

Attention has already been called to the fact that the postulated monomeric nitroso compound resulting from the Barton Reaction may dimerize (see preceding section). An instance of this kind in the steroid series has been reported (*vide supra*, 37).

In the absence of steric factors unfavorable to dimerization of the intermediate mononitroso precursors, dimerization is indeed widely observed. P. Kabasakalian and his co-workers of these Laboratories have recently begun a detailed study of the photolysis of simple organic nitrite esters. In contrast to earlier work, their experiments were carried out in solution: this would presumably favor the Barton Reaction and interaction with solvent molecules. Rigorous qualitative identification of reaction products was carried out in many cases; in others, quantitative estimation by ultraviolet spectrometry was employed.

As an initial study,[44] the photochemistry of n-octyl nitrite (44) was investigated. When the reaction was carried out in heptane (no oxygen present), the principal product was found to be the dimer of 4-nitroso-1-octanol (45). The latter was thermally isomerized to oxime 46, which was oxidized and hydrolyzed to 4-ketoöctanoic acid (47). Reduction of the ketone gave a hydroxyacid convertible to the γ-lactone (48). These transformation products were known compounds[45] which had been prepared earlier in these Laboratories.



$$CH_3(CH_2)_6CH_2ONO \rightarrow [CH_3(CH_2)_3CHNO(CH_2)_2CH_2OH]_2$$

44 45

$$CH_3(CH_2)_3CO(CH_2)_2CO_2H \leftarrow CH_3(CH_2)_3\underset{NOH}{C}(CH_2)_2CH_2OH$$

47 46

$$\rightarrow CH_3(CH_2)_3\,CH(CH_2)_2-C{=}O$$

48

No substitution in any but the 4-position could be observed: this strongly supports the concept of a six-membered cyclic transition state. The notion that the initial step is dissociation of the nitrite to alkoxy radical and NO is buttressed by the finding that the addition of excess NO drastically reduces the quantum yield of the reaction: the reverse of the dissociation 44 to 49 would result in just that.

$$\underset{49}{CH_3(CH_2)_6CH_2O\cdot} + NO \rightleftharpoons \underset{44}{CH_3(CH_2)_6CH_2ONO}$$

The photochemistry of certain aromatic alkyl nitrites[34] has already been discussed (*vide supra*).

An examination of the yield of nitroso-dimers from photolysis of a variety of nitrites of diverse structure[46] led to the following observations:

(a) The Barton Reaction, leading to nitroso-dimers, always requires a six-membered ring transition state.

(b) Yields of nitroso-dimer[47] drop sharply when the hydrogen to be abstracted

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[44] P. Kabasakalian and E. R. Townley, *J. Amer. Chem. Soc.* In press.

[45] D. Papa, E. Schwenk and H. Ginsberg, *J. Org. Chem.* 14, 726 (1949).

[46] P. Kabasakalian, E. R. Townley and M. D. Yudis, *J. Amer. Chem. Soc.* In press.

[47] As determined by ultraviolet analysis; molar absorptivity of pure nitroso dimer is ca. 9500.

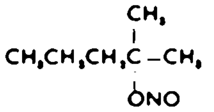
intramolecularly is primary rather than secondary or tertiary. (This drop is partially offset in the case of 4-heptyl nitrite (50), where the statistical availability of two

$$CH_3CH_2CH_2\underset{ONO}{CH}\,CH_2CH_2CH_3$$

50

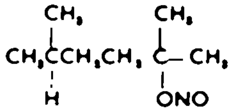
primary hydrogens provides compensation.) This is in accordance with the greater energy requirements of primary C—H bond rupture.[16]

(c) Nitroso-dimers may also be obtained by pathways different from the Barton Reaction, i.e. C—C bond fission (*vide infra*). This is apparent from product analysis, and begins to show up for some secondary nitrites. In the case of certain tertiary nitrites (i.e. where the hydrogen to be abstracted is primary), such competing pathways may operate. For example, 2-methyl-2-pentyl nitrite (51) does not readily undergo the Barton Reaction, whereas 2,5-dimethyl-2-hexyl-nitrite (52) does so in good yield.[48]



$$CH_3CH_2CH_2\overset{CH_3}{\underset{ONO}{C}}-CH_3$$

51



$$CH_3\overset{CH_3}{\underset{H}{C}}CH_2CH_2\overset{CH_3}{\underset{ONO}{C}}-CH_3$$

52

It should be pointed out that no nitroso dimers were obtained in the photolysis *in solution* of t-butyl, 1-propyl and ethyl nitrites. This is in contrast to earlier work[4,9,12,13] carried out in the *vapor phase*.

In addition to the application of the Barton Reaction to aliphatic, aromatic and steroidal compounds, this method has also been applied to a variety of special classes of substances. Tables 1 and 2 list two of these[49] together with the absorptivities due to the nitroso-dimers.

TABLE 1. NITROSO-DIMER FORMATION WITH SEVERAL ISOPRENOID NITRITES

Nitrite	a^{*}_{max}	λ
Farnesol	2000	288
Geraniol	2000	292
Menthol	4800	290
Citronellol	2700	294
Nerol	2800	294

* a_{max} ~9500 (for pure nitroso-dimer).

