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Advances in the Chemistry of Aliphatic *N*-Nitrosamines

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The review gives for the first time a systematic account of the extensive literature data on the chemistry of aliphatic nitrosamines. A separate chapter summarises the work on the physical properties, structure, and spectra of *N*-nitroso-derivatives. The chemical behaviour of the nitrosamines is determined largely by the characteristics of the *p*-π-conjugation in the $\rangle\ddot{N}-\ddot{N}-O$ fragment. The principal chemical reactions of nitrosamines are treated from this standpoint: the denitrosation reaction, the formation of complexes, the cyclisation to sydnones and sydnoneimines, and the synthesis of lactams. In conclusion, certain aspects of the practical applications of nitrosamines are considered.
The bibliography includes 272 references.

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I. INTRODUCTION

N-Nitrosamines occupy an important place in the large class of nitroso-compounds. The reason for this is not only the high chemical reactivity of the nitroso-group but also the valuable products formed as a result of various reactions. It is sufficient to say that *N*-nitroso-compounds are widely used in the synthesis of diazo-derivatives and dialkylhydrazines, and are employed to prepare nitramines, sydnones, sydnoneimines, and complex compounds. The *N*-nitrosation reaction is closely related to the chemistry of carbonium ions. *N*-Nitrosamines are excellent objects for the investigation of p-π-conjugation, n-π^* and π-π^* transitions, and rotational isomerism.

Despite the large number of studies that have been made on nitrosamines and their theoretical and practical importance, we were unable to find any reviews on this field of chemistry. The existing reviews deal mainly with aromatic nitrosamines, or deal with highly specific problems [1-5].

The present review is the first attempt to fill this gap, and covers the fundamental studies on aliphatic nitrosamines up to 1968-1969.

The study of the chemistry of aliphatic nitrosamines began in 1863, when Geuther obtained *N*-nitrosodiethylamine by the reaction of diethylamine hydrochloride with sodium nitrite [6,7]. Subsequently the *N*-nitrosation reaction was employed by many investigators, who improved and developed it. A number of interesting studies on the chemistry of nitrosamines have been made by Soviet chemists. Significant advances in the understanding of the structure of nitrosamines were made in the 1950's and 1960's. During this period, many new reactions of nitrosamines were discovered.

II. NITROSATING AGENTS AND NITROSATION

It is believed that nitrosation is achieved by agents related to nitrous acid having the structure NOX, where X = OAlk, NO_2, NO_3, halogen, or OH_2^+. Depending on the experimental conditions, any member of this series may become the main nitrosating agent.

In the reaction of alkali metal nitrites with inorganic acid, nitrous acid is formed, its subsequent fate being determined by the reaction conditions. Thus two nitrous acid molecules can be converted via a stage involving "self-protonation" and nucleophilic attack by the nitrite ion into nitrogen trioxide, which is 6–10 times weaker than protonated nitrous acid [8,9]:

$$2HONO \rightleftarrows H_2\overset{+}{O}\cdot NO + NO_2^-,$$

$$H_2\overset{+}{O}\cdot NO + NO_2^- \rightleftarrows N_2O_3 + H_2O.$$

If a halide ion serves as the nucleophilic agent, nitrosyl halides are formed. This happens when the nitrosation is carried out in hydrogen halide solution [10,11].

In a highly acidic medium, nitrogen trioxide and nitrous acid cannot exist in a free form, and, for example in 70–80% sulphuric acid, are converted into the nitrosonium salt $NO^+HSO_4^-$. [12] Nitrosyl sulphate acid readily dissociates with formation of a nitrosonium cation [13]:

$$N_2O_3 + 3H_2SO_4 \rightarrow 2NO^+ + 3HSO_4^- + H_3O^+.$$

The nitrosonium cation is one of the most active nitrosating agents. Nitrosonium tetrafluoroborate is an interesting nitrosating substance [14]. Recently nitrosylsulphuric anhydride $HOSO_2ONO$ was proposed as an effective nitrosating compound [15].

Certain investigators [16] explain the nitrosating activity of nitrogen tetroxide by the existence of the latter in the nitrosyl nitrate form $NO.ONO_2$, which serves as a source of nitrosonium cations, like the nitrosonium salt of sulphuric acid already mentioned. The nitrosonium cation is present at high concentrations only at high acidities. In a weakly acidic medium or in the presence of an active nucleophilic agent, for example hydroxide ions, the nitrosonium cation is converted into nitrous acid and further into nitrite ions [13]:

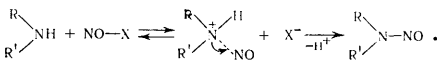
$$NO^+ + OH^- \rightleftarrows HNO_2 \rightleftarrows H^+ + NO_2^-.$$

At pH $\geqslant$ 7 the equilibrium in the reaction is completely displaced to the right.

Depending on changes in the acidity in the reaction zone, various nitrosating agents are present, which can be arranged in the following series in terms of increasing activity [11]: $NO.NO_2$, NOCl(Br, F), $NO.OH_2^+$, NO^+. Nitrous

acid and alkyl nitrites are absent from this series because free nitrous acid does not exhibit nitrosating activity [11]. In addition nitrous acid salts of primary and secondary amines have been described in a number of papers [17,18]. Alkyl nitrites are as a rule rarely recommended for *N*-nitrosation reactions.

In its simplest form the nitrosation of amines includes electrophilic attack by the nitrosating species on the lone pairs of sp^3 electrons of the nitrogen atom and subsequent deprotonation of the alkylnitrosimmonium cation [11]. In the case of secondary dialkylamines the reaction may be represented by the following scheme:



The amine participates in the reaction in a non-protonated form and therefore it is desirable to carry out the nitrosation of highly basic amines in a weakly acidic medium. Under these conditions, the comparatively inactive nitrogen trioxide or at best a nitrosyl halide will function as the nitrosating agent. With amines having a low electron density at the nitrogen atom, nitrogen trioxide proved to be less effective than the nitrosonium cation. This makes it necessary to carry out the reaction in a highly acidic medium.

Thus the acidity of the medium plays a dual role in the nitrosation of amines. Its increase enhances the concentration of the more powerful nitrosating agent ($H_2O^+.NO$, NO^+), but lowers the concentration of the active (non-protonated) form of the amines, i.e. the excess acid has an inhibiting effect, which is shown particularly clearly in the case of highly basic aliphatic amines. When the basicity of the amine is low, part of it may exist as the non-protonated species even in the presence of a considerable excess of the acid [11] and this species is in fact acted upon by the powerful nitrosating agent.

These factors must be taken into account in the nitrosation of various types of secondary amines.

III. METHODS OF SYNTHESIS OF *N*-NITROSAMINES

The methods of preparation of *N*-nitrosamines may be divided into three principal groups: 1) nitrosation of secondary amines in an acidic medium, which should include also the nitrosation of the hydrochlorides, hydrogen nitrates, and hydrogen sulphates of secondary amines by metal nitrites; 2) nitrosation with the aid of NOCl, N_2O_3, and N_2O_4; 3) nitrosation by cleaving tertiary amines. In addition, several methods of nitrosation have been described which are not of general importance at the present time.

1. Reaction of Alkali Metal Nitrites with Solutions of Amines in Acids

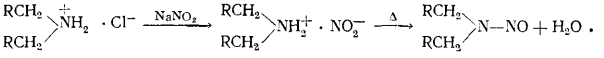
After the discovery of *N*-nitrosodialkylamines [6] the efforts of investigators were concentrated on the development of a convenient and reliable method for their synthesis. As early as 1865, Fischer found that, when dimethylamine hydrochloride acidified with sulphuric acid is treated with sodium nitrite in an aqueous medium, *N*-nitrosodimethylamine is formed in a high yield [19]. Subsequently acetic [20-25] or nitric [26-29] acid was employed in addition to sulphuric acid, but hydrochloric acid in fact found the widest application [30-51].

Various modifications of Fischer's method are distinguished by the procedures employed to isolate the desired products or by the temperature conditions. Nitrosamines have been extracted from the reaction medium by steam distillation [19,52-54], extraction by different solvents [20,21,30,37,50], and other methods [6,20,21,31-36]. Some investigators carried out the nitrosation reaction with cooling (usually to 0–5°C), [20,27,36,40,41,45-51,55-58] while others heated the reaction mixture [6,22,31,36,38,52,54,59-61]. However, temperature is in fact an important factor in the reaction. In an acidic medium it is desirable to carry out the process at a low temperature to avoid denitrosation, which is acid-catalysed. If the acidity in the reaction zone is low, the process usually takes place at an elevated temperature [60,61], which has a favourable effect on the yield of the final product and reduces the duration of the reaction. It is not fortuituous that, in the synthesis of nitrosamines, many investigators treated secondary amine hydrochlorides with an excess of sodium or potassium nitrite at room or higher temperature without additional acidification [6,21,37,55,59,62-69].

By virtue of its simplicity, nitrosation in an acidic medium has been more widely used than other methods [70-72]. The considerable range of applications of "acid" nitrosation is shown by its employment to synthesise many nitrosamines containing various substituents in the alkyl residue: aryl groups [23,35,36,39,57,63,73-75], halogens [21,59,76,77] and keto- [22,41,64], ester [32-34,62,78,79], carboxy- [37,40,45,50,56], hydroxy- [21,57,61,73], alkoxy- [20,53], nitrile [26,46-49,51,78,80], nitrate [27], sulphate [81], and nitro-groups [55]. Nitrosation in an aqueous solution of an inorganic acid has been used to synthesise dinitroso-compounds based on *N*-alkyl-substituted ethylenediamines [30,68] and nitrosamines containing an olefinic residue at the nitrogen atom [22,82]. In acetic acid a number of labelled [^{14}C]-*N*-nitrosodialkylamines have been synthesised [83].

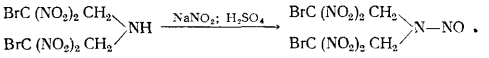
Taylor and Price [84] attempted to determine the concentration of nitrous acid necessary for successful reaction. They showed for dimethylamine that, when equimolar amounts of the reagents (0.05 *N* amine + 0.05 *N* HNO_2) are mixed, the reaction does not occur. With increase of the concentration of nitrous acid to 0.1 *N*, an adduct with the composition $[(CH_3)_2NH_2]^+.[NO_2]^-.[HNO_2]$ is formed, but the formation of *N*-nitrosodimethylamine was not observed.

