

# **N-Nitrosamines**

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**Jean-Pierre Anselme**

**ACS Symposium Series 101**

# *N*-Nitrosamines

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*University of Massachusetts at Boston*

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## FOREWORD

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## PREFACE

Over the past twenty-odd years, *N*-nitrosamines, previously compounds of moderate academic interest, have assumed a prominent place in our daily lives. In Jekyllesque fashion, *N*-nitrosamines have revealed themselves as carcinogens in animals and possibly as ubiquitous guests of man's environment. Even the average public is already fully aware of the term "nitrosamine," thanks to the extensive coverage accorded the topic in the news media. The progress made since the "modern era" began in the mid-fifties has made it apparent that a great deal of the basic organic chemistry of *N*-nitrosamines remains unexplored. Equally evident is the fact that a sound knowledge of the chemistry of these compounds is essential if chemists and biologists are to unravel the mechanism of biological action. The important discoveries of the magnetic non-equivalence and of the base-lability of the  $\alpha$ -hydrogens of nitrosamines have not only opened new vistas on the chemistry of this class of compounds but also have suggested the  $\alpha$ -position as a possible trigger of the carcinogenic process ( $\alpha$ -hydroxylation). The major concern over the existence of unrecognized sources of nitrosamines in the body and in the environment has provided additional impetus to an already active field.

The papers delivered at a symposium on nitrosamines (NERM 8, June 26, 1978, Boston) constitute the bulk of this volume. Some of the leading contributors discussed their most recent results in this new frontier encompassing both chemistry and biology. Unfortunately, Prof. Baldwin's paper could not be included in this book. Dr. Wiessler, an invited speaker, was good enough to provide his manuscript even though illness prevented him from participating in the symposium. Dr. Keefer elected to deliver only an oral presentation because he felt that those results of greatest potential importance could be discussed freely, regardless of their preliminary nature at the time; instead of a paper based on his talk, Dr. Keefer has provided a manuscript dealing with a different aspect of *N*-nitrosamines. In addition, Prof. Chow has prepared a review of his most recent investigations of the photochemistry of *N*-nitrosamides, while Prof. Loepky's contribution deals with a novel reaction of certain *N*-nitrosamines. Finally, I have prepared a brief survey of the organic chemistry of *N*-nitrosamines in order to give perspective to the remaining chapters of the book.

I would like to acknowledge the help of the Chairman of the morning session, Prof. C. G. Overberger, whose ever gracious willingness to help is never found wanting, despite a very heavy schedule of commitments. The superb cooperation of the Meeting Chairman, Prof. E. I. Becker, made it a pleasure to organize the symposium.

University of Massachusetts at Boston  
Boston, Massachusetts  
March 27, 1979

JEAN-PIERRE ANSELME

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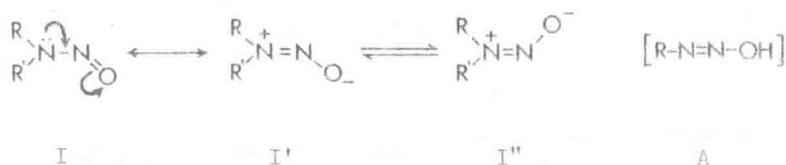
# The Organic Chemistry of N-Nitrosamines: A Brief Review

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Although N-nitrosamines (I) have been known since the nineteenth century, it was not until quite recently that they became the subject of intensive investigations. This renewed interest was spurred in large part by the report of Magee and Barnes (1) on the carcinogenicity of these compounds. Since then, research into the chemistry and biological properties of N-nitrosamines has accelerated. This brief survey is intended to serve both as a summary of some of the frontiers in this area and as an introduction to the chemistry of N-nitrosamines discussed in the remaining chapters of this Volume.

N-Nitrosamines have the nitroso group attached directly to the amine nitrogen (2-7). As with C-nitroso compounds however, in general only those N-nitrosamines where neither R nor R' is a hydrogen atom, have any existence; when one of the substituents is a hydrogen, the equilibrium favors the tautomeric diazoic acid (A) (8). There are reported cases of stable primary N-nitrosamines;



it is likely, however, that in those instances these N-nitrosamines exist as the tautomeric N-nitrosimines (9).

Although there is a large body of information on N-nitrosamides (i.e., N-nitrosamines where one of the substituents is either acyl or sulfonyl), this brief survey will deal mainly with N,N-di-alkyl- and N,N-aralkylnitrosamines.

