Tetrahedron Vol. 46, No. 12, pp. 4303–4332, 1990
Printed in Great Britain

0040–4020/90 $3.00+.00

AROMATIC TERTIARY AMINES AND n-BUTYL NITRITE

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(*Received in UK* 26 *March* 1990)

Abstract - The reaction between alkyl nitrites, particularly n-butyl nitrite, and tertiary aromatic amines under a variety of experimental conditions promptly yielded products of N-dealkylation-N-nitrosation, ring nitration, ipso-substitution and, occasionally, combinations of these processes. Aminoethers were detected as final products and intermediates on the way to N-nitrosations. Reaction pathways are suggested for some of the observed behaviours on the basis of experimental evidences whereas other alternatives are discarded.

Introduction

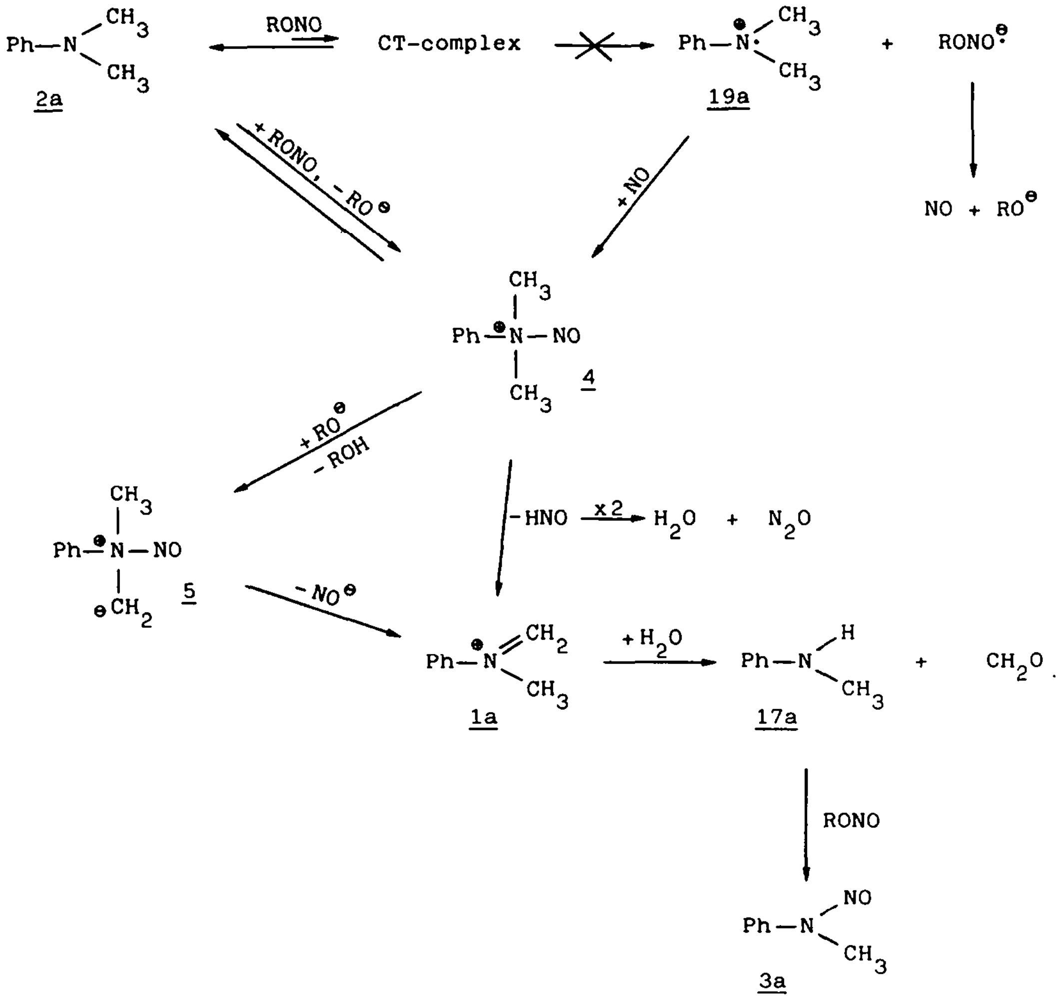
Contrary to earlier beliefs, grown against continuous scattered evidences reported in the literature, tertiary amines of widely different structures undergo N-dealkylation-N-nitrosation upon treatment with nitrogen oxides,[1] "nitrous acid",[2] nitrosyl halides[3] and other nitrosating agents. Among the latter are nitrite esters, as definitively established by one of us[4] and later confirmed by others.[5] Nitrite esters are, on the other hand, well known N-nitrosating agents both for secondary amines (yielding N-nitrosamines)[6] and primary amines (aprotic diazotisation).[7]

Whereas studies are available on the mechanisms of N-nitrosation with "nitrous acid" with several amines, the reaction with alkyl nitrites has not been extensively examined especially in the field of aromatic amines. This work aims at contributing a wider and better understanding of this reaction.

Results and Discussion

N,N-Dimethylbenzeneamine (2a) was found to undergo N-dealkylation-N-nitrosation to N-methyl-N-nitrosobenzeneamine (3a) in 35-52% yield upon treatment with an excess n-propyl or amyl nitrite (AN): the intermediacy of N-methylN-methylenebenzeneimmonium ion (1a) was inferred from the isolation and identification of its coupling-rearrangement product with 2a. It was also unveiled how 3a was produced, but it was left to be decided which were the events leading to 1a among a number of possible alternatives,[4] shown in scheme 1. Being unlikely the preliminary thermal decomposition of the alkyl nitrite under the experimental conditions we chose to work at, namely below 100°C,[8] we are left with two routes converging to N,N-dimethyl-N-nitrosobenzeneammonium ion (4), one of which may select to move on directly to 1a. Beside the N-S_N2 reaction by the amine nitrogen onto the nitroso nitrogen to yield 4, an electron transfer reaction between the nitrite and 2a, perhaps mediated by the intermediacy of a CT-complex, may lead to a nitrite radical ion, which eventually breaks down to an alkoxy anion and nitrogen monoxide, as it is suggested by negative ion mass spectrometry.[9]

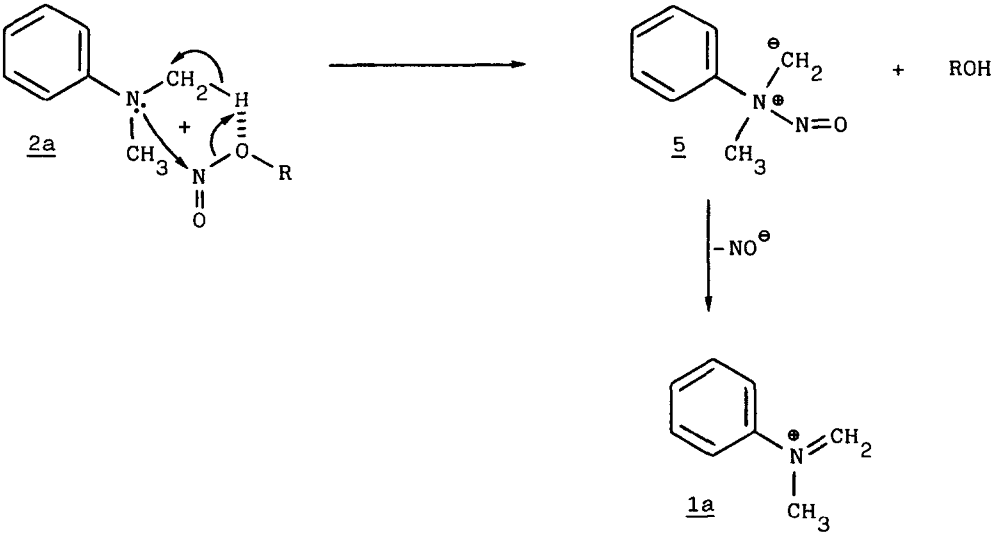
Scheme 1



The implication of aminium ions was put forward[10] in order to rationalize the formation of chain oxygenated products in the reaction of "nitrous acid" with tributylamine and in other experiments[11] with "HNO_2". The radical route appeared readily untenable on the basis of the observed incompatibility of the redox properties (in acetonitrile) of 2a (0.71-0.68 V)[12] and butyl nitrite (BN, -1.68 V). Escape of nitrogen monoxide from the reactants cage could be expected to be a rather efficient process in this case, but evolution of this gas was very minor, if it occurred at all and dimerization products were detected.