The formation of nitrous acid salts in the reaction between secondary α-arylamine hydrochlorides and sodium nitrite in ethanol was observed even earlier by Curtius [17,85,86]. On prolonged refluxing in ethanol, the nitrite salt of the amine is converted into the corresponding nitrosamine:



Ring-substituted *N*-nitrosodibenzylamines have been synthesised in this way. Some investigators employed silver nitrite instead of sodium nitrite [87,88]. The results of the studies quoted [17,84-88] confirm that in the nitrosation of fairly basic amines the reaction must be carried out at comparatively high temperatures.

The dependence of the reaction conditions on the basicity of the amine is also illustrated, for example, by *N*-nitrosodi-(2-bromo-2,2-dinitroethyl)amine, which was obtained by treating di-(2-bromo-2,2-dinitroethyl)amine with sodium nitrite in concentrated sulphuric acid [29]:



In trifluoroacetic acid and trifluoroacetic anhydride, *N*-nitrosodi-(2,2,2-trinitroethyl)amine was obtained from di-(2,2,2-trinitroethyl)amine [89].

In contrast to the work of Curtius and Taylor, in the studies quoted above the nitrosation of weakly basic amines was investigated and the reaction carried out in a strongly acidic medium.

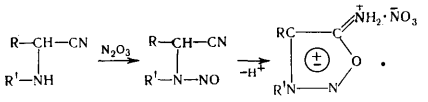
2. Reaction of Nitric Oxide, Nitrogen Trioxide, Nitrogen Tetroxide, and Nitrosyl Chloride with Secondary Amines

The first studies where the application of nitrogen trioxide as the nitrosating agent in the series of aliphatic amines was reported were carried out towards the end of the nineteenth century. Paulman [90], who investigated the properties of sarcosine, found that it reacts readily with "gaseous nitrous acid", forming a nitroso-derivative. Subsequently nitrosiminodiacetic acid [91,92] and di-(2-azapropyl-2-nitroso-3-phenyl)methanol [93] were synthesised in a similar way. The reaction was carried out in an aqueous medium:

$$(HOOCCH_2)_2NH \xrightarrow{N_2O_3;\ H_2O} (HOOCCH_2)_2N{-}NO\ .$$

The dinitrile and the dimethyl esters of nitrosiminodiacetic acid were obtained with nearly quantitative yields in ether [94].

Brookes and Walker [95], who allowed nitrogen trioxide to react with α-aminoacetonitriles, observed that the former is not only a nitrosating agent but also promotes the cyclisation of the intermediate *N*-nitrosoacetonitriles to sydnoneimines:



Despite the fact that the method of introduction of the nitroso-group with the aid of nitrogen trioxide gives as a rule good results, it has not found as wide an application as "acid" nitrosation. This is probably because the process is complicated by the necessity to obtain nitrogen trioxide. The latter is usually obtained from sodium nitrite and sulphuric acid [95] or by the reaction of nitric acid with arsenic oxides [94].

Above its boiling point nitrogen trioxide readily decomposes into NO and NO_2. This property constitutes the basis of the synthesis of nitrosamines. Thus *N*-chlorodialkylamines are readily converted into *N*-nitrosodialkylamines when acted upon by nitric oxide in solutions containing the redox system Fe^{3+}/Fe^{2+} or Cu^{2+}/Cu^{+}. [96] Similarly *N*-nitrosodi(trifluoromethyl)amine was synthesised from *N*-bromodi(trifluoromethyl)amine [97]. A radical mechanism was proposed for the reaction:

$$R_2N{-}Hal \rightarrow R_2N^{\cdot} + Hal^{\cdot},$$
$$Hal^{\cdot} + NO \rightarrow \dot{N}O,$$
$$R_2N^{\cdot} + \dot{N}O \rightarrow R_2N{-}NO\ .$$

The gas-phase or liquid-phase nitrosation of secondary alkylamines probably takes place by a radical mechanism [98,99]. The reaction is performed in an autoclave at a high temperature, after mixing nitrogen oxides and the amine. Judging from patent data, *N*-nitrosodialkylamines are formed when nitric oxide reacts with secondary amines under pressure in the presence of transition metal salts, metallic nickel, palladium, or rhodium [100]. *N*-nitrosodiethylamine is formed when the adduct of diethylamine with nitric oxide is decomposed in the presence of oxygen [101]. The kinetics of the reaction of diethylamine with nitric oxide have been investigated. The reaction is of first order with respect to diethylamine and proceeds via the intermediate adduct $(C_2H_5)_2NH.N_2O_2$, which reacts with a second molecule of nitric oxide and then with diethylamine. The activation energy for the reaction is 12 kcal mole^{-1}. [102]

The use of nitrogen tetroxide and nitrosyl chloride as nitrosating agents has been insufficiently investigated although they have been known for a long time and are used for the nitrosation of amines and amides [16,89,103]:

$$[(NO_2)_3CCH_2]_2NH + N_2O_4 \xrightarrow{CH_3COOH+CH_3COOK} [(NO_2)_3CCH_2]_2N{-}NO + HNO_3\ ,$$
$$Et_2NH_2 \cdot NO_3 + NO \cdot NO_3 \rightarrow Et_2N{-}NO + 2HNO_3\ .$$

The reaction of nitrosyl chloride with secondary amines was investigated by Solonina [104]. When nitrosyl chloride was passed into a solution of the amine in ether, *N*-nitroso derivatives of dipropyl-, di-isobutyl-, and dipentyl-amines were synthesised. Later it was shown that the reaction of nitrosyl chloride with diethylamine hydrochloride results in a quantitative yield of the *N*-nitroso-derivative:

$$Et_2NH_2 \cdot Cl + NOCl \rightarrow Et_2N{-}NO + 2HCl\ .$$

The synthesis of *N*-nitroso-di-t-butylamine in 23% yield from di-t-butylamine and nitrosyl chloride has been described [105].

3. Cleavage of Tertiary Amines Accompanied by Nitrosation. Syntheses of Nitrosamines from Primary Amines

Until recently there has been no unanimous view on the cleavage of tertiary amines with nitrous acid. Not until 1967 was it shown convincingly that tertiary amines can be converted into nitrosamines by nitrous acid [106], although examples of this reaction were known in the past century. Geuther [107] obtained *N*-nitrosodiethylamine from triethylamine, but Heintz [108] was unable to reproduce his results and arrived at the erroneous conclusion that tertiary amines do not react with nitrous acid. This initiated the controversy which continued for more than one hundred years. Subsequently the validity of Geuther's results was confirmed by Solonina [109], who investigated the cleavage of forty nitrite salts of amines and in all cases observed the formation of nitrosamines, and also by other investigators [110-112]. The cleavage of tertiary amines by nitrous acid is discussed in detail in the literature [106,112].

The most probable mechanism of the cleavage includes attack by the nitrosating agent on the free electron pair of the nitrogen atom and the formation of the nitrosimmonium ion. The latter splits off the "nitroxyl" (HNO) and hydrolyses under the reaction conditions to a secondary amine. A ketone or an aldehyde is formed as a side product [106]:

$$R_2N{-}CHR_2' \xrightarrow{HNO_2} R_2\overset{+}{N}\!\!<^{CHR_2'}_{NO} \rightarrow R_2\overset{+}{N}{=}CR_2' + HNO\ ,$$
$$R_2\overset{+}{N}{=}CR_2' \xrightarrow{H_2O} R_2'C{=}O + R_2\overset{+}{N}H_2 \xrightarrow{HNO_2} R_2N{-}NO\ ,$$
$$2HNO \rightarrow H_2N_2O_2 \rightarrow H_2O + N_2O\ .$$

The degree of conversion of the tertiary amine into the nitrosamine reaches 50–70%.

The cleavage of tertiary amines with nitrous acid and nitrosyl chloride has been described [103]. Thus, on refluxing in alcohol with nitrous acid, tribenzylamine is smoothly converted into *N*-nitrosodibenzylamine and benzaldehyde.

The results obtained with nitrosyl chloride are contradictory. In an early study Solonina noted that tri-isobutylamine is cleaved with nitrosyl chloride to *N*-nitrosodi-isobutylamine [104]. According to these data [114], when cyclohexyldimethyl- and dicyclohexylmethyl-amines are acted upon by nitrosyl chloride, *N*-nitrosocyclohexylmethyl- and *N*-nitrosodicyclohexyl-amines are formed respectively. In another publication [115] it was noted that the reaction of trimethylamine with nitrosyl chloride gives only the hydrochlorides of di- and tri-methylamines: the reaction with tribenzylamine results in the formation of the hydrochlorides of tribenzylamine and dibenzylamine and of benzaldehyde [106]. The same products are formed in the reaction of tribenzylamine with nitrosonium tetrafluoroborate [106]. Probably the basicity of the nitrogen atom is important for the cleavage of tertiary amines to the corresponding *N*-nitroso-compounds. For example, triglycineamine, the basicity of the nitrogen atom in which is reduced, is incapable of undergoing cleavage with nitrosation [116]. Diethylaminotrimethylsilane is readily cleaved by nitrosyl chloride [117]:

$$(C_2H_5)_2NSi(CH_3)_3 + NOCl \rightarrow (C_2H_5)_2N{-}NO + (CH_3)_3SiCl .$$

In 1920 a method for the preparation of *N*-nitrosodialkylamines by the cleavage of tertiary amines with tetranitromethane was discovered. The reaction takes place when alcoholic solutions of tertiary amines are heated with tetranitromethane in the presence of pyridine [118]:

$$R_1R_2NCH_2R + C_5H_5N + C(NO_2)_4 \rightarrow R_1R_2N{-}NO + RCHO + C_5H_5N \cdot HC(NO_2)_3 .$$

A large series of *N*-nitrosodiaryl-, *N*-nitrosoarylalkyl-, and *N*-nitrosodialkyl-amines was synthesised by this procedure. Subsequently a similar cleavage was achieved in the absence of pyridine in acetic acid [119]. Nitroform is formed as a side product.

In connection with the nitrosating activity of tetranitromethane, it is interesting to note that this compound exhibits nitrosating and nitrating properties in relation to aromatic compounds [120-122], a nitro-group can be replaced by a halogen [123,124] or an alkyl residue in polar aprotic solvents [125], and is tetranitromethane capable of a number of other extremely interesting reactions [126-128].

Cleavage of tertiary amines accompanied by nitrosation takes place also under the action of bromonitroform in chloroform. This is accompanied by the bromination and nitration of the benzene ring. Thus the reaction of bromotrinitromethane with dimethylaniline leads to the formation of *N*-methyl-*N*-nitroso-*p*-bromoaniline and *NN*-dimethyl-*p*-nitroaniline [129].

In his study of the reaction of silver nitrite with the hydrochlorides of n-propyl- and n-butyl-amines, Meyer observed that, together with other products, low yields of *N*-nitrosodipropyl- and *N*-nitrosodibutyl-amines are formed in this process [130,131]. Deamination of n-propylamine gave a mixture of propanol, 2-propanol, and *N*-nitrosodipropylamine [132].