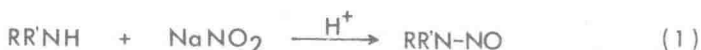
## Structure

In 1957, Looney, Phillips and Reilly (10) were the first to

demonstrate that  $\alpha$ -hydrogens of N,N-dialkylnitrosamines are magnetically non-equivalent as a result of the large contribution of the dipolar mesomeric structure. The existence and the separation of configurational isomers (I' and I'') have been reported (13). These findings confirmed the suggestion that N-nitrosamines are polar and served to usher a major advance in the chemistry of this class of compounds.

### Synthesis

The nitrosation of secondary amines with sodium nitrite in the presence of acids is by far still the most widely used method for the preparation of N-nitrosamines. Several variations of this



procedure are known (2-7). Other nitrosating agents such as nitrosyl fluoroborate, dinitrogen trioxide, dinitrogen tetroxide have been utilized. A recent modification (14) involves the nitrosation of the anion of the amines with nitrosyl chloride. Trans-nitrosation with 3-nitro-N-nitrosocarbazole allows nitrosation to occur in neutral medium (37). Of particular interest is the ability of nitroprusside [ $\text{Fe}(\text{CN})_5\text{NO}^-$ ] to nitrosate amines under aqueous alkaline conditions (15).



A novel method to degrade tertiary amines proceeds through the formation of secondary N-nitrosamines (16).



### Reactions

Reactions of the Nitroso Group. Up until recently, the chemistry of N-nitrosamines was restricted to the reaction involving the nitroso group. It was not until the usefulness of N-nitrosamines in synthesis [concept of "Umpolung" (3)] was demonstrated, that the long-known denitrosation of N-nitrosamines became impor-

tant. Although numerous methods have been reported for this purpose, the action of mineral acids remains the most common procedure (Eq. 4).

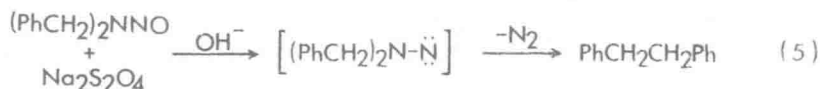


There has been some controversy regarding the site of attack of the proton; on the basis of the dipolar structures I' and I'', it might be inferred that the proton attack should occur on the oxygen atom; the fact that N-nitrosamines form O-complexes and O-alkylated products would seem to support this view (17). However, it is currently believed that the N-protonated form is the one that leads to denitrosation, irrespective of whether or not initial protonation occurs on oxygen (18).



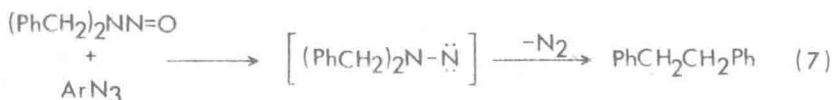
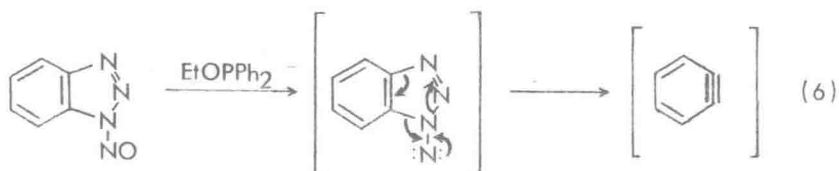
Scheme 1

One of the oldest-known reactions of N-nitrosamines is their reduction to 1,1-disubstituted hydrazines discovered by Fischer (19). The most common method to perform this transformation has been zinc dust in acid, generally acetic acid; tetrazenes are sometimes formed as by-products (20) and denitrosation can also occur. Several other reducing methods have been investigated; reduction with lithium aluminum hydride and catalytic hydrogenation are sometimes useful. Sodium dithionite reduction of benzyl substituted N-nitrosamines in base can result in fragmentation to



the hydrocarbons (Overberger-Lombardino reaction). The "abnormal" reduction of N-nitrosamines presumably proceeds via the N-nitrene (or N-nitrenoid) which then may extrude nitrogen to yield the observed hydrocarbons (6). N-Nitrosamines can be considered as N-nitrene N-oxides and indeed are deoxygenated to the putative N-

nitrenes with ethyl diphenylphosphinite [Eq. 6] (21), iron penta-



carbonyl (22,23), aryl azides [Eq. 7] (24) or phenacylcarbonium ions (25).

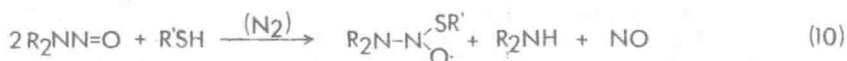
N-Nitrosamines have been oxidized to the corresponding N-nitramines. Trifluoroperacetic acid and nitric acid/ammonium persulfate are the reagents of choice for this purpose.



It has been found that, though stable to light in neutral solution, N-nitrosamines can rearrange to the corresponding amidoximes (4,26,27) in acid solution; other products can also be formed (4).