We have searched by means of electronic and ^{1}H-NMR spectroscopy evidences for complexation and/or preliminary fast reactions between 2a and BN. In fact, if one admixes the two compounds a bright yellow colour develops, but dilution with isooctane practically yielded an UV spectrum which is the exact sum of the components. The ^{1}H-NMR spectrum in a concentrated solution of $CDCl_3$ showed tiny upfield shifts for almost all peaks of BN and equivalent downfield shifts for 2a, which is qualitatively what one would expect for a very loose association, as that generated by permanent dipoles in the molecules.

The N-nitrosation step could therefore be either a one step N-S_N2 reaction or a concerted mechanism producing the zwitterion 5:



When the reaction was carried out between an excess of BN and 2a at reflux temperature in inert atmosphere just for the time needed to achieve the complete disappearance of the original amine (20 min), besides the major reaction product 3a (50%) there was the quite sizable production of N-(n-butoxymethyl)-N-methylbenzeneamine (6a, 31.3%) and N,N-di(n-butoxymethyl)benzeneamine (7a, 2.9%) together with lesser amounts of 4-nitro-N,N-dimethylbenzeneamine (8, ca. 2.8%) and 2-nitro-N,N-dimethylbenzeneamine (9, ca. 2%).

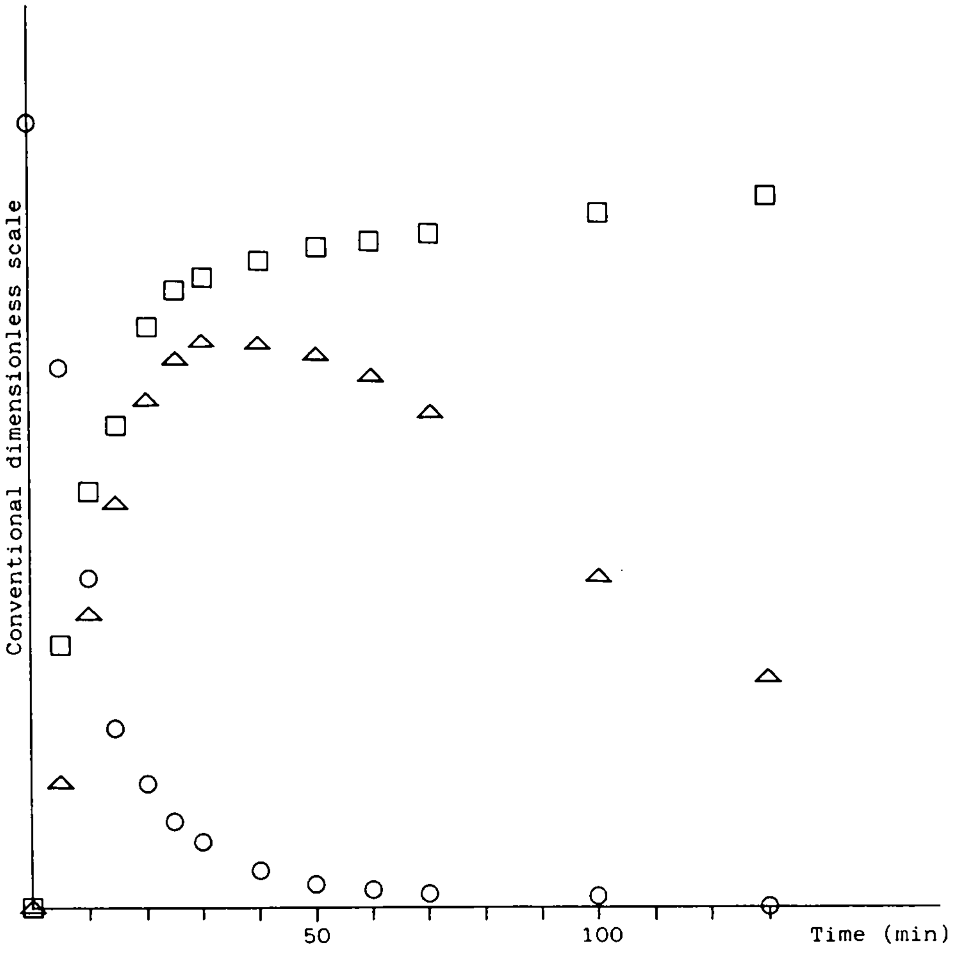
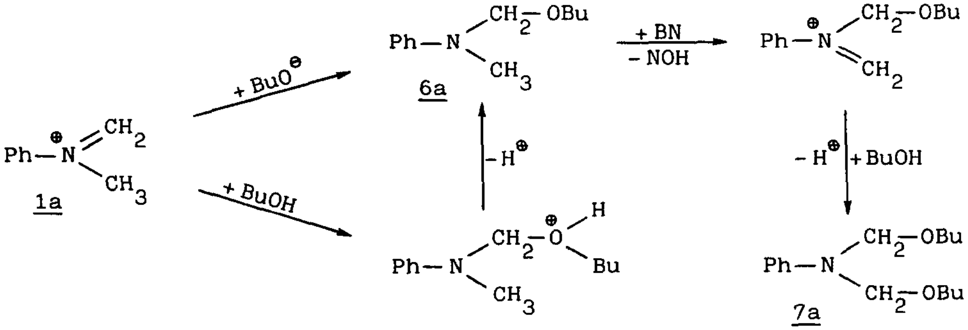


Figure 1. - The course of the reaction between 2a and BN at 65°C. See experimental part, reaction A.

○ [2a]; △ [6a]x10; □ [3a]x2

The numerical values are the peak area ratio of the observed compound vs the peak area of the added standard.

The aminoether 6a may have been formed when 1a intercepted a butoxide ion, possibly escaping from its original ion pair. On the other hand, n-butanol (BuOH) may be formed irreversibly and rapidly by deprotonation of very acidic quaternaries like 4 and be available for reaction with 1a. It could well be this deprotonation which would prevent a slow Fisher-Hepp type rearrangement to the never observed 4-nitroso-N,N-dimethylbenzeneamine (10).