TABLE 2. NITROSO-DIMER FORMATION FROM NITRITES OF SOME FATTY ALCOHOLS

Nitrite	% Nitroso-dimer by U V
Dodecanol	29·2
Tetradecanol	37·2
Hexadecanol	55·2
Octadecanol	33·0

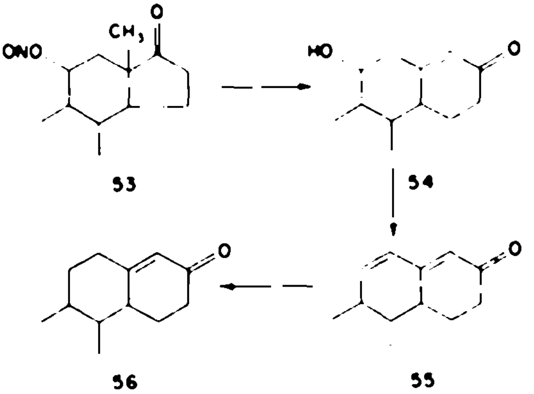
---

[48] The product of the Barton Reaction in this case is actually the 5-nitroso monomer. This seems to be generally true when tertiary hydrogens are abstracted.

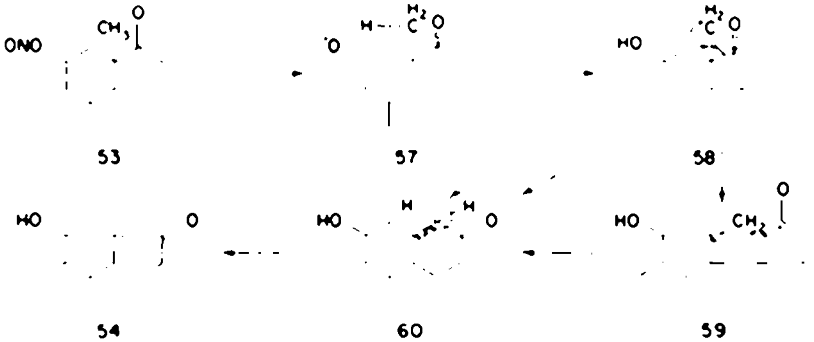
[49] P. Kabasakalian, unpublished work.

B. *Alkyl Radical Intermediate Rearrangement with C-C Fission: Termination by Loss of* H-*Atom*

We come now to a case which starts out as a typical Barton Reaction—a carbon radical is formed via the usual intramolecular hydrogen abstraction in the six-membered cyclic transition state—but the resulting alkyl radical does not recombine with NO: instead, a rearrangement takes place. Partial structure (53), when irradiated in toluene,[60] gave an α,β-unsaturated ketone which turned out to be the 18-nor-D-homosteroid (54), as proved by conversion to (55) and hydrogenation to the known 56.[61]



Sequence 53 to 54 is rationalized in the following manner:



(Arrows indicate single electron movements).

This mechanism is strengthened by writing the structure as depicted in partial formula (59): such relatively stable radicals have been implicated in the autoöxidation of benzaldehyde, etc.[62]

A possible alternative view would be the direct rearrangement (58) to (60).

The free radical rearrangement recently reported[63] as formally of the Wagner-Meerwein type would seem to be another example of the same order as the one here described.

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[60] H. Reimann, A. S. Capomaggi, T. Strauss, E. P. Oliveto and D. H. R. Barton, *J. Amer. Chem. Soc.* In press.

[61] The actual compound was 18-nor-D-homo-4,13(17a)-androstadiene-3,17-dione. See H. Heusser, J. Wohlfahrt, M. Müller and R. Anliker, *Helv. Chim. Acta* **42**, 2140 (1959).

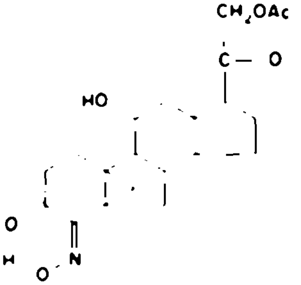
[62] W. A. Waters, *Physical Aspects of Organic Chemistry* (4th Ed.), p. 196. Van Nostrand, New York (1950).

[63] J. A. Berson, C. J. Olsen and J. Singh Walia, *J. Amer. Chem. Soc.* **82**, 5000 (1960).

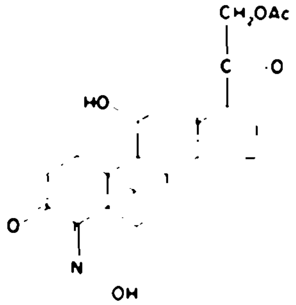
C. *Alkyl Radical Intermediate Rearrangement by Addition to an α,β-Unsaturated Ketone*

Another case commencing by intramolecular hydrogen abstraction but terminating by a path other than immediate recombination with NO has been encountered during nitrite photolysis.

Further examination[13a] of the mother liquors from the irradiation of corticosterone acetone nitrite[19] (2, R = HO, X = H_2) -already shown to contain nitrone 43 - yielded two additional products which, on the basis of subsequent structure elucidation work, were formulated as the α-oximinoketones 61 and 62.