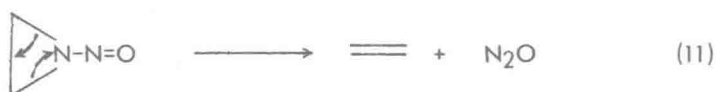


A very recent communication (28) reports the addition of thiyl

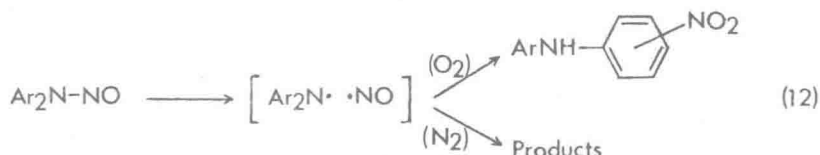


radicals to N-nitrosamines to give the corresponding nitroxide radicals.

The chelotropic elimination of nitrous oxide from N-nitrosoaziridines is a reaction restricted to this class of compounds (29-36).

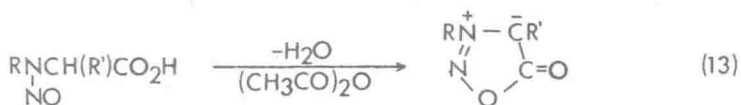


Diarylnitrosamines undergo fission at the nitrogen-nitrogen bond upon heating (37,38). In the presence of oxygen, the ring nitro substituted amines are obtained (37); in the absence of



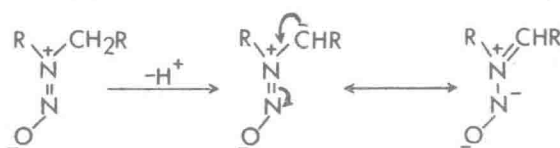
oxygen, products resulting from the diarylamino radical are formed (38).

A much older reaction of N-nitroso  $\alpha$ -aminoacids is their cyclization to the mesoionic sydnone (39,40,41,42); more recently, N-nitroso  $\alpha$ -aminonitriles have been cyclized to the corresponding sydnone imines (40,41,42,43).



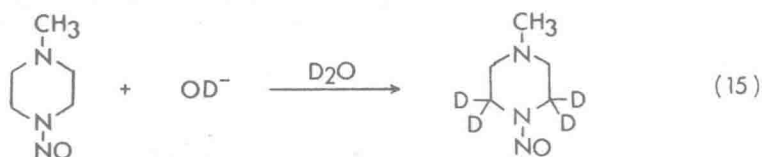
Reactions Caused by the Nitroso Group. A major consequence of the strongly dipolar nature of N-nitrosamines - a fact now firmly established by the work of Phillips (10) and of Karabatsos (11) - has been a better understanding of the chemistry of N-ni-

trosamines and the elaboration of new reactions based on the acidic nature of the  $\alpha$ -hydrogens of N-nitrosamines. Although resonance stabilization of the negative charge may be difficult to envision (44,46), the experimental data leave little doubt as to the reality of the inductive effect.



Scheme 2

The first indication of the effect of the positive charge on the  $\alpha$ -hydrogen came from the isomerization of trans-N-nitroso-2,5-diphenylpyrrolidine to the cis-isomer in aqueous base (45). Keefe and Fodor (46) were the first to demonstrate the deuterium exchange of the  $\alpha$ -hydrogens and the alkylation of anions of N-nitrosamines. Seebach and his group (3) have developed this discovery into a major synthetic process; they have coined the word "Umpol-

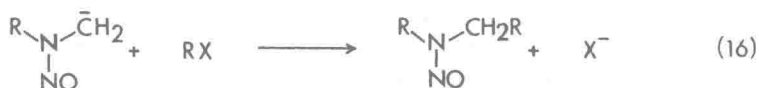


ung" to indicate that the nitroso group attached to the amine ni-

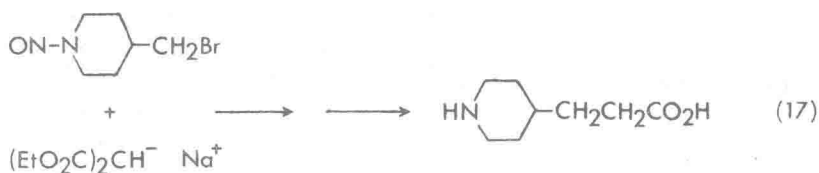


Scheme 3

trogen has reversed the normal "polarity" of the  $\alpha$ -carbon (Scheme 3). N-Nitrosamino anions have also been added to carbonyl compounds, to  $\alpha,\beta$ -unsaturated ketones and nitroolefins, to nitriles and other