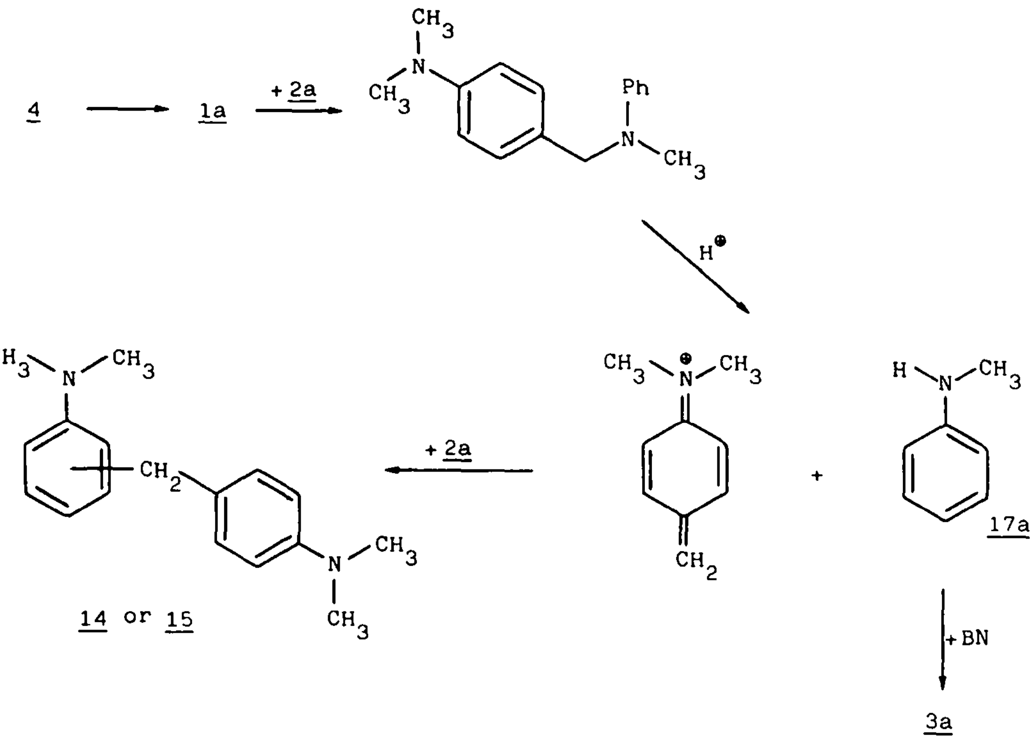


Monitoring of the products of the reaction between 2a and BN alone as they formed showed that the formation of 3a was prevalent at the initial stages, but later the formation of the ether 6a became more and more important (Fig. 1). Later on and rather slowly, the concentration of 6a was depressed by its slow reaction with excess nitrite.

The appearance of the diether 7a can in fact be rationalised as a subsequent reaction of BN with 6a according to the usual scheme. There were no traces of any gem-diether (11a) which was evidently not favoured kinetically.

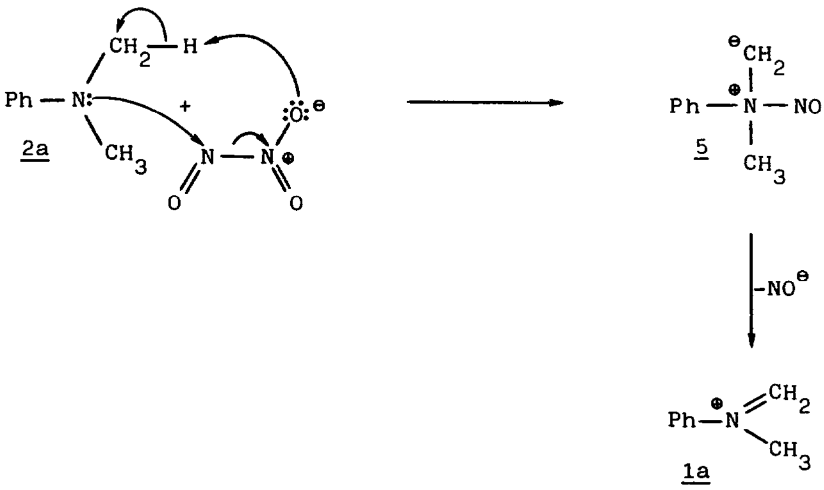
The concentration of water and acid, as well as the nature of the latter, had a dramatic influence on the reaction. An equimolecular amount of water with only one tenth equivalent of ammonium chloride, allowing part of the salt to dissolve, elevated the yield of 3a to 87% under identical physical conditions. Only some 9% of 4-nitro-N-nitroso-N-methylbenzeneamine (12) was the other GC volatile amine product in the reaction mixture, which contained a substantial amount of di(n-butoxy)methane (16). This result has the only obvious explanation in a catalytic effect of the added and dissolved salt in the breakdown of the aminoether 6a by attack of BuOH. Water has here the only role of dissolving part of the salt.

The reaction between an excess 2a, ensuring a very basic environment, and BN deserves a further comment. First of all, we have fully confirmed the initial report[4] about the mechanism of formation of N-nitroso-N-methylbenzeneamine (3a) with alkyl nitrites from an excess of 2a.



Obviously, under these conditions it is impossible to envisage the production of nitrosoacidinium cation and therefore of free nitrosonium ion. The relative aqueous pK_A of the amine and "nitrous acid" might be strongly altered in 2a as a solvent: in particular NO_2^- should be much more basic due to the absence of solvation by hydrogen bonding molecules and therefore the acid less dissociated, but simply hydrogen bonded to 2a. Under these conditions a reaction like

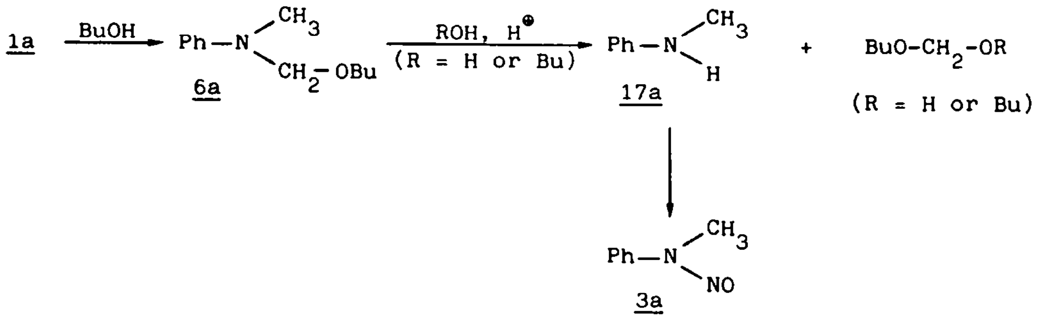
of the nitrous acid being formed by hydrolysis becomes more likely, with the subsequent attack at the nitrogen of the amine by N_2O_3.



This reaction must be much faster than the dissociation of N_2O_3 and/or subsequent reactions of NO_2, leading to nitration products, which, indeed, were found only in trace concentrations. Interestingly, also the formation of the aminoether 6a is essentially quenched, perhaps because of concentration competition by 2a for 1a. But a different reaction seemed to remove 6a, namely that producing 4-(n-butoxymethyl)-N,N-dimethylbenzeneamine (13). In any case, the really surprising departure from the reaction in which BN was the excess reagent is the massive production of diphenylmethane derivatives, especially the two isomers 4,4'-di(dimethylamino)diphenylmethane (14) and, most likely, 2,4'-di(dimethylamino)diphenylmethane (15). These products derive from the direct coupling of 1a on 2a, followed by two N to C rearrangements. The hypothesis of the reaction between CH_2O, freed from 1a by hydrolysis, was ruled out by an appropriate experiment.[4]