Under thermolysis conditions, the nitrite salts of methyl- and ethyl-amines tend to undergo similar reactions [18].

When ethyl- and isobutyl-amines were treated with nitrosyl chloride in ether, *N*-nitrosodiethyl- and *N*-nitrosodi-isobutyl-amines were formed together with corresponding alkyl chlorides. It is interesting that the author explained "their formation (nitrosamines) via the preliminary synthesis of secondary amines by the action of the alkyl chlorides on the primary amines". Seconday amines are then converted into nitroso-compounds [133].

Although the method of preparation of the nitrosamines from primary amines has no preparative importance, it is interesting from the theoretical standpoint. Since the mechanism of the denitrosation of amines is presumed to involve the formation of an intermediate carbonium ion [11], the results described above can be accounted for by the alkylation of the primary amine by the carbonium ion:

$$RNH_2 \xrightarrow{HNO_2} R{-}N{=}N{-}OH \xrightarrow{H^+} R^+ ,$$

$$RNH_2 + R^+ \rightarrow \underset{\displaystyle R}{\overset{\displaystyle +}{R}}NH_2 \xrightarrow[-H_2O]{HNO_2} R_2N{-}NO .$$

Cleavage of amines accompanied by nitrosation is of preparative interest as a method for the purification of secondary amines. Thus, when a mixture of primary, secondary, and tertiary amines is treated in succession with a nitrosating agent and potassium permanganate, only the *N*-nitrosodialkyl-amine remains [134]. A method for the synthesis of pure *N*-nitrosodialkylamines by the nitrosation of a mixture of di- and trialkylamines has also been described [104,110].

4. Other Methods

The preparation of *N*-nitrosodipropylamine from the nitrite salt of dipropylamine by fusing the latter or heating it in water has been described [135]. *N*-Nitrosodimethyl- and *N*-nitrosodiethyl-amines are formed when nitrite [18] and nitrate salts of dimethyl- and diethyl-amines are heated [136], via the following mechanism:

$$(CH_3)_2NH \cdot HNO_3 \xrightarrow{\Delta} (CH_3)_2NH \cdot HONO \rightarrow (CH_3)_2N{-}NO + H_2O + O .$$

N-Nitrosodibenzylamine was isolated when tetrabenzylhydrazine [137] and *NN*-dibenzylhydroxylamine were treated with nitric acid [35]:

$$(C_6H_5CH_2)_2N{-}X \xrightarrow{HNO_2} (C_6H_5CH_2)_2N{-}NO;\ X{=}OH;\ N(CH_2C_6H_5)_2 ,$$

It has been reported that *N*-nitrosodibenzylamine is formed when isopentyl nitrite reacts with dibenzylamine [138]. Titov employed benzyl nitrite to nitrosate diethylamine [139]; a continuous method for the synthesis of *N*-nitrosodimethylamine with a yield in excess of 90% by the nitrosation of dimethylamine in alcohol with methyl nitrite has been described [140].

The formation of *N*-nitrosodi-isopropyl-, *N*-nitrosodibutyl-, and *N*-nitrosodi-(β-nitroxyethyl)amines has been observed in the catalytic nitration of the corresponding amines in the presence of zinc chloride [27,141]. In this connection, one may note that the catalytic effect of Cu^{2+} ions in the nitrosation of diethylamine in methanol with nitric oxide under pressure has also been investigated [142,143]. The effects of temperature, pressure, and the concentration of nitrogen oxides on the mode of reaction have been studied. The optimum yield of *N*-nitrosodiethyl-amine (93.8%) is attained in the reaction carried out at 30°C at a pressure of 1 atm. The reduction of temperature to −30°C, an increase of pressure, and an increase of the concentration of nitric oxide leads to a fall of the yield of the nitrosamine to 11–15% owing to the formation of methyl nitrite. The nitrosating species is $CuNO^{2+}$. The kinetics of the reactions were investigated.

According to patent data, when 1,1,1,6-tetranitro-3,6-diazaheptane is nitrated with a mixture of acetic anhydride and nitric acid, 1,1,1,6-tetranitro-3-nitroso-3,6-diazaheptane is formed [144]. We believe that this result is most probably "fortuituous". It is likely that the authors employed nitric acid containing a high content of nitrogen oxides, which were in fact responsible for the nitrosation of the amine.

Nitration of a ternary mixture of ammonium chloride, the ammonium salts of nitroform and di-(2,2,2-trinitroethyl)amine, formed in the condensation of methylenediamine hydrochloride with 2,2,2-trinitroethanol, and nitric acid in acetic anhydride leads to the formation of *N*-nitrosodi-(2,2,2-trinitroethyl)amine with an admixture of the nitramine [89]. The authors attribute the appearance of the *N*-nitroso-derivative to the catalytic effect of the chloride ions. The capacity of a mixture of acetic anhydride and nitric acid to behave as a nitrosating agent was noted by Wright and coworkers [27]. However, the nitrosation of di-(2,2,2-trinitroethyl)amine in this mixture can also take place in the absence of chloride ions under the action of N_2O_4.

The formation of *N*-nitrosodi-(2,2,2-trinitroethyl)amine was observed in the condensation of 2,2,2-trinitroethanol with hydroxylamine and also in the reaction of nitroform with formaldoxime in the presence of sulphuric acid [89]. The mechanism of the reaction was not established:

$$2\,HC(NO_2)_3 + 2\,CH_2{=}NOH \xrightarrow{H_2SO_4} [(NO_2)_3CCH_2]_2N\text{-}NO.$$

IV. PHYSICAL PROPERTIES, STRUCTURE, AND SPECTRA

1. General Characteristics

In the wide class of *N*-nitrosodialkylamines, the properties of the simplest members (*N*-nitrosodimethyl- and *N*-nitrosodiethyl-amines) were most fully investigated. The lower *N*-nitrosodialkylamines are yellow or yellow-green non-hygroscopic liquids, which are partially soluble in water and readily soluble in organic solvents. Their boiling points increase with the increasing size of the alkyl substituents and lie in the range 150–220°C. As a rule, substituted nitrosamines are yellow crystalline compounds. In this connection, it is important to note that *N*-nitrosopolynitroalkylamines are colourless, which is undoubtedly due to the effect of the polynitroalkyl substituents on the $p-\pi$ conjugation in the nitrosamines. Compared with the related nitramines, *N*-nitrosodialkylamines have lower boiling and melting points. The densities of the majority of nitrosamines are relatively low and lie in the range 0.9–1.2 g cm^{-3}, increasing with the molecular weight.

The dipole moments of *N*-nitrosodialkylamines are evidence of a considerable polarity of the molecules. For example, the dipole moment of *N*-nitrosodimethylamine is 3.98 D, [145] while that of *N*-nitrosodibutylamine is 4.32 D. [146] The introduction of electron-accepting substituents into the molecule leads to a decrease of the dipole moment. Thus the dipole moment of *N*-nitroso-*N*-phenylaminoacetic acid is 3.18 D [147] and those of *N*-nitrosomethylaniline and *N*-nitrosodiphenylamine are 3.62 and 3.39 D respectively [148]. The replacement of each methyl group by a phenyl group leads to a decrease of the dipole moment of the nitrosamine by 0.3 D. [148] Therefore we believe that it is of interest to investigate the dipole moments of nitrosamines with other electronegative substituents such as trifluoro-, trichloro-, and trinitromethyl groups, which will make it possible to trace their effect on the conjugation in the nitrosamino-group by the dipole moment method.

The average refraction of the N–N bond in *N*-nitrosodialkyl-amines hardly differs from the value in asymmetric dialkyl-hydrazines and amounts to 1.99. The refraction of the >N–N=O fragment is 7.748 and slightly exceeds the group refraction in dialkylhydrazines [54,149]. The parachors of the N=O and >N–N=O groups in a number of *N*-nitrosodialkylamines have been determined and the average values of these quantities have been found to be 53.4 and 68.0 respectively [54,149].

The literature quotes certain thermochemical parameters for *N*-nitrosodimethylamine: heat of combustion (382 ± 1.5 kcal $mole^{-1}$), heat of formation in the standard state (−10.7 ± 1.5 kcal $mole^{-1}$), heat of evaporation (9.9 ± 0.5 kcal $mole^{-1}$), and heat of formation in the gas phase (−0.8 ± 2 kcal $mole^{-1}$). [150]

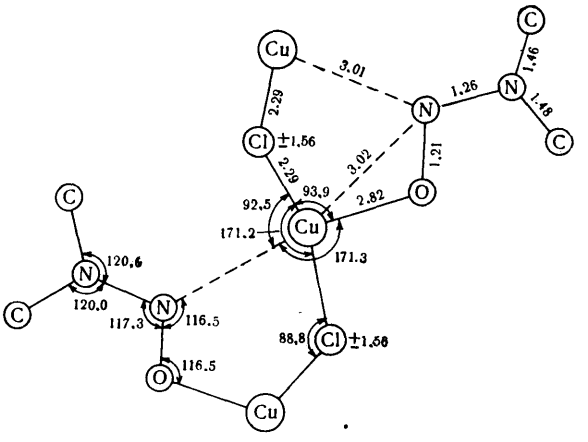
The dissociation energy of the N–N bond in *N*-nitrosodimethylamine, determined by the electron impact method, is 43 kcal $mole^{-1}$, [151] while according to other data it is 32 kcal $mole^{-1}$. [152] This quantity was recently estimated more accurately in a study already quoted [150] and was found to be 55.2 kcal $mole^{-1}$. Thus, contrary to earlier data, the N–N bond in *N*-nitrosodimethylamine proved to be stronger than in *N*-nitro-di-methylamine to the extent of 14.1 ± 5.2 kcal $mole^{-1}$ according to thermochemical data and 11.3 ± 3.0 kcal $mole^{-1}$ according to kinetic data [150]. These data appear to be the most correct, since they are consistent with the hypothesis of $p-\pi$ conjugation in the nitrosamine group, as a result of which the amount of N–N multiple bond character in nitrosamines is enhanced (about 49%) compared with that in nitramines (about 15%). [153–155]

2. Structure and Spectra

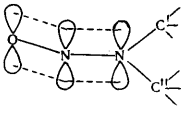
The molecules of aliphatic nitrosamines have coplanar structures in the gaseous and crystalline states. Both nitrogen atoms are in the state of sp^2 hybridisation, which is confirmed by the C′–N–N (120.3°), C″–N–N (116.4°), and N–N–O (113.6°) valence angles in *N*-nitrosodimethylamine. The bond lengths in *N*-nitrosodimethylamine are as follows: 1.235 Å for N–O, 1.344 Å for N–N, 1.461 Å for C–N, and 1.129 Å for C–H. It is interesting that the N–N bond in *N*-nitrosodimethylamine is shorter by 0.04 Å than in *N*-nitrodimethylamine, which has been attributed to the greater electron-accepting activity of the nitroso-group compared with the nitro-group [156]. The N–N bond length in *N*-nitrosodimethylamine agrees well with its enhanced multiplicity and strength compared with those in *N*-nitrodi-methylamine.