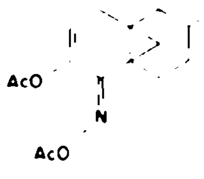


61

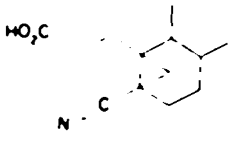


62

For detailed discussion, the original paper should be consulted, but some of the salient points may be mentioned. The less polar 61 could be converted to 62 by heat. Absence of the typical spectroscopic features of Δ^4-3-ones implicated ring A of the molecule. Consideration of the ultraviolet spectra permits the *syn* and *anti* assignments as shown, by analogy with the corresponding benzil monoximes, and infrared data support the assignment. Mild acetylation of 61 gave structure 63 with its rather typical behavior in the ultraviolet, whereas 62 underwent a second order Beckmann rearrangement, giving rise to a nitrilo-acid formulated as in 64. (Nitrile absorption is modified by conjugation with the cyclopropane ring.) This acid was also obtained

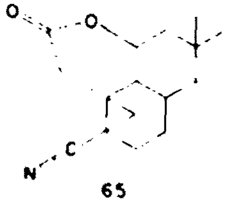


63



64

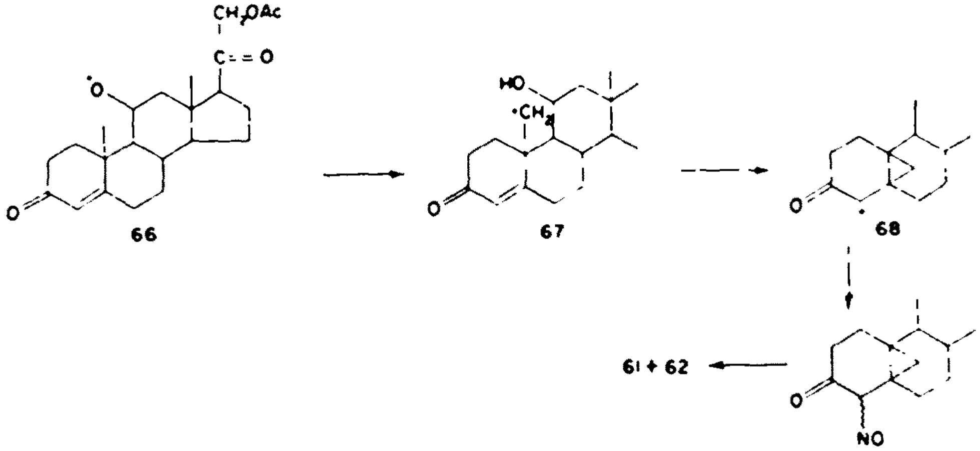
from both monoximes by use of $POCl_3$/pyridine. A slight change in the workup[64] gave instead a nitrilolactone, 65



65

The origin of these two keto-monoximes, 61 and 62, can be rationalized as follows:[65]

The alkoxide radical 66 abstracts a hydrogen atom from the C-19 angular methyl group to give the alkyl radical 67. The latter adds to the α,β-unsaturated system of



Ring A to generate another alkyl radical (68) having the unpaired electron at C-4. Recombination with NO gives 69 which rearranges to the two isonitroso derivatives 61 and 62.

Just as the foregoing rearrangement was considered formally analogous to that of Wagner–Meerwein, the rearrangement here discussed bears a corresponding resemblance to the Michael addition.

II. INTERMOLECULAR HYDROGEN ABSTRACTION

A commonly encountered product in the liquid-phase photolysis of a host of organic nitrites has been the corresponding alcohol. The propensity of alkoxy radicals for abstracting hydrogen from other molecules (e.g. solvent) is well documented,[66] and *inter*molecular hydrogen abstraction can be expected to compete with the *intra*molecular mode of hydrogen transfer (Section I) and indeed with all the decay reactions of an alkoxy radical:

$$R\cdot O + XH \text{ (e.g. solvent)} \rightarrow R{-}OH + X\cdot$$

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[64] Observation by H. Reimann of these Laboratories.

[65] Private communication from Dr. J. M. Beaton, Institute for Medicine and Chemistry, Cambridge, Massachusetts.

[66] See ref. 15, pp. 267–272 for a discussion of this topic.

However, the extent to which this undesirable competition occurs is greatly influenced by the nature of the solvent, as will be seen below. At this point, the reservation must be made that, in the case of primary and secondary alkoxy radicals, disproportionation reactions (i.e. hydrogen transfer from one radical to another) can also lead to alcohols (and, necessarily, carbonyl compounds; see Section III A) thus:

$$2R_1R_2CH{-}O\cdot \rightarrow R_1R_2C{=}O + R_1R_2CHOH$$

Striking evidence for intermolecular hydrogen abstraction has been secured recently from detailed studies with 1-octyl nitrite.[44] Photolysis of this nitrite, in benzene solution, gave as the major product dimeric 4-nitroso-1-octanol (the genesis of this nitrosodimer has already been discussed in Section I) together with lesser amounts of 1-octanol and 1-octanal. The formation of the two last-named products can be attributed to hydrogen abstraction (A) and disproportionation processes (B) as shown:

$$CH_3(CH_2)_6CH_2ONO \rightarrow CH_3(CH_2)_6CH_2O\cdot + NO$$

$$CH_3(CH_2)_6CH_2O\cdot + XH\ (\text{solvent}) \rightarrow CH_3(CH_2)_6CH_2OH + X\cdot \tag{A}$$

$$2CH_3(CH_2)_6CH_2O\cdot \rightarrow CH_3(CH_2)_6CH_2OH + CH_3(CH_2)_6CHO \tag{B}$$

The extent to which intermolecular hydrogen abstraction occurs will depend on the efficiency of the solvent (XH) as a hydrogen donor, and indeed studies with a variety of solvents show that the highest yield of 4-nitroso-1-octanol dimer (the product of *intra*-molecular hydrogen abstraction) occurs when benzene, a poor donor, is used.