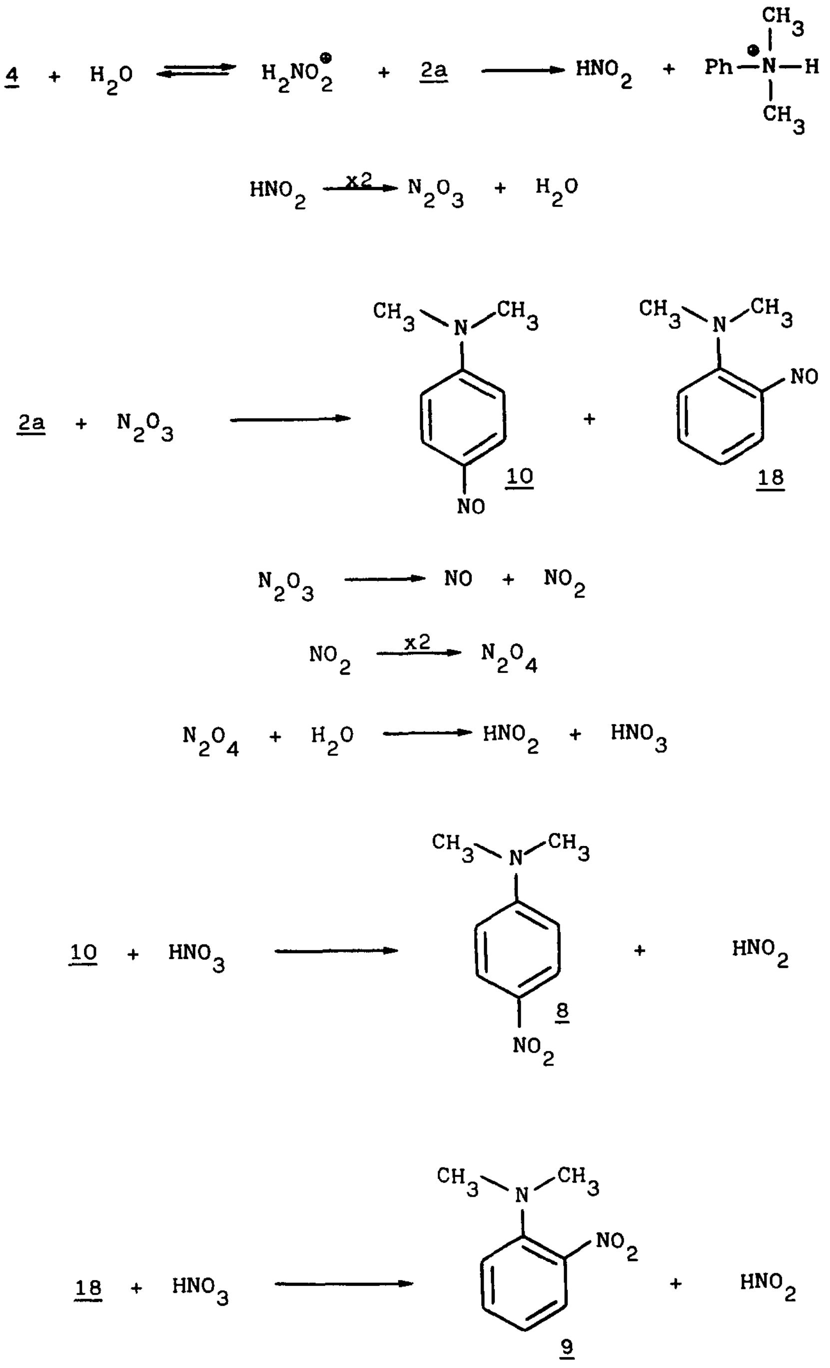
The reaction between 2a and BN, run in an excess of the latter, quenches completely the route leading to 14 and 15. This surprising result indicates that 2a was tied up by excess BN much more rapidly than 1a may react irreversibly with 2a to 14 or 15. The factor that might make the difference could be the rate of the reaction of protonation of NO- by BuOH, which could be more reactive with a lesser concentration of 2a. The same effect would be felt in the reaction with 1a.

When water or BuOH were added to the reaction run in excess BN, the actual rate of their reaction with 6a leading to di(n-butoxy)methane (16) and N-methylbenzeneamine (17a) is much higher than that of butoxylation of the second methyl group of 2a to 7a: the reaction, thus, provides an alternative route to 3a (see also scheme 1):



The incidence of this route should be minor, when the reaction is carried out in rigorously aprotic, namely alcohol and water free, reagents. In fact, the previously described experiment performed in presence of added water (ca. 3/1 mol/mol water/2a) gave quite a different pattern of products: 3a (37%), 8 (26.5%) and 9 (20.3%), the balance being essentially accounted for unreacted 2a. The expectation that addition of an acid might have a similar effect turned out to be fully met by an experiment with 10% equivalent of p-toluenesulfonic acid monohydrate (PTSA), when a slight increase of the reaction rate was also observed: after 15 min. 3a (36.4%), 8 (27.5%) and 9 (21.3%) were formed. Nitrite esters may hydrolyse under acidic as well as basic conditions to "HNO_2" and alcohols,[13] but our present conditions do not seem to act on BN, but most likely on some reaction intermediate(s). The dramatic increase of nitroderivatives, whose occurrence is very minor in absence of added water or acid, is of great interest. p-Nitration of 2a was previously recorded in a reaction with nitrosyl sulfate in moist ethanol or ether.[14] Acidic conditions of a very different nature as provided by BF_3 on N_2O_3 in nitroethane at 0°C produced a quantitative yield of 10.[15] This reaction most probably involved a complex able to transfer an NO^+ group to that ring position. In fact, the estimated pK_A of BN (ca. 8)[16] is forbiddingly high in order to allow BN to compete with 2a for the limited concentration of acidic protons. Water enters the pattern on the cation 4 regenerating 2a and forming "HNO_2", which under these peculiar conditions partly follows a decomposition route taking it to nitrate ion and partly may act as a not so selective o- and p-nitrosation agent on the substrate 2a. The nitrate ion would then oxidize the intermediate nitrosamines 10 and 18 to the observed nitroderivatives extremely rapidly (Scheme 2). In this scheme, the amine acts partially as the catalyst for the hydrolysis of BN. Moreover, water and protic acids may make more difficult the probably essential formation of the zwitterion 5 on the way to 1a: a proposed concerted loss of "HNO" from 4, requiring a 5 member transition state, seems less likely.[17]

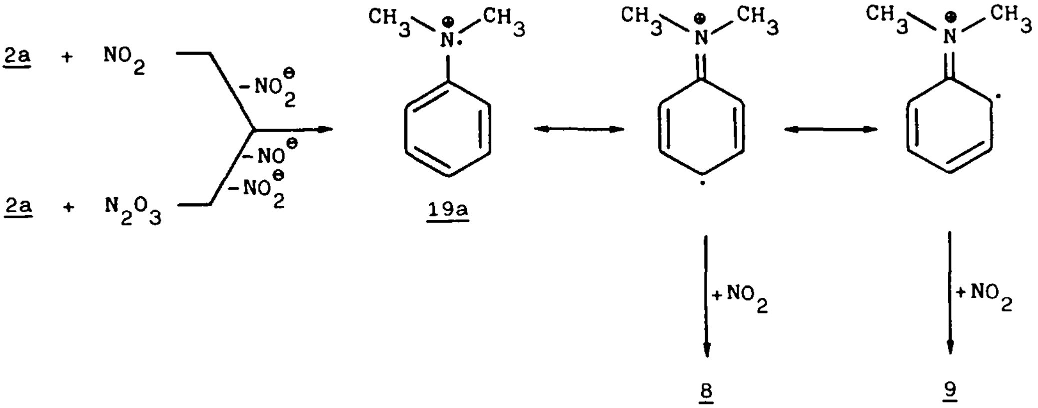
Scheme 2


4
H2O
H2NO2⊕
2a
HNO2
Ph—N⊕(CH3)(CH3)—H
x2
N2O3
10
18
NO
NO2
N2O4
HNO3
8
9

The peculiar feature of the ring nitrations is undoubtedly the low p/o ratio, whereas the classical nitrosation with sodium nitrite in dilute acid near to 0°C in water leads exclusively to the p-nitroso isomer in almost quantitative yield, although the same species are assumed to be involved, i.e., N_2O_3 and 2a. If one refuses the likelihood of a strong change of selectivity due to the grossly different experimental conditions, other mechanistic alternatives must be invoked.