The planar disposition of the nitrosoamino-group has been established by an X-ray diffraction study of the adduct of *N*-nitrosodimethylamine with copper chloride. The bond between the copper atom and the nitrosamine is formed via the oxygen atom of the nitroso-group. The nitrogen atom of the nitroso-group is located at equal distances from the neighbouring copper atoms. The considerable difference between the Cu–O and Cu–N distances may be due to the fact that the copper atom is displaced by 0.2 Å from the plane passing through the chlorine atoms [157]. The shortening of the N–N bond in the complex compared with the free nitrosamine can be

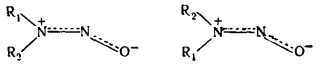
accounted for by the transfer of electron density from the dimethylamino-group to the nitroso-group [156]:



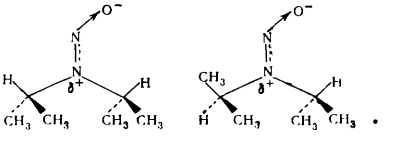
The disposition of the atoms in the nitrosamino-group in one plane naturally facilitates the overlapping of the *p* orbital of the amino-nitrogen atom with the π-electron cloud of the N⋯O bond. The force constant of the N⋯O bond in nitrosamines is 6.8 mdyn $Å^{-1}$. [158] According to this value, the multiplicity of the N⋯O bond in nitrosamines is between 1 and 1.5:



In a number of studies the internal rotation about the N–N bond with partial double bond character was investigated. The barrier to rotation about this bond is estimated as approximately 24 kcal $mole^{-1}$. [159–161] This leads to the appearance of *s-cis-trans* isomerism in nitrosamines. The presence of the isomers of a large number of *N*-nitroso-derivatives has been demonstrated by NMR spectroscopy [162,163]:



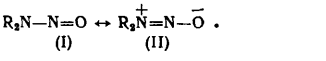
Only the *cis*-methyl isomer has been detected for *N*-nitrosomethylphenylamine. Both isomers have been found for *N*-nitrosoethylphenylamine and *N*-nitrosoisopropylphenylamine. The conformations of the alkyl substituents in *N*-nitrosoisopropylmethyl-, *N*-nitroso-t-butylmethyl-, and *N*-nitrosodi-isopropyl-amines are discussed in the same paper. The following conformations are characteristic of *N*-nitrosodi-isopropylamine:



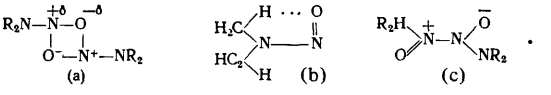
ΔH for the *cis–trans* isomerisation of *N*-nitrosobenzylmethyl-amine is less than 1 kcal $mole^{-1}$. [158] The *cis-trans* isomers of benzyl-2,6-dimethyl-*N*-nitrosoanilines were separated by thin-layer chromatography. The bulky 2,6-dimethylphenyl group evidently stabilises the isomers. Both substances are stable in the crystalline state [162]. Rotational isomerism has also been observed for *N*-nitrosobenzylisopropylamine [164,165]. The equilibrium mixture of the isomers was separated into its components by crystallisation from carbon disulphide [165]. The ratios of the areas of proton signals for certain *cis*- and *trans*-isomers have been investigated as a function of the bulk of the alkyl substituents. The screening of the protons of the *cis*-isomers is more pronounced than that of the protons of the *trans*-isomers, owing to the diamagnetic anisotropy of the N=O bond [166].

In a study of the optical rotatory dispersion it was observed that an intense cotton effect is characteristic of various nitrosamines in the range 350–400 nm. [167] The $n-\pi^*$ and $\pi-\pi^*$ transitions are active in the nitrosochromophores [168–171]. For example, in aqueous solution of *N*-nitrosodimethylamine the $\pi-\pi^*$ transition is shown in the region of 228 nm and the $n-\pi^*$ transition in the region of 332 nm. [169] The studies on the optical circular dichroism of nitrosamines have been reviewed in a monograph [172]. The sector rule for nitrosamines and its correlation with the stereochemistry of these compounds have been described [161].

Although a large number of infrared spectra of nitrosamines have been described in the literature, few systematic accounts of the assignments of the absorption frequencies are available [77,159,173–180]. In one of the first detailed studies of the infrared spectroscopy of nitrosamines, Haszeldine and Jander [174] drew attention to the inconsistency between the absorption bands of the N=O bond in nitrosamines and those for nitramines, nitrites, and *C*-nitroso-compounds. They observed in the infrared spectra of nitrosamines three relatively intense bands in the region of 7.1–7.4, 7.6–8.6, and 9.15–9.55 μm. The first two were assigned to the vibrations of the N=O bond and the last to the vibrations of the N–N bond. The appearance of the 7.6–8.6 μm band was attributed by the authors to the resonance of the following limiting structures:



To confirm these conclusions, a study was made of the effect of various solvents and the state of aggregation on the nature of the spectral changes [77,175]. It was found that the spectra of nitrosamines in the liquid state differ from those recorded in solvents (carbon tetrachloride and chloroform), particularly in the range of frequencies characteristic of the N=O bond. The authors attribute these changes to three causes: (a) dipole–dipole interaction between molecules, (b) intramolecular binding of the alkyl hydrogen by the oxygen atom of the nitroso-group, and (c) dimerisation of the molecules:



The predominance of a particular type of interaction depends on the conditions under which the nitrosamine exists. In the gaseous states the molecules are of course not associated and therefore the N=O absorption band is closer to that in the spectra of nitramines. In the liquid state monomer–dimer equilibrium obtains and the N=O absorption band is displaced towards longer wavelengths (6.74 and 6.93 μm respectively for *N*-nitrosodiethylamine).

Polar solvents have a similar effect. The N–N absorption band varies in exactly the same way. For example, in the spectrum of gaseous *N*-nitrosodiethylamine it is in the region of 9.55 μm and in that of the liquid substance it is displaced to 9.35 μm. The idea of a monomer–dimer equilibrium in nitrosamines was supported by Tarte [176] and by Piskorz and Urbański [177].

An interesting observation was made in a study of the infrared spectrum of *N*-nitrosodi-(2,2,2-trifluoroethyl)-amine, one of the few *N*-nitroso-derivatives containing electron-accepting substituents [77]. In this substance the N=O absorption bands are displaced under the influence of the trifluoroalkyl groups towards shorter wavelengths and are located in the region of 6.45 μm for the gaseous nitrosamine and in the region of 6.60 μm for the liquid substance. The displacement of the bands was attributed by the authors to a decrease of the polarity of the *N*-nitrosodi-(2,2,2-trifluoroethyl)amine molecule, which reduces sharply the interaction between the individual molecules. It is interesting that the N–N bond vibration frequencies in *N*-nitrosodi-(2,2,2-trifluoroethyl)amine in solution, or following a change in the state of aggregation, are displaced less than for unsubstituted nitrosamines.

Williams et al. [178], who postulated the occurrence of mesomerism in nitrosamines, suggested that, when the spectra are recorded in polar solvents, the absorption bands associated with the N=O bond vibrations (6.6–6.7 μm) should be displaced towards longer wavelengths. On the other hand, the N–N absorption band should be shown at lower wavelengths. This hypothesis was confirmed experimentally. In the spectra of *N*-nitrosodimethylamine in carbon tetrachloride and methylene bromide $\lambda_{N=O}$ is 6.85 and 6.94 μm, the corresponding values for the N–N absorption band (λ_{N-N}) being 9.66 and 9.52 μm. An analogous situation was found in the spectra of other nitrosamines.

The wavelength corresponding to the N=O bond in the nitrosamines is much higher than for *C*-nitroso-derivatives which can be accounted for by the greater contribution to the structure of nitrosamines of the canonical form (II). [178] The hypothesis of the dimerisation of nitrosamines put forward by Haszeldine and coworkers was rejected by Williams [178] and other investigators [171,179,180].

The Table summarises the principal literature data on the infrared spectra of nitrosamines.

Comparison of the infrared spectra of *N*-nitrosodi-(2,2,2-trifluoroethyl)amine with those of unsubstituted analogues demonstrates that electron-accepting substituents have a significant influence on the structure of the nitrosamino-group, probably by reducing the degree of p-π conjugation. This conclusion has been confirmed experimentally in a study of the chemical properties of *N*-nitrosopolynitroalkylamines. It is significant that in the infrared spectrum of *N*-nitrosodi-(2-bromo-2,2-dinitroethyl)amine and *N*-nitrosodi-(2,2,2-trinitroethyl)amine, bands with ν_{NO} = 1490 and 1520 cm^{-1} and ν_{N-N} = 980 and 1020 cm^{-1} respectively are characteristic of the nitrosamino-group†.

In the ultraviolet spectra of nitrosamines there are two absorption bands in the region of 235 and 365 nm, [174] 230 and 374 nm, [177] 230 and 365 nm, [77] and 228 and 332 nm [169] (in water). The first of these is more distinct than the second. The bands were assigned by comparing the spectra of nitrosamines with those of nitrites and nitramines. In the ultraviolet spectra of nitramines, there is a strong absorption in the region close to 235 nm and in the spectra of nitrites in the region of 375 to 380 nm. [77,175] Therefore the absorption band in the region of 230–235 nm in the spectra of nitrosamines characterises the N–N bond and the absorption in the region of longer wavelengths is due to the N=O bond [175].

The positions of the bands in the ultraviolet as well as infrared spectra, depend greatly on the nature of the solvent. For example, on passing from a non-polar solvent to water, the 365 nm band is displaced to 331 nm. This shows that the N=O bond is sensitive to external effects. A similar observation was made in a study of the ultraviolet spectrum of *N*-nitrosodi-(2,2,2-trinitroethyl)amine [89].

Infrared spectra of certain nitrosamines R_2N-NO.