With heptane as solvent, however, not only was 4-nitroso-1-octanol dimer (see Section I) formed, but other nitroso dimers were generated in appreciable quantities. These new products proved to be nitrosoheptane dimers and nitrosoheptane-4-nitroso-1-octanol *mixed dimers*. These results have been explained as follows (equations 1-6).

$$CH_3(CH_2)_6CH_2ONO \xrightarrow{h\nu} CH_3(CH_2)_6CH_2O\cdot + NO \tag{1}$$

$$\left.\begin{array}{l} CH_3(CH_2)_6CH_2O\cdot \rightarrow CH_3(CH_2)_2\underset{\cdot}{C}H(CH_2)_2CH_2OH \\ CH_3(CH_2)_2\underset{\cdot}{C}H(CH_2)_2CH_2OH + NO \rightarrow CH_3(CH_2)_2CHNO(CH_2)_2CH_2OH \end{array}\right|\ \text{Barton Reaction}\quad \begin{array}{r}(2)\\(3)\end{array}$$

$$\begin{array}{l} CH_3(CH_2)_6CH_2O\cdot + CH_3(CH_2)_4CH_2CH_3 \rightarrow CH_3(CH_2)_6CH_2OH \\ \qquad + CH_3(CH_2)_4\underset{\cdot}{C}HCH_3\text{—intermolecular hydrogen abstraction}^{14a} \end{array} \tag{4}$$

$$CH_3(CH_2)_4\underset{\cdot}{C}HCH_3 + NO \rightarrow CH_3(CH_2)_4CHNOCH_3 \rightarrow \text{dimer} \tag{5}$$

$$CH_3(CH_2)_4CHNOCH_3 + CH_3(CH_2)_3CHNO(CH_2)_2CH_2OH \rightarrow \text{mixed dimer} \tag{6}$$

The 2-nitrosoheptane formed according to equations 4 and 5 can dimerize either with another 2-nitrosoheptane molecule or with a molecule of 4-nitroso-1-octanol.

Substitution of toluene for heptane as solvent resulted (not unexpectedly) in the formation of dimeric ω-nitrosotoluene as well as 4-nitroso-1-octanol dimer.

III. DECOMPOSITION REACTIONS

A. C—H *Bond Fission*

The formation, without carbon skeleton change, of aldehydes and ketones from primary and secondary alkyl, alicyclic and aryl substituted nitrites has been widely observed:

$$RCH_2{-}ONO \xrightarrow{h\nu} RCHO$$

$$R_1R_2\,CH{-}ONO \xrightarrow{h\nu} R_1R_2CO$$

[14a] Abstraction from C-2 is here pictured. In actual fact statistical abstraction of the secondary hydrogens was observed.

These findings are conveniently explained either by alkoxy radical decomposition through loss of an α-hydrogen (e.g. equation 1) or by a disproportionation process (cf. Section II).

$$R_1R_2CH{-}O\cdot \rightarrow R_1R_2C{=}O + H\cdot \qquad (1)$$

It has been argued[57] that C–H bond fission should not be a major factor in the decomposition of alkoxy radicals, on the assumption (by analogy with alkyl radicals and normal molecules) that C–H fission will be energetically less favoured than C—C fission.

However, the generation of alkoxy radicals in dilute solution (as in the present work) will surely suppress the alternative disproportionation mechanism. This general effect can be supplemented, in particular cases, by factors of structural origin such as steric compression (as in the case of a steroidal 11β-alkoxy radical) or the difficulty of a fruitful collision between two alkoxy radicals because of nearby bulky groups (this would be particularly true in the steroid series where nitrosodimer formation is rarely seen, presumably for similar steric reasons; see Section IA).

In cases where these factors are all operative at one and the same time, it can therefore be supposed that C–H fission will predominate over disproportionation reactions.

B. C–C *Fission*

Previous sections of this review have dealt with the Barton reaction (together with deviations which nevertheless proceed *via* intramolecular hydrogen abstraction) and trivial competing reactions—hydrogen abstraction from solvent, disproportionation, C–H fission.

We shall now consider another reaction path which frequently competes with the Barton reaction, namely alkoxy radical decomposition by C—C cleavage:

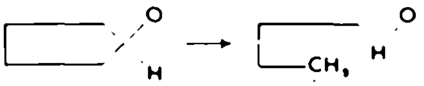
$$RCH_2O\cdot \rightarrow R\cdot + CH_2O \qquad (1)$$

$$R_1R_2CHO\cdot \rightarrow R_1\cdot + R_2CHO \text{ or } R_2\cdot + R_1CHO \qquad (2)$$

$$R_1R_2R_3CO\cdot \rightarrow R_1\cdot + R_2R_3CO \text{ or } R_2\cdot + R_1R_3CO \text{ or } R_3\cdot + R_1R_2CO \qquad (3)$$

In the case of alkoxy radicals derived from alicyclic nitrites, ring fission can occur as shown:

e.g.[58]



(4)

Specific examples for processes (1) to (4) will now be given.