In one of this N_2O_3 or NO_2 or NO^+ would act as electron acceptors yielding the aminium ion 19a, which subsequently reacts with formed NO_2 in both o- and p-positions (Scheme 3).

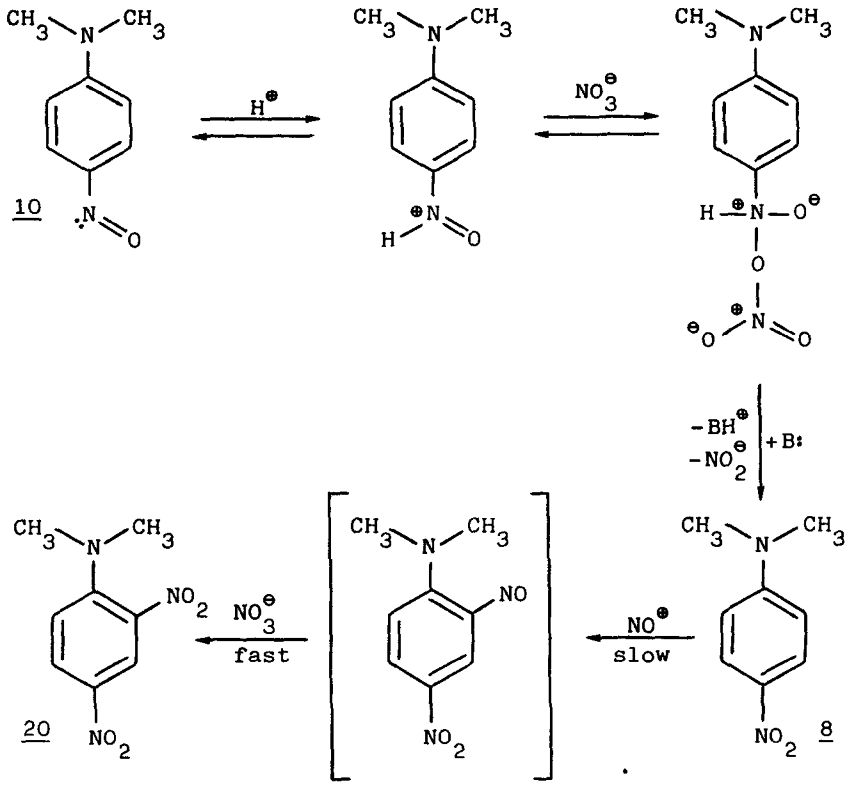
Scheme 3



A number of evidences have been recently gathered for this type of mechanism in the reaction of active substrates with "nitrous acid".[18] This mechanism does not need to invoke the hypothesis of the disproportionation reaction yielding NO_3^-.

The accurate analysis by GC-MS of the whole reaction mixture of a standard nitrosation test of 2a applied to 10 allowed to find traces of 8 and 2,4-dinitro-N,N-dimethylbenzeneamine (20) along side some 90% unreacted starting material.

We observed that 10 does not react at all at room temperature in 10% aqueous nitric acid: heating this solution at 90°C, the corresponding nitroderivative is first formed, then the reaction goes on to the 2,4-dinitroderivative 20 to finally yield the single product N-methyl-2,4-dinitrobenzeneamine (21). The reaction yields the experimental proof of the correctness of the oxidation hypothesis, at the same time proposing an example of a nitrosation-oxidation in o-position and a conclusive oxidative cleavage of one of the methyl groups.

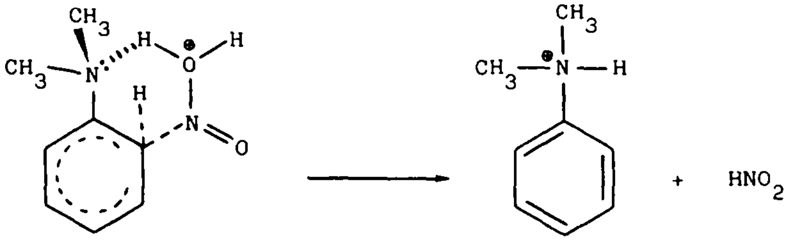


A direct o-nitration by HNO_3 is out of question: the acid of this concentration gave no reaction fter 6 hours heating with 2a at 90°C. Interestingly, at this temperature a further addition of some sodium nitrite to the solution sorted no effect. 50% Nitric acid in the cold during 3 hours brought 2a directly to 2,4-dinitro-N,N-dimethylbenzeneamine (20), most likely according to the nitrosation mechanism charted above, where some "nitrous acid" may be initially formed by some redox reaction with the organic substrate.

But none of these mechanisms may apply to the observed nitrations with BN. Even if partial hydrolysis may free "HNO_2" and some nitrogen oxides could also yield the nitrate ion, the conditions are here essentially very basic and one could hardly invoke efficient C-NO protonation. A more convincing argument against the plain nitrosation-oxidation sequence is the isomeric distribution of the nitration of 2a. By and large, the reaction does not lead from the p-nitro (8) to the o,p-dinitroderivative (20), but, almost with the same observable rate, to p- and o-derivatives 8 and 9. Moreover, 10, refluxed with BN, ammonium chloride and water failed to yield more than 1.4% 8, but underwent polymerisation (100%

yield by wt). The same reaction without ammonium chloride gave after 2 hours (the minimum for the disappearance of 2a), only 8.1% 8.

The reaction of tertiary amines with "HNO_2", usually produced by acidification of an alkali nitrite with a dilute mineral acid, leads to o-nitration when the p-position is occupied. The reason why the o-nitroso isomer cannot be produced has never been elucidated. It was simply associated with a very prompt oxidation of the intermediate nitroso derivative. It is not clear either why the p-orientation is so exclusive,



whereas under the slightly acidic reaction conditions one would expect some o-nitrosation too, in view of the small steric requirement of the NO group. What is wrong with the reaction? Does it really occur with the intermediacy of the nitroso derivative in the ortho position? Even the N to C nitroso rearrangement (Fischer-Hepp reaction) avoids completely the o-position.[19] Another datum is that an alternative preferred to the o-nitrosation is the N-dealkylation-N-nitrosation reaction or even ipso-substitution as we have observed with 4-bromo-N,N-dimethylbenzeneamine (2b), which underwent N-nitrosation *vs* 2-nitration in the ratio ca. 3:1 ($NaNO_2$ + CCl_3COOH). The o-nitroso derivative could not be detected during the reaction.

We tested a few of the reaction described above with the sterically larger reagent amyl nitrite (AN) obtaining essentially the same results. When, though, AN was left standing during one week with 2a in the ratio 4:1, a new product, namely N,4-dinitroso-N-methylbenzeneamine (22, 30%) was formed along with 3a (30%). Interestingly, 22, which is singularly stable at high temperatures, was not produced either by N-nitrosation of 10 or p-nitrosation of 3a, as shown by the appropriate experiments.