R	Liquid		Soln. in CCl_4		Пар	
	$\nu_{N=O}$, cm^{-1}	ν_{N-N}, cm^{-1}	$\nu_{N=O}$, cm^{-1}	ν_{N-N}, cm^{-1}	$\nu_{N=O}$, cm^{-1}	ν_{N-N}, cm^{-1}
CH_3	1445	1048	1460	1041	1488	1015
C_2H_5	1448	1069	1459	1061	1485	1048
n-C_3H_7	1455	1069	1460	1067	1486	1049
iso-C_3H_7	—	—	1438	1139	—	—
s-C_4H_9	—	—	1437	1135	—	—
n-C_5H_{11}	1460	1084	—	1082	—	—
$C_6H_5CH_2$	—	—	1463	1120	—	—
C_6H_{13}	1460	1090	—	1085	—	—
F_3CCH_2	1515	1052	1528	1046	1550	1046

Electron-accepting substituents have an appreciable effect on the absorption by the nitroso-group. Whereas the absorption by the N=O bond in *N*-nitrosodiethylamine occurs in the region of 360 nm, in the *N*-nitroso-derivatives of di-(2,2,2-trinitroethyl)-, di-(2-bromo-2,2-dinitroethyl)-, and di-(2,2,2-trifluoroethyl)amines it is displaced to the region of 380 nm. Information about these effects of the nature of the substituent on the >N–N=O fragment is also provided by mass spectrometric data. For example, *N*-nitrosodimethylamine dissociates with formation of $C_2H_4N^+$ as the major ion (19.2%), while *N*-nitroso-di(trifluoromethyl)amine gives the CF_3^+ major ion (37.8%). [181]

V. CHEMICAL PROPERTIES

Aliphatic nitrosamines are highly reactive. The reason for their reactivity is that the nitrosamino-group has four lone pairs of electrons, which make nitrosamines potential Lewis bases. The occurrence of p-π conjugations with the withdrawal of the electron cloud towards the oxygen atom is responsible for many interesting reactions of nitrosamines. In the first place these are the complex-formation reactions, reaction with inorganic acids, reduction to *NN*-substituted hydrazines, oxidation and nitration, cyclisation to sydnones, and sydnoneimines, and photochemical reactions.

†The absorption frequencies were assigned by the authors of the review on the basis of the spectra quoted by Grimes et al. [89]

2. Reaction with Inorganic Acids, Hydrogen Bonds, and Complex-formation Capacity of Nitrosamines

When inorganic acids act upon nitrosamines, the nitroso-group is split off with formation of amine salts. In one of the first studies [6] it was already noted that, when hydrogen chloride is passed into an emulsion of *N*-nitrosodiethylamine in water, the nitroso-derivative rapidly dissolves. When an ethereal solution of *N*-nitrosodiethylamine is treated with hydrogen chloride, a salt with the composition $(C_2H_5)_2NNO.HCl$ is formed, and then readily decomposes on addition of water or alcohol [52].

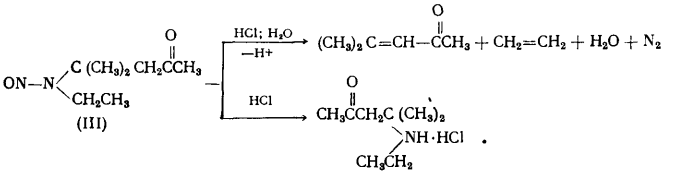
N-Nitrosodimethylamine decomposes on heating with hydrochloric acid into dimethylamine hydrochloride and nitrous acid. Hydrochloric acid acts similarly on *N*-nitrosodibutylamine [31], *N*-nitrosomethylallylamine [82], *N*-nitrosodibenzylamine, and others [43,55,182]:

$$R_1R_2N{-}NO \xrightarrow{HCl;\ H_2O} R_1R_2NH \cdot HCl + HNO_2 .$$

Hydrogen chloride has a more pronounced denitrosating activity [6,42,113,134]. Some investigators have also proposed a method for the preparation of pure secondary amines involving the treatment of nitrosamine solutions in ether or toluene with hydrogen chloride [42,134].

It is interesting that the denitrosation takes place more readily than the hydrolysis of the nitrile group. Thus, in an attempt to hydrolyse the dinitrile of *N*-nitrosiminodiacetic acid, Curtius [94] isolated as the main product the hydrochloride of the dinitrile of iminodiacetic acid.

The carbonyl group has a significant influence on the result of the denitrosation. When the nitroso-derivative (III) is treated with hydrochloric acid, ethylene and mesityl oxide are formed [41]. In contrast to hydrochloric acid, hydrogen chloride has only a denitrosating effect:



It has been noted that, when *N*-nitrosopolynitroalkylamines are denitrosated, it is impossible to isolate the salts of polynitroalkylamines or the free amines. Evidently in this case a more profound degradation of the molecule takes place, owing to the reduced basicity of the amino-nitrogen in polynitroalkylamines [89,183].

Apart from hydrochloric acid and hydrogen chloride, bromine and sulphuric acid have been used as denitrosating agents [113,184]:

$$(C_6H_5CH_2)_2N{-}NO \xrightarrow[-NO]{Br_2} (BrC_6H_4CH_2)_2NH \cdot HBr .$$

The study of the kinetics of the cleavage of aliphatic nitrosamines by acids led to the hypothesis that the splitting off of the nitroso-group is preceded by the occurrence of an equilibrium between the nitrosamine and its protonated form. The protonated nitrosamine then splits off the nitroso-group in the form of the nitrosonium cation and is itself converted into the corresponding amine:

$$R'RN{-}N{=}O + H^+ \leftrightarrows R'R\overset{+}{N}H{-}N{=}O ,$$
$$R'R\overset{+}{N}H{-}N{=}O \rightarrow R'RNH + \overset{+}{N}O \ (\text{slow}) .$$

The hydrolysis is easier the more electrophilic is the R or R′ group. In hydrochloric acid the denitrosation takes place more readily than in sulphuric or perchloric acid. The authors explain this by the nucleophilic reaction

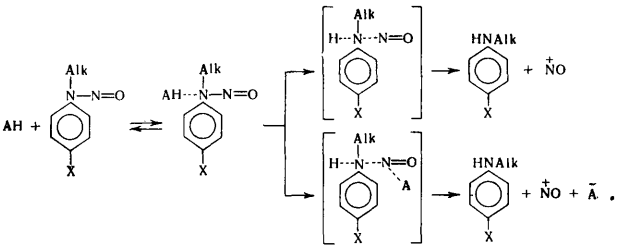
$$\overset{+}{N}H{-}N{=}O \xrightarrow{Cl^-} \overset{+}{N}H{-}N\begin{matrix}Cl\\O^-\end{matrix} \rightarrow NH + NOCl .$$

The rate of hydrolysis obeys the Hammett equation [185,186]:

$$\lg K + H_0 = \text{const.}$$

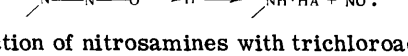
According to the data of Porai-Koshits and coworkers [187–190], the denitrosation of aliphatic-aromatic nitrosamines takes place by a "push–pull" mechanism. Preliminary protonation of the nitrosamino-group was not observed. The splitting off of the nitroso-group is promoted by the additional polarisation of the N–N bond owing to the formation of a hydrogen bond involving the nitrogen atom of the amino-group. The formation of the new N–H bond takes place simultaneously with the splitting off of the nitroso-group.

The presence of electron-accepting substituents in the *para*-position of the aromatic ring lowers the basicity of the amino-nitrogen in the nitroso-derivative and in this case the nucleophilic attack by the acid anions plays a decisive role. However, acid anions participate in the splitting off of the nitroso-groups only in the presence of hydrogen ions. On the basis of the results obtained, the following reaction mechanisms have been proposed as a function of the structure of the nitrosamine:

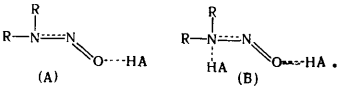


The results of studies on the formation of hydrogen bonds in aliphatic nitrosamines and also their chemical behaviour show that the reaction centre is located at the oxygen atom of the nitroso-group, which is inconsistent with the above hypothesis concerning the denitrosation of nitrosamines.

We believe that a more correct mechanism of the denitrosation of aliphatic nitrosamines involves electrophilic attack on the oxygen atom of the nitroso-group. The latter is readily eliminated as a result of the generation of partial positive charges at the nitrogen atom [157]:



The reaction of nitrosamines with trichloroacetic acid in cyclohexane takes place with formation of one or two hydrogen bonds and may be described by the following structures [168]:



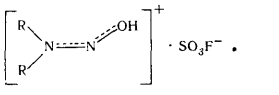
A number of changes takes place in the ultraviolet spectrum of *N*-nitrosodimethylamine in aqueous sulphuric acid solution due to acid–base interaction [169]:

$$R_2NNO \ldots (H_2O)_x \overset{H_2SO_4}{\rightleftharpoons} R_2NNO \ldots (H_2O)_x H_2SO_4 ,$$
$$R_2NNO \ldots (H_2O)_x \leftrightarrows R_2NNO \ldots (H_2O)_x HSO_4^- ,$$
$$R_2NNO \ldots (H_2O)_x HSO_4^- \rightleftarrows R_2NNOH^+ \ldots (H_2O)_x ,$$
$$R_2NNO \ldots (H_2O)_x HSO_4^- \leftrightarrows R_2NNO \ldots (H_2O)_x (H_2SO_4)_2 ,$$
$$R_2NNO \ldots (H_2O)_x HSO_4^- \rightleftarrows R_2NNO \ldots (H_2O)_x (HSO_4)_2 .$$

The attempts to isolate the salts of the nitrosamine and sulphuric acid were unsuccessful, but unstable white 1 : 1 crystalline adducts of 72% perchloric acid with *N*-nitrosodi-n-heptylamine, *N*-nitrosodi-n-octylamine, and *N*-nitrosodi-(2-ethylhexyl)amine were obtained, which indicates the possibility of proton transfer to the oxygen atom of the nitroso-group.

Nitrosamines form hydrogen bonds with formic, acetic, and trifluoroacetic acids and with alcohols, phenols, and amines [171 191-193]. The proton-donating activity of alcohols in the formation of the hydrogen bond increases in the series primary > secondary > tertiary. The equilibrium constants for the hydrogen-bonded complexes of nitrosamines and phenols increase linearly with the pK_a of the phenols [191].

A detailed study of the protonation of *N*-nitrosodimethyl- and *N*-nitrosodiethylamines and also *N*-nitrosopiperidine by NMR spectroscopy was undertaken [194]. The characteristic signal associated with the interaction of the proton with the nitrosamine occurs only in fluorosulphonic acid at 0°C and below. In other acids the spectra also show changes characteristic of structure (A); the dialkylamino-group is not protonated. The spectra shows that the formation of the hydrogen bond or protonation involves the oxygen atom of the nitrosamino-group. A structure with a delocalised positive charge has been proposed for the adducts of nitrosamines with fluorosulphonic acid:



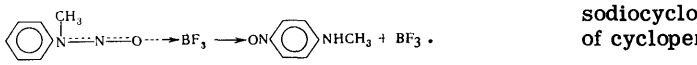
The delocalisation of the positive charge probably prevents further protonation of the molecule.