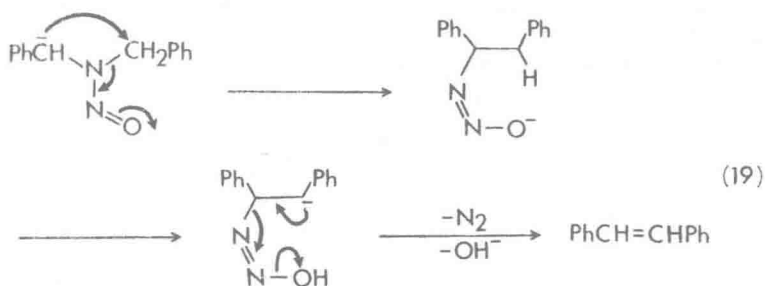
electrophiles (3). It is of historical interest that as early as in 1944, Koelsch (47) used the N-nitroso group as a removable protective group in the synthesis of 4-(piperidino)propionic acid.



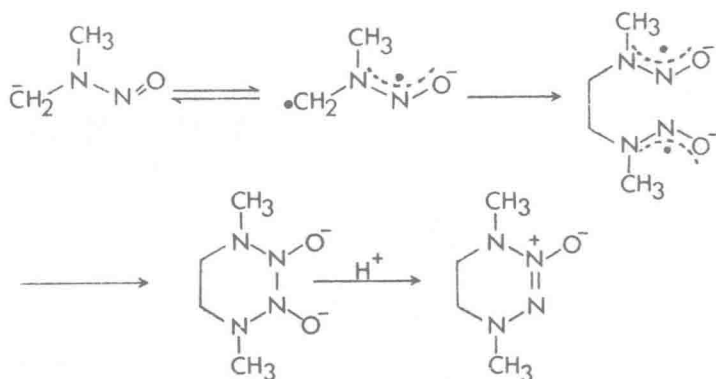
Some difficulties may be encountered during the metallation of N-nitrosamines. Elimination may occur in either of two ways. For example, N-nitrosomorpholine yields the N-nitrosoenamine while loss



of  $[\text{HNO}]$  results in the formation of imines (3). The formation of trans-stilbene from the anion of N-nitrosodibenzylamine may proceed by a mechanism akin to that of the Ramberg-Bäcklund, at least in its early stages (3).

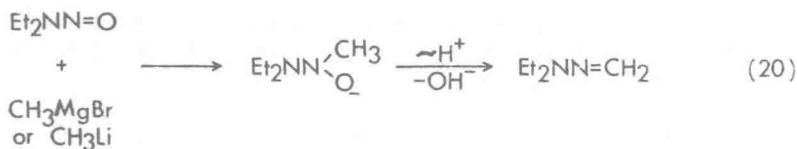


The interesting "dimerization" of lithiated N-nitrosamines to cyclic tetrazene N-oxides has been described (48) and provides another route to the novel cyclic tetrazenes (49,50). A radical path has been suggested for this reaction [Scheme 4] (3).

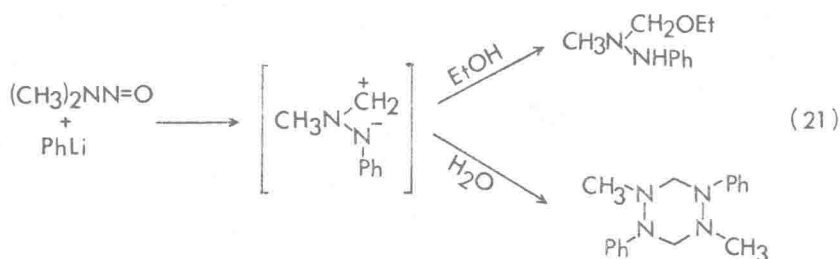


Scheme 4

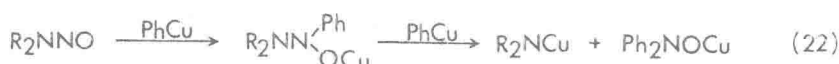
The reaction of organometallics with N-nitrosamines has been investigated in the early part of this century mainly by Wieland and his students (51,52,53,54). More recent work (55,56,57) indicates that Grignard and organolithium reagents may either abstract  $\alpha$ -hydrogen or add to the nitroso group. Some of the azomethine imines have been intercepted with 1,3-dipolarophiles.







With phenylcopper (58) or with lithium or magnesium metal (59), denitrosation to the amines is the major reaction path; N,N-diphenylhydroxylamine a significant by-product of the reaction, is believed to arise as shown in Eq. 22 after hydrolysis (58).



In the short span of twenty-five years, the hitherto rather prosaic N-nitrosamines have revealed themselves to possess a rich and varied chemistry as subsequent chapters of this volume will further demonstrate.