The reaction between N,N-dimethylbenzeneamine (2a) and AN in ethanol saturated with HCl was described over a century ago to give a quantitative yield of the corresponding p-nitroso derivative.[20] The acidity provided by acetic acid had quite a different effect on 2a when it was treated with an excess AN: beside much polymeric material some 3a (13%) was formed. On the other hand, extreme basic conditions provided by sodium butoxide equally quenched any reaction between BN and 2a, although BN did not seem affected by the presence of the base. The latter result may be rationalised only in terms of some active role of the strong base in a very early stage of the reaction between BN and 2a, like the CT-complex. Dilution by the alcohol used as the solvent could be an additional inhibitory factor.

It was now of interest to observe the behaviour of a tertiary aromatic amine with the p-position occupied by a substituent in the reaction with BN.

4-Bromo-N,N-dimethylbenzeneamine (2b) reacted with excess BN under similar aprotic conditions to yield only 20.6% 4-bromo-N-methyl-N-nitrosobenzeneamine (3b), but extensive (68.8%) amounts of N-(n-butoxymethyl)-N-methyl-4-bromobenzeneamine (6b) were detected: the reaction time necessary for the complete disappearance of the starting material at 65°C was definitively much longer than that for 2a at the same temperature. The slower rate may be attributed to the effect of the electronegative bromine atom on the initial attack of BN by the amine, which is also the rate determining step for any observed product of transformation of the amino group at variance with what was proposed[1e] for the reaction with "HNO_2". At least in one case it was evidenced that secondary amines react with an alkyl nitrite without a catalyst in a one step reaction to yield protonated nitrosamines, nor-analogs of 1, and alkoxide ion, eventually and quickly going to the observable products, i.e., nitrosamines and alcohol.[5e]

The theoretical conversion to N-nitrosamine from *dry*, BuOH free, BN via the immonium route may be 100% only if any butanol or water formed actually react with the intermediate 1 (water only) or 6 (water or butanol); the stoichiometry of the reaction being:

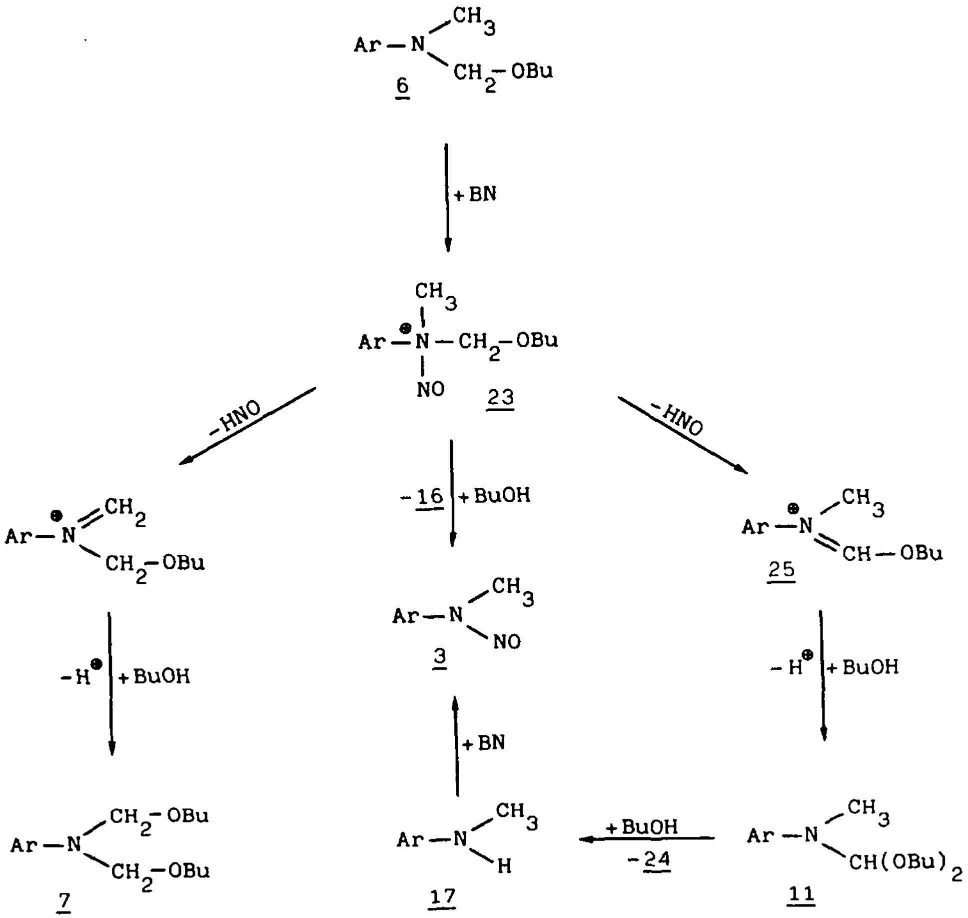
$$2\ R_1R_2N\text{-}CH_3 \quad + \quad 4\ BN \longrightarrow 2\ R_1R_2N\text{-}NO \quad + \quad N_2O \quad + \quad 2\ (BuO)_2CH_2$$

Water is formed from the irreversible and fast decomposition of iponitrous acid $H_2N_2O_2$, derived from dimerization of "HNO" (Scheme 1).

Water, on the other hand, appeared to be not very reactive with 1 under the reaction conditions: this could be due both to its concentration, lower than that of the sum $[BuO^-] + [BuOH]$, and by its prevalent engagement with other hydrogen bonding entities present in solution. Therefore, 1 reacts prevalently with the organic oxygenated counterpart, namely BuOH, and goes to the aminoether 6. This explains an observation otherwise mysterious: the N-nitrosamine yield under carefully identical conditions is much lower from 2b, which yielded a larger amout of aminoether 6b. It is the protonation of this aminoether that allows the reaction to proceed to N-nitrosamine and the p-bromo aminoether 6b is less protonated than the unsubstitute analog 6a. It is difficult to envisage a remote effect of Br (*vs* H), which would give the reverse trend, on the per se high reactivity of the cation 1b. In fact, under these initially *dry* conditions and low medium protonating power, the stoichiometry of the reaction is hardly ever achieved.

This rationale received complete support by the reaction of 2b with BN under the same conditions, but with the addition of water (1 equivalent) and a catalytic amount of ammonium chloride (0.1 equivalent): not only a more than hundredfold acceleration of the rate of disappearance of the substrate was observed, an evidence for a role of water in the initial event of the process sequence, but also some 88% of 2b ended up as 3b. This result confirmed the similar observations made on the ring unsubstituted amine 2a. An active role for the counterion Cl- was ruled out[21] under these conditions, having obtained the same result by the catalysis of PTSA.

Scheme 4



In alternative to the hydrolysis and/or alcoholysis of 6, which should be catalyzed by nitrogen protonation, BN could act as a direct nitrosating agent to yield the N-nitrosoammonium cation 23, as we saw, which may undergo C-S_N2 attack at the methylene group by BuOH. We tested this hypothesis and we found that this reaction actually occurs in part, but seemingly at a very slow rate, anyhow not comparable with that of the observed partial formation of 3 from the starting material (Scheme 4).The aminoether 6 is slowly destroyed by the action of BN, leading in part to the symmetric aminoether 7, which may be formed in the reaction mixture when all 6 had reacted. The unsymmetrical aminoether 11, though, was not present, but these reactions consistently showed the formation of some tri(n-butoxy)methane (24). This compound is believed to be produced by the occurrence of the reaction shown in scheme 4. The unsymmetric aminoether 11 reacts faster with any quaternarization reagent in two steps perhaps because of a very favourable S_N1-type solvolysis.