1. *Primary alkoxy radical decomposition*

The surprising failure of ethyl and 1-propyl nitrites (which cannot furnish the 6-membered cyclic transition state needed for intramolecular hydrogen abstraction) to generate nitroso dimers in solution *via* C–C decomposition (equations 5–7) has already been noted [Section I A (2)].

$$R{-}CH_2{-}ONO \xrightarrow{h\nu} R{-}CH_2{-}O\cdot + NO \qquad (5)$$

$$R{-}CH_2{-}O\cdot \rightarrow R\cdot + CH_2O \qquad (6)$$

$$R\cdot + NO \rightarrow RNO \qquad (7)$$

Not observed where R is H, CH_3 or C_2H_5

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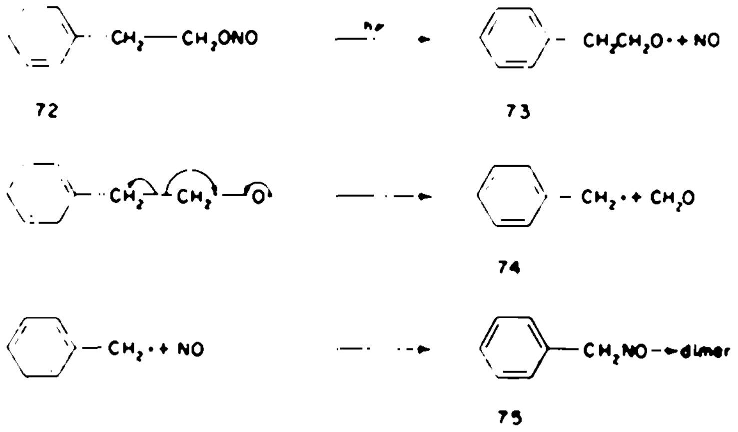
[57] ref 15, pp 275–276

[58] P. Kabasakalian, unpublished data.

Analogously, 1-butyl nitrite (70) failed[44] to give dimeric 1-nitrosopropane, the expected product of a decomposition reaction, although a modest yield of dimeric 1-nitroso-4-butanol (71) resulted via the Barton reaction.

$$\underset{70}{CH_3(CH_2)_2CH_2ONO} \rightarrow \underset{71}{(CH_2NO(CH_2)_2CH_2OH)_2}$$

The only primary alkoxy radical which has so far been shown to undergo C—C fission (see however, Section IIIB-5 on nitrites *bearing an oxygen function on the α-carbon* atom) is that derived from 2-phenyl 1-ethyl nitrite(38) (72). Photolysis of 72 in benzene gave ω-nitrosotoluene dimer (75) and formaldehyde in accord with the mechanism shown:

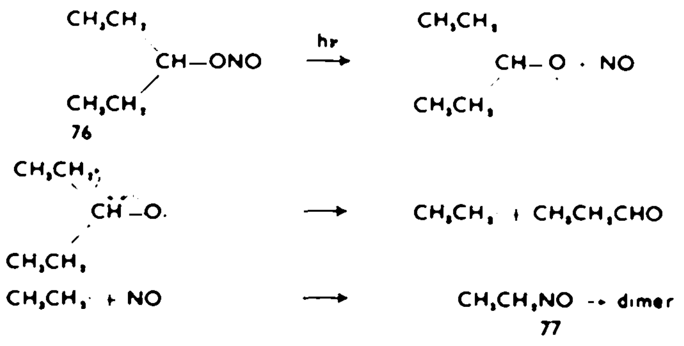


In this instance, then, the alkoxy radical (73) can suffer C–C fission to give the resonance-stabilized benzyl radical (74).

2. *Secondary alkoxy radical decomposition*

A large group of secondary alkyl nitrites has been investigated recently[46] and the salient results will be summarized here.

In the case of 2-propyl nitrite,[46] where methyl radicals are the only possible result of C–C fission, no nitrosodimer was observed. However, 3-pentyl nitrite (76) which can decompose to give *ethyl* radicals gave (albeit in low yield) dimeric nitrosoethane (77):

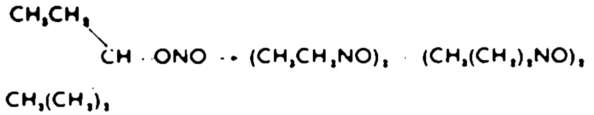


$$\underset{76}{(CH_3CH_2)_2CH\text{—}ONO} \xrightarrow{h\nu} (CH_3CH_2)_2CH\text{—}O\cdot\ NO$$

$$(CH_3CH_2)_2CH\text{—}O\cdot \longrightarrow CH_3CH_2\cdot + CH_3CH_2CHO$$

$$CH_3CH_2\cdot + NO \longrightarrow \underset{77}{CH_3CH_2NO \rightarrow \text{dimer}}$$

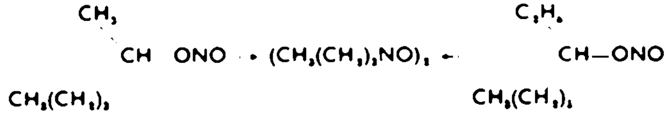
3-Hexyl nitrite[46] (78) can give rise to *ethyl or propyl* radicals by the carbon-carbon fission reaction. In fact, *both* 1-nitrosopropane dimer (80) and 1-nitrosoethane dimer (79) were formed (as well as 1-nitroso-4-hexanol dimer, the intramolecular hydrogen abstraction product).



$$\mathrm{CH_3CH_2{-}CH(CH_3(CH_2)_2){-}ONO} \rightarrow \mathrm{(CH_3CH_2NO)_2} + \mathrm{(CH_3(CH_2)_2NO)_2}$$

78 79 80

The point is further illustrated by 2-hexyl nitrite[46] (81) and 3-heptyl nitrite[46] (82) both of which gave only 1-nitroso butane dimer (83) by the C—C fission reaction (as well as good yields of the intramolecular hydrogen abstraction products).



$$\mathrm{CH_3{-}CH(CH_3(CH_2)_3){-}ONO} \rightarrow \mathrm{(CH_3(CH_2)_3NO)_2} \leftarrow \mathrm{C_2H_5{-}CH(CH_3(CH_2)_3){-}ONO}$$

81 83 82

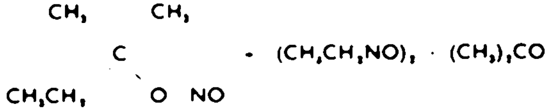
These examples, then, suggest that in C—C fission reactions of secondary nitrites, cleavage leading to the larger of two radicals is generally more likely.