A study of the competing protonation of *N*-nitrosodimethylamine and dimethylformamide by trifluoroacetic acid in 2-nitropropane showed that the nitrosamine is a weaker base [194].

The basic nature of the oxygen atom is shown by the capacity of nitrosamines to give rise to brightly coloured stable complexes with bromoplatinic acid, the composition of which corresponds to the formula $[R_2NNO.H]_2PtBr_6$. [195] Complexes of nitrosamines with boron trifluoride are formed when equimolar amounts of the nitrosamine and boron trifluoride-ether are mixed or when an ethereal solution of the nitrosamine is treated with boron trifluoride [196]:

$$R_1R_2N{-}N{=}O + BF_3 \rightarrow R_1R_2N \overset{\cdots}{=} N \overset{\cdots}{=} O \cdots\rightarrow BF_3 .$$

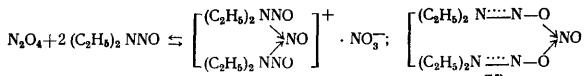
The stability of the complexes increases with the electron-donating capacity of the substituent linked to the nitrogen atom. The complex with *N*-nitrosodiphenylamine could not be isolated. It is interesting that in the adduct of boron trifluoride and *N*-methyl-*N*-nitrosoaniline the N–N bond is so much weakened that rapid rearrangement to *N*-methyl-*p*-nitrosoaniline takes place:



The results of spectroscopic analysis showed that the oxygen atom of the nitrosamino-group behaves as the electron donor in these complexes, although the possibility of the involvement of the amino-nitrogen in the formation of the donor-acceptor bond has also been suggested [158].

The NMR spectra of the adducts of *N*-nitrosodimethylamine with BF_3, PCl_5, $SbCl_5$, $AlCl_3$, and $ZnBr_2$ showed that the methyl groups are non-equivalent, as in the free nitrosamine. The non-equivalence of the methyl groups is evidence that the amino-nitrogen in the complexes remains in a state of sp^2 hybridisation. Consequently the acceptor is linked to the oxygen atom [197]. This structure is also confirmed by the high dipole moments (7.3 and 7.5 D) of the complexes of *N*-nitrosodiethyl- and *N*-nitrosodipropyl-amines with boron trifluoride.

N-Nitrosodiethylamine forms a 2 : 1 complex with nitrogen tetroxide, which was confirmed by studies of the phase diagram, viscosity, and electrical conductivity of nitrosamine–N_2O_4 mixtures [103,198,199]. On the basis of ultraviolet spectroscopic data, structure (IV) was attributed to the complex [199], but, in the light of the above concepts concerning the structure of nitrosamines, structure (V), where the oxygen atom of the nitrosamino-group functions as the electron donor, is evidently more likely:



(IV) (V)

Recently it was discovered that *N*-nitrosodialkylamines readily form complexes with di(trinitromethyl)mercury in water [200-202]. The compounds are stable on storage and can be readily purified:

$$R_2NNO + Hg[C(NO_2)_3]_2 \xrightarrow{H_2O} R_2NNO \rightarrow Hg[C(NO_2)_3]_2 .$$

N-Nitrosopolynitroalkylamines, for example *N*-nitrosodi-(2,2,2-trinitroethyl)amine, do not react with di(trinitroethyl)mercury, in contrast to their unsubstituted analogues. This finding can be accounted for by a weakening of the electron-donating activity of the oxygen atom of the nitroso-group owing to a decrease of the degree of p-π conjugation caused by the polynitroalkyl groups.

The reactions of nitrosamines with other electrophilic agents are based on the complex-forming capacity of the former. For example, on heating to 60°C, *N*-nitrosodimethylamine reacts with methyl iodide [203]:

$$(CH_3)_2NNO + 2\,CH_3I \rightarrow [(CH_3)_4N]^+I^- + NO + {}^1/_2\,I_2 .$$

The reaction with triethyloxonium hexachloroantimonate in the cold results in the formation of ethoxydimethyldiazonium hexachloroantimonate [202,203]:

$$(CH_3)_2NNO + (C_2H_5)_3OSbCl_6 \rightarrow [(CH_3)_2NNOC_2H_5]^+SbCl_6^- .$$

O-Alkylnitrosimmonium salts are formed in high yields when nitrosamines are allowed to react with triethyloxonium fluoroborate or a mixture of alkyl iodide and silver perchlorate [204,205]:

$$R_2N{-}N{=}O + (C_2H_5)_3OBF_4 \rightarrow]R_2N \overset{\cdots}{=} N \overset{\cdots}{=} OC_2H_5]^+BF_4^- + (C_2H_5)_2O ,$$

$$R_2N{-}N{=}O + CH_3I + AgClO_4 \rightarrow [R_2N \overset{\cdots}{=} N \overset{\cdots}{=} OCH_3]^+ClO_4^- + AgI .$$

The study of the chemical behaviour of the salts and their infrared spectra showed that they are *O*-derivatives.

Dimethyl sulphate alkylates *N*-nitrosodimethylamine with formation of trimethylnitrosimmonium methyl sulphate. It is interesting that this adduct readily reacts with sodiocyclopentadienyl, forming the monomeric hydrazone of cyclopentadienone [206]:

$$(CH_3)_2N{-}NO + (CH_3)_2SO_4 \rightarrow [(CH_3)_2N \overset{\cdots}{=} N \overset{\cdots}{=} OCH_3]^+CH_3SO_4^- .$$

2. Reduction to *NN*-Substituted Hydrazines

The reduction of the nitroso-group to the amino-group is one of the characteristic reactions in the nitrosamine series. It was discovered by Fischer in the synthesis of dimethylhydrazine [19]. The reaction takes place when an acetic acid solution of *N*-nitrosodimethylamine is treated

with zinc dust. Apart from dimethylhydrazine, ammonia and dimethylamine were isolated. Later diethylhydrazine [207], piperidylhydrazine [208], isobutylmethylhydrazine [209], etc. were synthesised in this way; dimethylhydrazine was obtained in a higher yield [52].

When *N*-nitrosodiethylamine is reduced with the zinc and acetic acid, the formation of tetraethyltetrazene together with diethylhydrazine was observed [210]. A similar reaction was noted in the reduction of nitrosamines with hydrogen in the presence of palladium deposited on calcium carbonate [211]:

$$2\,(C_2H_5)_2N{-}NO + H_2 \rightarrow (C_2H_5)_2N{-}N{=}N{-}N(C_2H_5)_2\,.$$

Several ring-substituted dibenzyl derivatives of hydrazine were described by Curtius [17,212,213] and other investigators [87,88]. Using a modified method of reduction in ethanol and milder reaction conditions, they increased the yields of the desired products to 75%. A number of arylalkyl and dialkyl derivatives of hydrazines were synthesised by the same method [137,214,215].

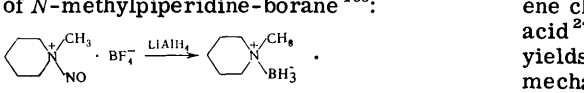
Apart from zinc and acetic acid, sodium amalgam [78,113] and also tin and hydrochloric acid [113] were employed to reduce nitrosamines. In the latter case hydrazine is not formed but the nitrosamine decomposes with elimination of the nitroso-group. The available data on the reduction with sodium amalgam are contradictory. Hydrazinoacetic acid and its dimethyl ester are formed from the corresponding nitrosamines in low yields, while *N*-nitrosodibenzylamine is converted into ammonia and dibenzylamine [113].

The method of reduction of *N*-nitrosodialkylamines with zinc in acetic acid is effective only for methyl-, ethyl-, and propyl-substituted nitrosamines [215]. Starting with the n-butyl derivative, secondary amines appear as the main reaction product. A general method of reduction with lithium aluminium hydride, developed for the synthesis of di-n-propyl-, di-n-butyl-, and di-n-pentylhydrazines as an example [215], has been proposed for the higher *N*-nitrosodialkylamines. Subsequently it was established that the result of the reaction depends on the nitrosamine: lithium aluminium hydride molar ratio. Thus for the reduction of *N*-nitrosodimethylamines the molar ratio of the components must be 1 : 2, [216] and in the case of *N*-nitrosodiphenylamine the ratio must be 1 : 1. [217] The yield of the desired product is affected also by the order of mixing of the components.

It is interesting that in the first stage of the reaction of the nitrosamine with lithium aluminium hydrides coloured complexes are formed, which are converted into dialkylhydrazines only on treatment with water [217,218]:

$$2\,R_2N{-}NO + 2\,LiAlH_4 \rightarrow (R_2N{-}N)_2AlLi + LiAlO_2 + 2\,H_2\,,$$
$$(R_2N{-}N)_2AlLi + 2\,H_2O \rightarrow 2\,R_2N{-}NH_2 + Li\,AlO_2\,.$$

The appearance of side products in the case of aromatic nitrosamines can be explained by the decrease of the polarity of the N–O bond owing to conjugation with the benzene ring. The reduction of *N*-methylpiperidine-nitrosyl fluoroborate with lithium aluminium hydride leads to the formation of *N*-methylpiperidine-borane [106]:



The catalytic hydrogenation of nitrosamines on the palladium catalyst in the presence of iron salts under pressure [219], reduction with zinc and aluminium in the presence of mercury salts or reduction with zinc in hydrochloric acid [220], and other reduction processes [221] have been described. The reaction of *N*-nitrosodialkylamines with zinc dust in formic acid in the presence of mercury(II) chloride results in the formation of an interesting class of compounds–*N*-isocyanodialkylamines [222].

Numerous modifications of the methods of hydrogenation of *N*-nitrosodialkylamines are quoted in the patent literature [223–233]. Compared with catalytic hydrogenation, the reduction of nitrosamines with sodium in liquid ammonia or alcohol [234] gives lower yields of dialkylhydrazines.

Nitrosamines can be reduced electrochemically to the corresponding hydrazines [235–237] or amines with elimination of one nitrogen atom in the form of ammonia. *NN*-Substituted hydrazines are formed via the mechanism

$$R_2NNO + 4\,H^+ + 4e \rightarrow R_2NNH_2\,.$$

The studies on the electrochemistry of nitrosamines have recently been reviewed in a monograph [238] and therefore they will not be discussed here.