The role of the oxygen stabilized isomeric cation 25 may be enhanced in the reaction of 2b in comparison of that of 2a bacause the ring may have lost some electron releasing power.

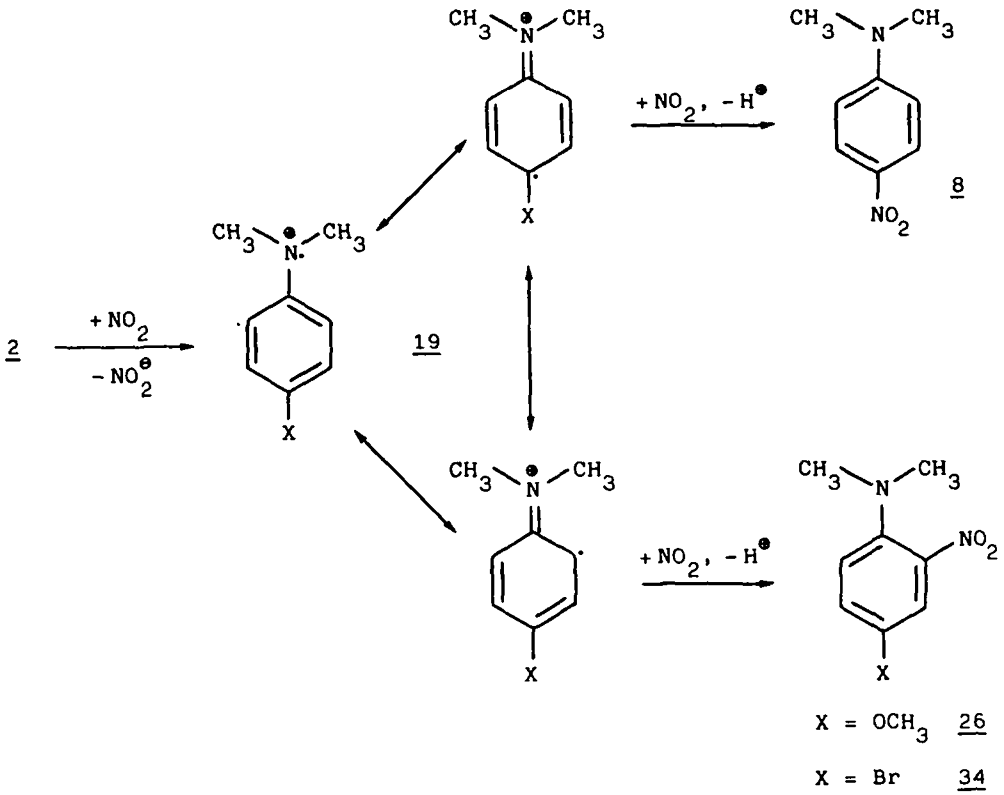
At this point we cannot in fact rule out that it were mainly just this reaction which lead from the aminoether 6 to more 3 when the former was treated with BN. From this unexpected continuation on a side path of the reaction between tertiary aromatic amines and BN, it is clear that the stoichiometry of the actual overall process leading to N-nitrosamines requires more than two equivalents of BN.

The N,N-dimethylbenzeneamine (2a) bearing a strong electron donating substituent like $-OCH_3$, namely 2c, could be expected to react very promptly at the nitrogen atom with BN, but the reaction was not appreciably faster than that of 2a. This was so perhaps because of the unexpected occurrence of much ring nitration (ca. 30%) to 4-methoxy-2-nitro-N,N-dimethylbenzeneamine (26). The material balance after 18 min when the starting material was no more present was complete with the observation of 4-methoxy-N-nitroso-N-methylbenzeneamine (3c, 40%) and the two alkoxy derivatives 6c (23%) and 7c (3%). Even in this reaction, which was run in an oxygen free, dry atmosphere, part of the nitrogen of BN ended up as N_2O, but there was also formation of NO.

As we observed in the reactions with 2a, also p-substituted aromatic amines showed the occurrence of ring nitrations both in the o- and p-(ipso)positions under initially dry and strictly anaerobic conditions;[22] these reactions were enhanced by water and/or acid addition: they are seemingly related to the formation

$$\mathrm{BN} + \mathrm{H_3O^{\oplus}} \rightleftharpoons \mathrm{BuOH} + \mathrm{HNO_2} + \mathrm{H^{\oplus}}$$

and decomposition of "nitrous acid" and the interception by the very reactive nitrogen dioxide thus produced with a residing aminium cation like 19 produced by the previous reaction between the amine and another molecule of NO_2 as for the case of the nitration of phenols and other reactive aromatics by this reagent.[23]