In addition, the last two examples show that the Barton reaction involving intramolecular hydrogen abstraction at a secondary carbon atom is favored over the C—C fission reaction. This generalization is supported[46] by the observation that 5-nonyl nitrite, which has two available secondary carbon atoms for intramolecular hydrogen abstraction, gave no evidence for products of C—C fission.

3. *Tertiary alkoxy radical decomposition*

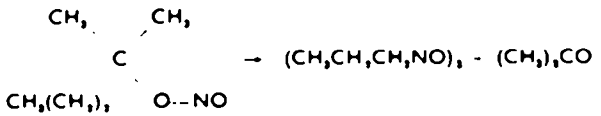
In contrast to the results obtained by vapor phase photolysis (*cf.* section entitled Early Work), t-butyl nitrite in solution[46] failed to produce nitrosomethane dimer. However, the formation of acetone testified to the expected C—C cleavage reaction, and hence to the formation of methyl radicals.

Interestingly, 2-methyl-2-butyl and 2-methyl-2-pentyl nitrites[46] (84 and 85 respectively) furnished nitrosoethane dimer and 1-nitrosopropane dimer respectively in good yield (equations 1 and 2).



$$\mathrm{(CH_3)_2C(CH_2CH_3){-}O{-}NO} \rightarrow \mathrm{(CH_3CH_2NO)_2} + \mathrm{(CH_3)_2CO} \qquad (1)$$

84



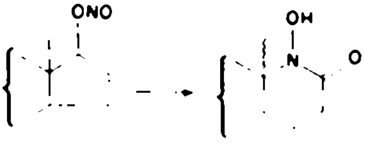
$$\mathrm{(CH_3)_2C(CH_3(CH_2)_2){-}O{-}NO} \rightarrow \mathrm{(CH_3CH_2CH_2NO)_2} + \mathrm{(CH_3)_2CO} \qquad (2)$$

85

In the case of 2-methyl-2-pentyl nitrite[46] (85) the results indicated that decomposition of a tertiary alkoxy radical by C—C fission is favored over intramolecular hydrogen abstraction from a *primary* carbon atom. However, when intramolecular hydrogen abstraction from a secondary or tertiary carbon is possible, no C—C fission is observed (see Section 1).

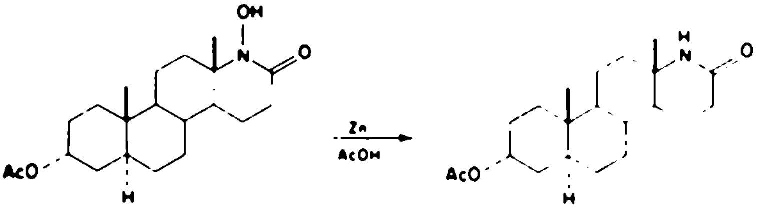
4. C—C *Fission reactions of alicyclic alkoxy radicals*

An example of ring fission suffered by an alicyclic alkoxy radical has recently been observed[59] in the steroid series through photolysis of steroidal 17-nitrites, such as 86, which resulted in the corresponding hydroxamic acids (part structure 87).



86 87

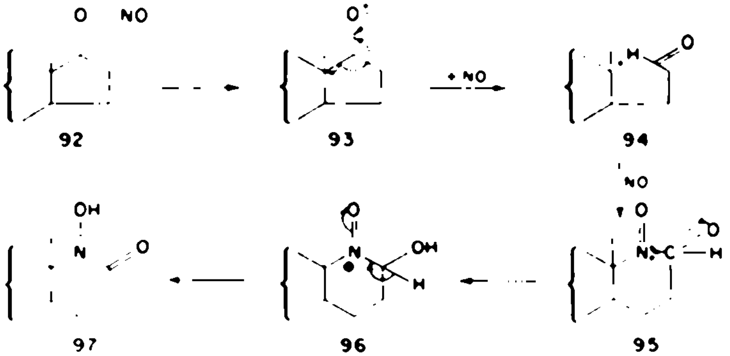
Structure-proof for the specific products 88 and 89 was obtained by reduction (zinc-acetic acid) to the lactams 90 and 91 respectively. The constitution of the lactam (91) is well established[60] and authentic lactam (90) was prepared in these laboratories by Beckmann rearrangement of the appropriate 17-oxime.