When *N*-nitrosodialkylamines are hydrogenated in sulphuric, hydrochloric, nitric, acetic, or oxalic acids in the presence of Group VIII elements on charcoal or silica gel under pressure, hydroxylammonium salts are formed [239].

Nitrosamines undergo far-reaching cleavage on treatment with sodium hydrosulphite in an alkaline medium or when acted upon by lithium in liquid ammonia. This is known as the Overberger–Lombardino reaction and takes place via the intermediate formation of *N*-nitrenes, which readily decompose with evolution of nitrogen:

$$(RCH_2)_2N{-}NO \xrightarrow{Na_2S_2O_4;\,OH^-} (RCH_2)_2N{-}NHOH \xrightarrow[-H_2O]{} (RCH_2)_2N{-}\ddot{N} \xrightarrow[-N_2]{} \rightarrow (CH_2R)_2\,.$$

The Overberger–Lombardino reaction has been discussed in detail in monographs [240,241].

3. Oxidation and Nitration

Nitrosamines are important starting materials for the synthesis of secondary *N*-nitramines. According to the existing hypotheses, this reaction is based on the oxidation of the nitroso-group to the nitro-group.

The use of hydrogen peroxide with nitric acid for the oxidation gives low yields of nitramines and the desired product is contaminated [242]. Best results were obtained when nitric acid mixed with ammonium persulphate was employed [27]. Trifluoroperacetic acid proved to be a very convenient oxidising agent for nitrosamines [243]. The simplicity of the process and the purity and high yields of the final products made the oxidation of nitrosamines with trifluoroperacetic acid a valuable preparative method for the synthesis of secondary nitramines. For example, when *N*-nitrosodiethyl- and *N*-nitrosodibutylamines were acted upon by a mixture of trifluoroacetic acid in 90% hydrogen peroxide, the corresponding *N*-nitramines were obtained in 80% yield. When 30% hydrogen peroxide was employed, the yield of nitramines fell. A mixture of hydrogen peroxide and trifluoroacetic anhydride in methylene chloride may serve as a source of trifluoroperacetic acid [244]. This modification of the oxidation reaction yields pure nitramines in yields of 90% and above. The mechanism of the conversion of nitrosamines into nitramines under the influence of trifluoroperacetic acid has not been investigated:

$$R_2NNO \xrightarrow{CF_3COO{\cdot}OH} R_2NNO_2\,.$$

When *N*-nitrosodiethylamine was oxidised with nitronium pyrosulphate, acetaldehyde and acetic acid were

formed. The oxidation of *N*-nitrosodiethylamine with nitrogen pentoxide is very vigorous. The reaction may be controlled only by diluting the reactants [199]:

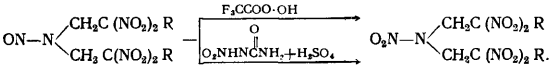
$$2\,(C_2H_5)_2NNO + N_2O_5 \rightarrow 2\,C_2H_5NO_2 + 2\,CH_3COOH + HNO_2 + HNO_3,$$
$$C_2H_5NO_2 + HNO_2 \rightarrow CH_3C(NOH)NO_2 + H_2O\,.$$

Until recently the reaction of nitrosamines with nitric acid was investigated only for aromatic compounds [245,246]. It has been shown [247] that ethyl *N*-isobutylcarbamate reacts with fuming nitric acid at −80°C to give a mixture consisting of 90% of ethyl *N*-isobutyl-*N*-nitrosocarbamate and 10% of ethyl *N*-isobutyl-*N*-nitrocarbamate. When the *N*-nitroso-derivative is subsequently treated with 100% nitric acid, the *N*-nitrated product is formed. The reaction was not investigated in detail. In other studies [29,144] it was shown that certain *N*-nitrosopolynitroalkylamines are readily converted into the corresponding nitramines under the influence of nitric acid or a mixture of nitric and sulphuric acids:

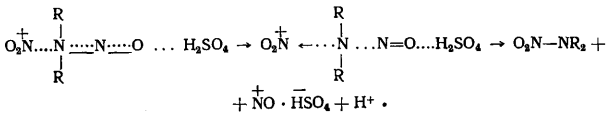
$$[BrC(NO_2)_2CH_2]_2N{-}NO \xrightarrow{HNO_3} [BrC(NO_2)_2CH_2]_2N{-}NO_2\,.$$

It is important to note that *N*-nitrosopolynitroalkylamines are resistant to oxidation by trifluoroperacetic acid [89,248]. If the oxidation of nitrosamines with trifluoroperacetic acid is assumed to be analogous to the hydroxylation of olefins, the negative results obtained in the oxidation of *N*-nitrosopolynitroalkylamines can probably be accounted for by the deficiency of electrons in the >N⁺⁻N⁺⁻O system owing to the electron-accepting influence of the substituents.

On the other hand, in *N*-nitrosopolynitroalkylamines the N–N bond should be weakened compared with the unsubstituted analogues. This leads to the possibility of an electrophilic substitution of the nitroso-group by a nitro-group in compounds of this kind. We believe that a convincing proof of the substitution of the nitroso-group is provided by the reaction of *N*-nitrosopolynitroalkylamines with nitrourea in sulphuric acid, leading to the formation of *N*-nitro-derivatives [248]. Nitrourea in sulphuric acid is known to be a source of nitronium cations [249]:



The reaction of *N*-nitrosopolynitroalkylamines with nitronium perchlorate in sulphuric acid is also accompanied by the formation of *N*-nitrosopolynitroalkylamines [248]. In an organic solvent (carbon tetrachloride) nitration does not occur. Since the presence of an acid and a nitronium cation is essential for the nitration of nitrosamines, the reaction can probably be described in terms of a "push–pull" mechanism:

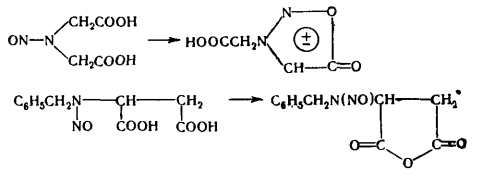


Thus the conversion of nitrosamines into nitramines can be achieved not only by the oxidation of the nitroso-group, but also by its electrophilic substitution by a nitro-group. The latter type of reaction is particularly characteristic of nitroso-derivatives containing electron-accepting substituents, for example polynitroalkyl derivatives.

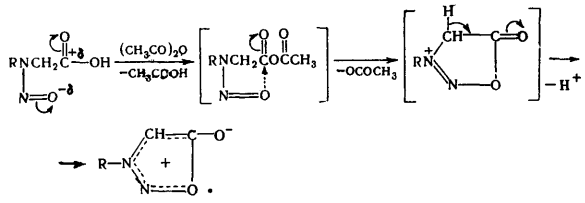
4. Cyclisation of α-Nitrosaminocarboxylic Acids and Their Nitriles into Sydnones and Sydnoneimines

In 1935 Earl and Mackney [250] obtained by treating *N*-nitroso-*N*-phenylglycine with acetic anhydride a cyclic compound, which was called sydnone (in honour of the place where it was first synthesised). Later it proved possible to introduce into the cyclisation reaction the nitriles of α-nitrosaminocarboxylic acids [95], which resulted in the formation of sydnoneimines. The initial discoveries were followed by an intense investigation of the methods of synthesis and properties of this interesting class of compounds. Two reviews dealing with the chemistry of sydnones and sydnoneimines were published [2,3] the second of which appeared comparatively recently and therefore we shall only mention the methods for the mechanism of the cyclisation of nitrosamines into these compounds.

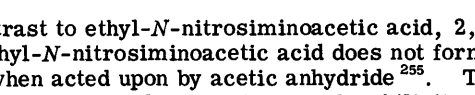
Usually acetic anhydride is employed for the cyclisation. However, trifluoroacetic anhydride, thionyl chloride, and *NN'*-di-isopropylcarbodi-imide can also be used for this purpose [251,252]. *N*-Nitrosodicarboxylic acids, for example nitrosiminodiacetic acid, are cyclised similarly to monocarboxylic acids [253,254], but cases are known where only the carboxy-groups are involved in the reaction [95]:



The formation of sydnones is based on the nucleophilic nature of the oxygen atom of the nitroso-group, and takes place via a mixed anhydride (when anhydrides are employed as the dehydrating agents), which already at room temperature splits off in succession an acetate ion and a proton [2,252]:

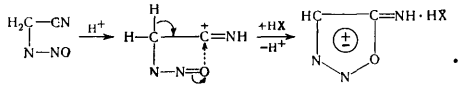


In contrast to ethyl-*N*-nitrosiminoacetic acid, 2,2,2-trinitroethyl-*N*-nitrosiminoacetic acid does not form a sydnone when acted upon by acetic anhydride [255]. This is probably due to the reduction of the nucleophilicity of the oxygen atom in the >N–N=O fragment under the influence of the trinitroethyl group. In the cyclisation of polynitroalkyl-*N*-nitrosaminoacetic acids, it is essential to employ trifluoroacetic anhydride, which increases the electrophilicity of the carbonyl carbon atom in the intermediate mixed anhydride:

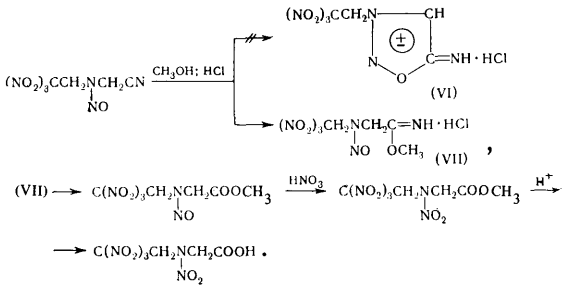


The nature of the cyclisation of the nitrile of α-nitrosaminocarboxylic acids to sydnoneimines is determined by the capacity of the nitrile group to combine with

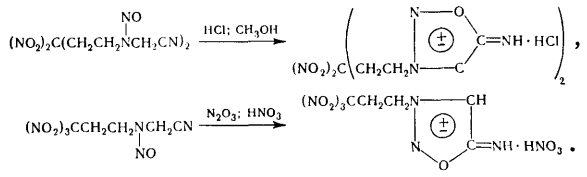
electrophilic agents. The reaction is achieved under the influence of hydrogen chloride [256] or nitrogen oxides [96]:



The powerful influence of the electron-accepting substituents on the conjugation in the >N⋯N⋯O fragment can be demonstrated yet again for the nitriles of polynitroalkyl-*N*-nitrosaminocarboxylic acids as an example. Thus, in attempts to cyclise the nitrile of 2,2,2-trinitroethyl-*N*-nitrosaminoacetic acid in methanol under the influence of hydrogen chloride, the imino-ether (VII) was isolated instead of the expected sydnoneimine (VI), the structure of (VII) being demonstrated unambiguously by its conversion into *N*-nitramino-2,2,2-trinitroethylacetic acid [257]:

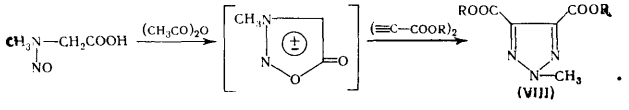


The formation of the imino-ether (VII) is possible only when the nucleophilic properties of the oxygen atom of the nitroso-group are weakened, as a result of which the intermediate carboimmonium ion $(NO_2)_3CCH_2N(NO)CH_2\overset{+}{C}=NH$ undergoes methanolysis, which competes with the ring-closure reaction. The removal of the nitro-groups to the γ-position relative to the nitrosamino-group weakens their influence on the polarisation of the oxygen atom and promotes the formation of the sydnoneimine [257]:

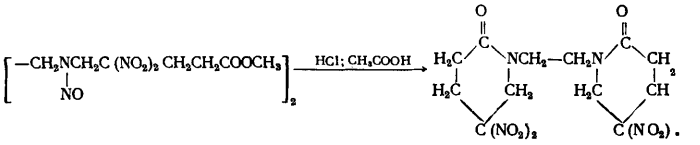


Sydnones and sydnoneimines are reactive mesoionic aromatic compounds. The hydrogen atom in the 4-position in the ring is readily substituted by halogens, nitro-groups, sulpho-groups, etc. Sydnones may be employed to synthesise hydrazines [45]. They undergo the 1,3-dipolar-cycloaddition reaction with unsaturated compounds, forming pyrazoline derivatives [258]. In contrast to sydnones, sydnoneimines undergo ring opening under conditions of alkaline hydrolysis, the amides of α-nitrosaminocarboxylic acids being formed [95]. Sydnoneimines form readily *exo*-*N*-nitroso- and nitro-derivatives.

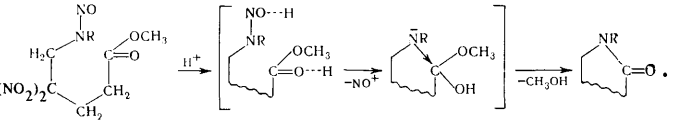
When *N*-nitrososarcosine is heated with acetic anhydride in the presence of acetylenedicarboxylic acid esters, carbon dioxide is evolved and a cycloadduct (VIII) is formed [259]:



Recently it has been established for esters of polynitroalkyl-*N*-nitrosaminocarboxylic acids that yet another type of cyclisation is characteristic of *N*-nitroso-compounds. When *N*-nitrosodi-(4-methoxycarbonyl-2,2-dinitrobutyl)amine and *NN*-dinitrosodi-(4-methoxycarbonyl-2,2-dinitrobutyl)ethylenediamine were treated with a mixture of acetic and hydrochloric acid, *N*-(4-carboxy-2,2-dinitrobutyl)-γγ-dinitro-δ-valerolactam and ethylenedi(γγ-dinitro-δ-valerolactam) were isolated [260]:

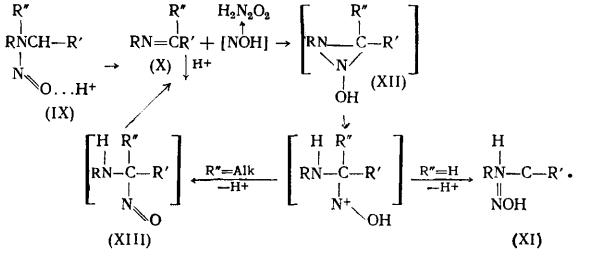


The reaction is accompanied by vigorous evolution of nitrogen oxides. The nature of closure to the lactam ring shows that the nitroso-group is split off as the nitrosonium cation with transfer of the bonding electron pair to the nitrogen atom of the amino-group. The presence of acid promotes the elimination of the nitroso-group and the protonation of the carbonyl carbon atom, while the presence of a five-membered carbon chain at the nitrogen atom creates favourable steric conditions for ring closure. The mechanism of the formation of the lactam ring can be represented as follows:



5. Photochemical Reactions of Nitrosamines

Several years ago reports appeared about a new reaction in the nitrosamine series: photolytic decomposition in the presence of acids [261,262]. On ultraviolet irradiation in methanol or water in the presence of hydrochloric acid, nitrosamines are converted into amidoximes, secondary amines, alkylideneimines, and other compounds. It is suggested that in the first reaction stage a complex (IX) is formed, which decomposes to the imine (X) and a nitroxyl in a solvent cage via an excited triplet radical-ion π-complex. The amidoxime (XI) is formed as a result of the recombination of (X) and NOH. The recombination is possible either via the addition of the monomer of hyponitrous acid and a proton to the C=N double bond of (X) or via the intermediate formation of *N*-hydroxyaziridine (XII) with subsequent rearrangement of the latter to the amidoxime:



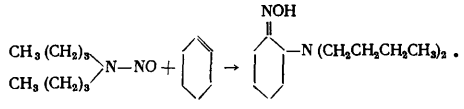
In this case, when the carbon atom of the C=N bond of (X) does not split off a proton (R″ ≠ H), for example in the photolysis of *N*-nitrosodicyclohexylamine, the OH group is lost and a *C*-nitroso-compound (XIII) is formed. Elimination of NOH from (XIII) again leads to the alkylideneimine (X). Therefore the retardation of the nucleophilic attack

on NOH is accompanied by the hydrolysis or polymerisation of the primary photolysis product. It is evident that the steric factor plays an important role in the photoelimination reaction and therefore *trans–anti* elimination of NOH from the photoexcited nitrosamine–proton complex takes place. The intermolecular mechanism of the photoisomerisation of *N*-nitrosodialkylamines has been discussed [263].

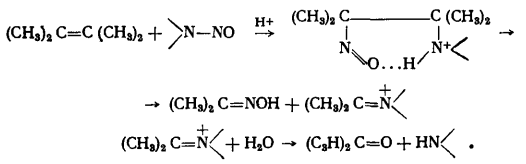
The photolytic decomposition of nitrosamines leads ultimately to the formation of aldehydes and ketones. For example, *N*-nitrosodibutylamine gives a high yield of butyraldehyde after the hydrolysis of the amidoxime (XI), while *N*-nitrosodicyclohexylamine gives rise to cyclohexanone [264].

In the presence of acids the photolytic addition of *N*-nitrosamines to various olefins takes place smoothly [265–267]. Formally the photoaddition reaction takes place via the dissociation of the N–N bond with subsequent addition of the nitroso- and amino-groups to the C=C bond and formation of a *C*-nitroso-compound as the primary reaction product. The latter undergoes secondary reactions, which lead to the final product [265].

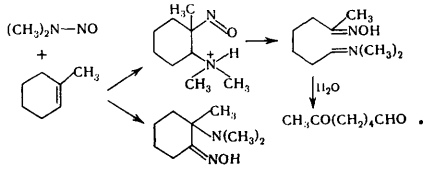
N-Nitrosodibutylamine adds to cyclohexene with formation of the oxime of 2-di-n-butylaminocyclohexanone in 38% yield [267]:



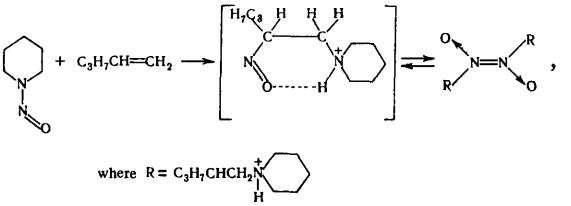
The nitroso-group adds as a rule to the most hydrogenated carbon atom. This observation made it possible to achieve the photolytic addition of nitrosamines to a multiple bond with subsequent dissociation of the C–C bond [266]. Thus irradiation of a mixture of tetramethylethylene and nitrosopiperidine leads to the formation of acetone and acetoxime:



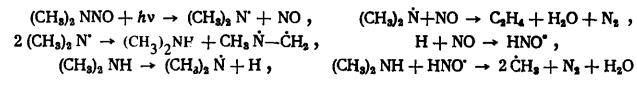
Similarly α-methylstyrene forms acetophenone and di-(1-piperidinyl)methane. When the carbon atom bound to the nitroso-group is combined with a hydrogen atom, the reaction stops at the stage involving the isomerisation of the *C*-nitroso-derivative to the oxime and the C–C bond is not ruptured. Sometimes intramolecular proton transfer can be faster than the isomerisation to the oxime. *N*-Nitrosodimethylamine reacts with 1-methylcyclohexene, forming predominantly 6-oxoheptanal [265]:



The addition of *N*-nitrosopiperidine to pent-1-ene is accompanied by the formation of a dimer of the *C*-nitroso-derivative via the mechanism [265]:



When *N*-nitrosodimethyl- and *N*-nitrosodiethylamines were photolysed in the vapour phase, hydrogen, nitrogen, alkanes, secondary amines, and nitrogen oxides were detected in the reaction products [152]. These results suggest that, in contrast to the low-temperature photolysis, the process has a radical mechanism:



VI. CERTAIN ASPECTS OF PRACTICAL APPLICATION

The lower *N*-nitrosodialkylamines, in particular *N*-nitrosodimethylamine, are largely employed in the synthesis of asymmetric dialkylhydrazines. Dimethylhydrazines are one of the most important components of rocket fuels [268,269]. A mixture of dimethylhydrazine, dimethylamine, and ammonia, obtained by the hydrogenation of *N*-nitrosodimethylamine in the vapour of liquid phase, has been recommended for guided rockets and missiles [228,229].

It has been noted in the patent literature that nitrosamines may be employed as antioxidants in fuels, lubricating oils, and rubbers [98]. There is an interesting prospect of the employment of nitrosamines as special fuels, stabilisers for aromatic halogeno-compounds, fungicides, insecticides, and bactericides and also as intermediates in the manufacture of medicinal preparations [61,98,270].

N-Nitrosodimethylamine is employed in the form of aqueous solutions or powders as a nematocide. In a dose of 112 kg per hectare it protects tomatoes from the nematode *Meloidogyne incognita* and in doses of 56 to 112 kg per hectare it is non-phytotoxic for carrots, tobacco, cabbage, and the cotton plant; however, it inhibits to some extent the growth of [lima] beans and peas [270].

N-Nitrosodimethylamine has been recommended as a solvent in the manufacture of fibre from polyacrylonitrile [271].

However, the high toxicity of nitrosamines should be noted. For example, *N*-nitrosodimethylamine has been included in the group of carcinogenic and irritant substances. It is recommended that the possibility of the contamination of air by this compound be completely prevented [272].

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