88 90

89 91

The formation of the hydroxamic acids can be rationalized in the following way (92 → 97):



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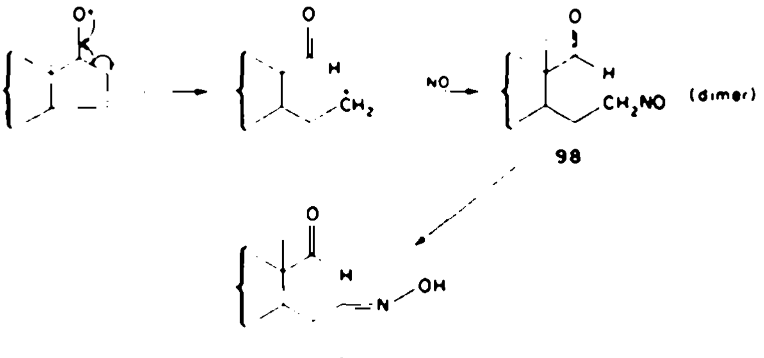
[59] C. H. Robinson, O. Gnoj, A. Mitchell, R. Wayne, E. Townley, P. Kabasakalian, E. P. Oliveto and D. H. R. Barton, *J. Amer. Chem. Soc.* **83**, 1771 (1961).

[60] B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.* **78**, 639 (1956). One of us (C. H. R.) wishes to thank Dr. Regan for an authentic specimen of compound 91.

The alkoxy radical (93) undergoes ring fission to give the tertiary radical (94) which combines with NO to give the tertiary nitroso-aldehyde (95). The steps 95 to 97 then constitute a plausible route from the nitrosoaldehyde (95) to the observed product 97.

Extension of the reaction to 17-nitrites of the 1,3,5(10)-estratriene series again led to the isolation of hydroxamic acids, the structures of which were secured by reduction to known[60] lactams. However, in addition, isomeric hydroxamic acids were also obtained from the reaction mixtures: these latter arise from isomerism at C-13, in accord with the proposed mechanism.[61]

The alternative decomposition pathway for a C—17 alkoxy radical, involving cleavage of the bond between C-16 and C-17, should lead to the nitroso aldehyde (98) and thence to the nitrosodimer or oxime (99):



98

99

It has not been possible, however, to isolate such compounds from the photolyses of 17-nitrites. Presumably cleavage to give a tertiary radical is greatly favored relative to the formation of a primary radical.

However, recent work[44] with cyclopentyl nitrite (100) has shown that the dimeric

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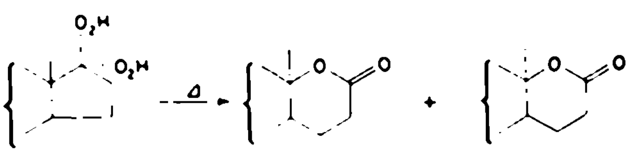
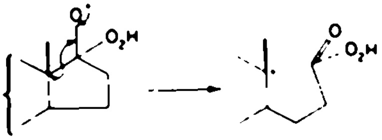
[61] The thermal decomposition of steroidal 17-bishydroperoxides has been investigated by Velluz and co-workers [*Bull. Soc. Chim. Fr.* 1484 (1952)] with the following results.



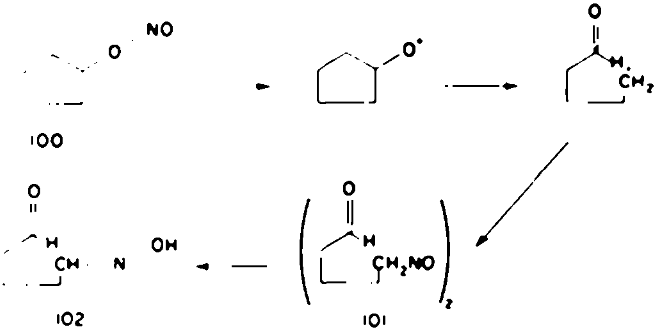
I II III

The decomposition of (I) most probably proceeds *via* the alkoxy radical (IV) which should cleave to the C-13 radical intermediate (V), subsequent ring closure giving rise to the epimeric lactones (II) and (III).



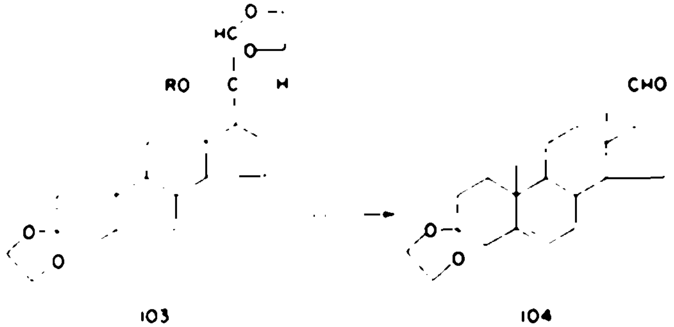
IV V

nitrosoaldehyde (101) is formed. The latter compound has been converted to the dialdehyde monoxime (102), characterized as the bis-oxime.



5. *Carbon-carbon fission in α-oxygenated nitrites*

An interesting series of degradative reactions has been observed in the steroid series.[42] In an attempt to extend the synthesis of 18-substituted substances related to aldosterone by the Barton reaction, the recently described 3,3:21,21-bis(ethylenedioxy)-5-pregnen-20β-ol (102, R = H)[43] was converted to its nitrite, and photolyzed.



The resulting material turned out to be the etio-aldehyde (104), as was proved by an independent synthesis (105[44] to 104).

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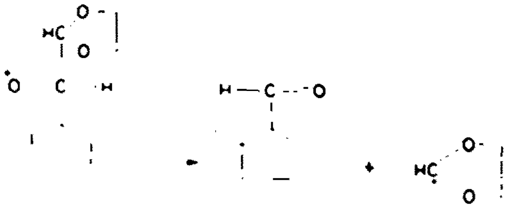
[42] A. L. Nussbaum, C. H. Robinson, E. P. Oliveto and D. H. R. Barton, in preparation. This work was stimulated by J. M. Beaton, who observed a transformation analogous to 103 to 104 in the 11-oxygenated series.

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

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

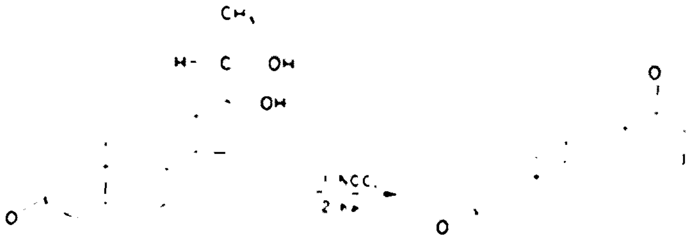
This carbon–carbon fission is very probably facilitated by the relative stability of the expelled fragment (106):



106

The question arose, what kind of substituents would favor such a fission reaction. A number of aliphatic 1,2-glycol dinitrites are known to suffer similar oxidative cleavage in pyrolytic experiments,[65] and a similar fate was expected by the photolytic method.

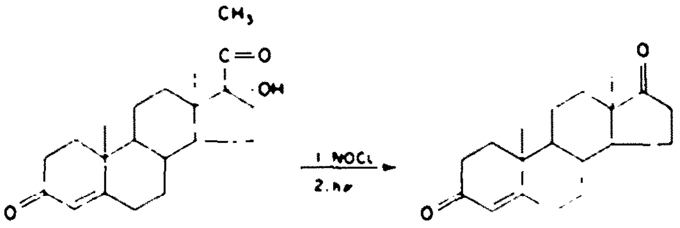
Indeed, the steroidal glycol $17\alpha,20\beta$-dihydroxy-Δ^4-pregnen-3-one[66] (107) gave a nitrite which, upon irradiation, gave rise to Δ^4-androstene-3,17-dione (108).



107

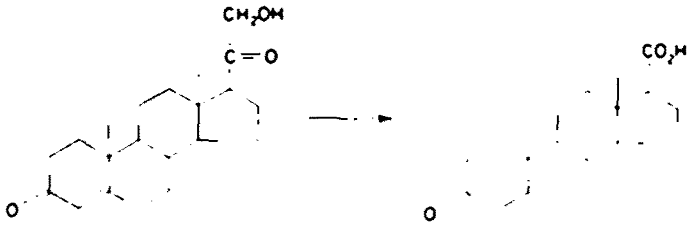
108

Two further examples involve α-hydroxyketones (109) and (110) which also underwent oxidative fission:



109

108



110

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[65] L. P. Kuhn and L. DeAngelis, *J. Amer. Chem. Soc.* 76, 328 (1954). See also J. Powling, quoted in ref. 15.
[66] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *J. Amer. Chem. Soc.* 73, 1528 (1951).

It would appear, then, that in the special case where a nitrite to be photolyzed is originally substituted by a certain type of oxygen-bearing moiety, an oxidative fission occurs during photolysis in competition with, and perhaps to the exclusion of, alternate modes of reaction. The full scope of this reaction is under investigation.

IV. ASSOCIATION WITH OTHER RADICALS

There is one instance in the course of recent work which would seem to bear out the concept of a photolytically generated alkoxy radical recombining directly with another fragment. Kabasakalian and Townley[44] observed that the photolysis of 1-octyl nitrite, in the presence of oxygen, results in a good yield of the corresponding nitrate. This may be rationalized by accepting the proposal of Hanst and Calvert.[67]

$$2NO + O_2 \rightarrow NO_2 \qquad (1)$$

$$CH_3(CH_2)_6CH_2O + NO_2 \rightarrow CH_3(CH_2)_6CH_2ONO_2 \qquad (2)$$

Alternately, the direct oxidation of light-activated nitrite may be considered

$$CH_3(CH_2)_6CH_2ONO + h\nu \rightarrow CH_3(CH_2)_6CH_2ONO^* \qquad (3)$$

$$2CH_3(CH_2)_6CH_2ONO^* + O_2 \rightarrow 2CH_3(CH_2)_6CH_2ONO_2 \qquad (4)$$

Considering, however, the mechanism proposed for nitrate formation during nitrite pyrolysis in the presence of NO_2[68], the present reviewers consider (1) and (2) preferable.

CONCLUSION

Recent developments in the photochemistry of organic nitrites have shown that all data may be explained by the known reaction pathways of alkoxy radicals. A special feature is the overriding importance of intramolecular hydrogen abstraction (Barton Reaction) when photolyses are carried out in solution, and when a postulated six-membered transition complex can form. From the preparative point of view, nitrite photolysis opens the way to a variety of structures heretofore not easily accessible.

Acknowledgements—We wish to thank Professor D. H. R. Barton for his kind interest in this review. Thanks are also due to Drs. M. M. Pechet, J. M. Beaton and their colleagues at the Research Institute for Medicine and Chemistry, as well as Drs. Kabasakalian, Oliveto and Reimann of these Laboratories for permission to present their data, some prior to publication. We are also indebted to Drs. Topliss, Herzog, Meyer and Mr. Shapiro, also of these Laboratories, for their helpful criticism during the preparation of this paper

[67] P. L. Hanst and J. G. Calvert, *J. Phys. Chem.* 63, 2071 (1953).

[68] See ref. 15, pp. 246, 247 and references cited therein.