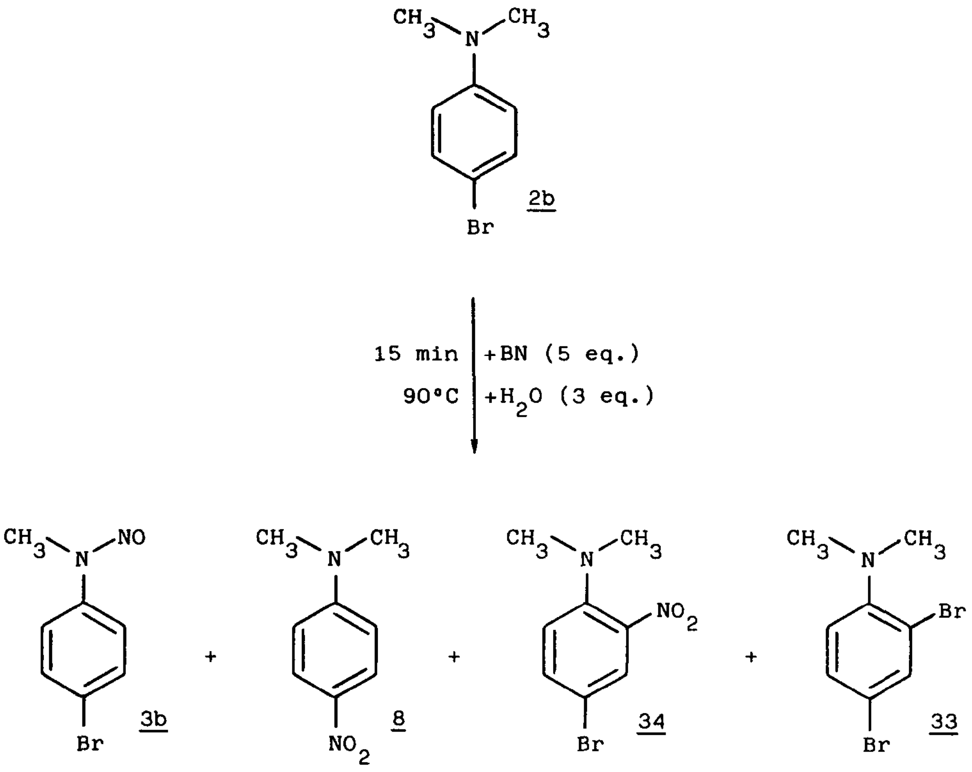
X = OCH_3 26

X = Br 34

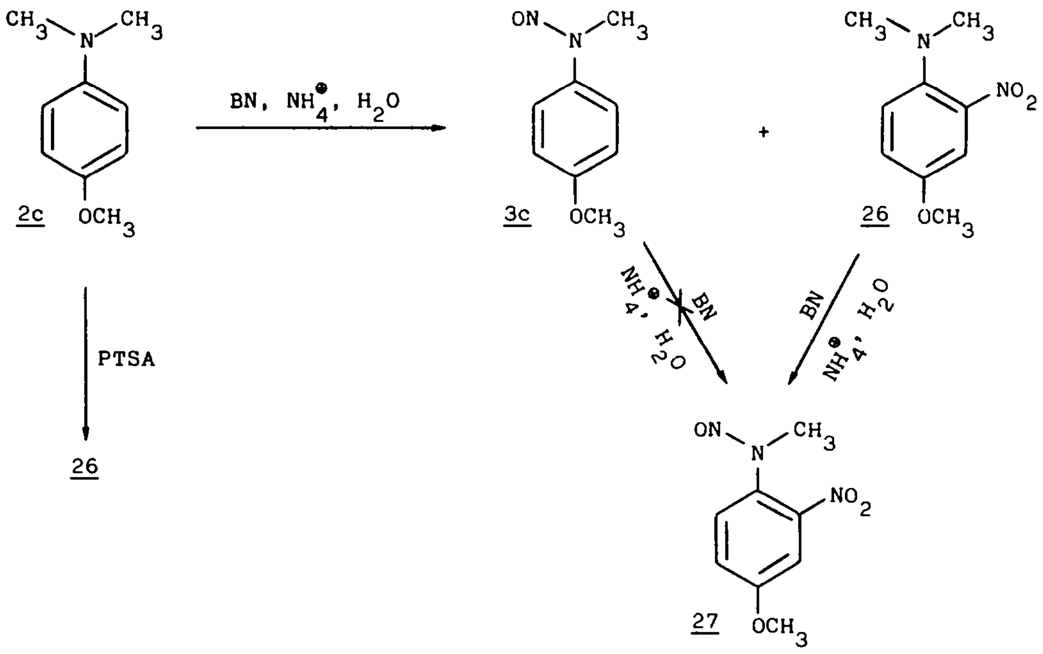
This behaviour rationalizes the production of nitrogen monoxide along with dinitrogen oxide. The aminium ion 19 may also be produced by the SET reaction between the corresponding amine and NO_2, which is a powerful oxidant. Our conditions rule out the occurrence of NO^+ definitively and, as we said earlier, make very unlikely the extensive production and/or the effective oxidizing action of HNO_3. The proposed oxidation may have some type of intermediate complex.

The great propensity of 3c to undergo nitration without catalysis by water or acids could be linked to the higher reactivity of this substrate in the reaction with NO_2.

The acidity of the medium has not only a catalytic effect on the hydrolysis of BN, but lowers as well the concentration of free amine for the direct reaction with the nitrite. The drive for the nitration reaction must be, compatibly with some rate determining step of some process in the initial part of the sequence, extremely high, if even ipso-substitution takes place, as it was observed with 2b, when water was admitted to the system.



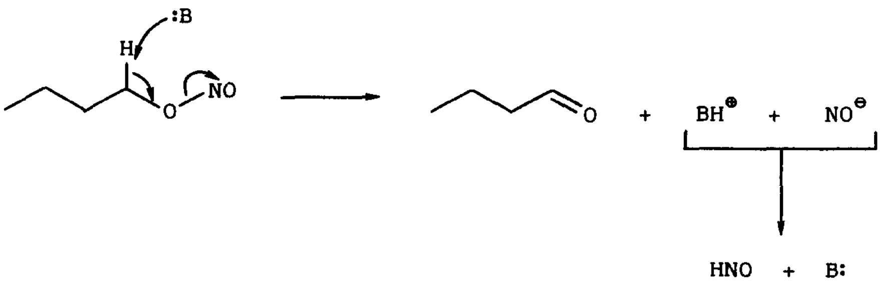
Once more we observe that the role of water is that of mobilizing the aminoether, here 6c, for the reaction with BN of its hydrolysed counterpart, i.e., 17c, as may be evinced by the material balance. The catalysis by ammonium chloride at 90°C made the reaction extremely prompt and generated some N-nitroso-2-nitroderivative (27) which was shown to be found by N-nitrosation of initially nitrated 2c. The effect of the addition of PTSA was that of addressing the reaction towards a significant (unoptimized) yield of 2-nitroderivative (26); the same compound was the outcome of the treatment of 2c with "nitrous acid",[24] as well as the only nitroderivative generated by the reaction between Tl(III) nitrate and 2c in acetonitrile.[25] The para-NO_2 addition product to any p-substituted amine could be at least in part the intermediate to the observed o-nitration products, as it was shown in the nitration of 4-methyl-N,N-dimethylbenzeneamine.[18b] Similar nitrations by "HNO_2" are since long well documented in the literature.[26] Nitration of aromatic amines seems therefore to necessitate both certain structural and electronic features, but neither "stereoelectronic" factors[17a] need to be invoked, nor homolytic N-N cleavage of intermediate nitroso ammonium ions.[27] In same cases there might be a significant incursion of NO_3- oxidation of intermediate C-nitroso derivatives, possibly produced also by a Fisher-Hepp type rearrangement of nitroso ammonium ions under suitable conditions.



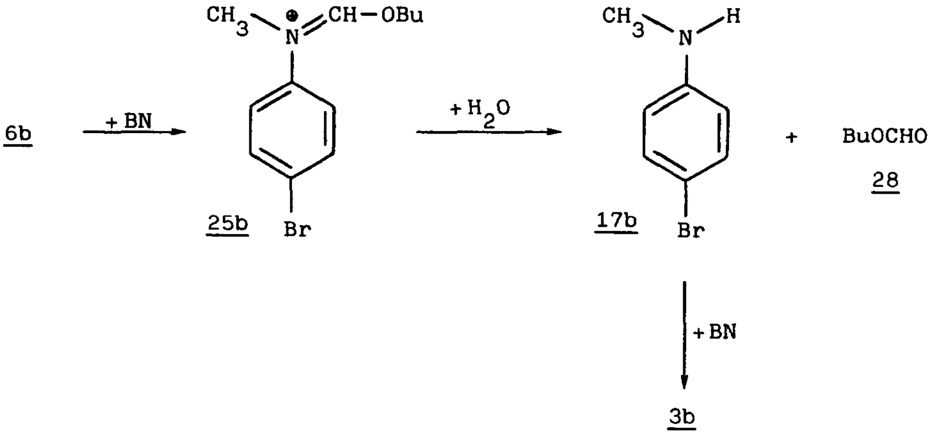
We have analyzed the headspace of BN by GC-MS after heating during 10 min at 90°C: we detected, beside the intact molecule, BuOH and n-butanal, the latter being the decomposition product of BN into "HNO", perhaps catalyzed by glass walls. More interesting was a complete analysis of the headspace of the reaction between 2b and BN at 90°C. We found that all the three nitrogen oxides N_2O, NO and NO_2 were present as individual compounds as well as N_2O_3 and HNO_2. The concentration of NO_2 increased for longer reaction times. The organic components were, beside BN, BuOH, n-butanal, n-butylformate (28) and methyl bromide: the concentration of 28 also increased with longer reaction times. The same reaction with added catalyst (water, NH_4Cl) showed the production of nitrogen dioxide (with hardly any nitrogen monoxide), nitrous acid and the other three oxygen butane derivatives: 28 built up at longer reaction times. 1-Butene was not detected, thus ruling out a possible route to HNO_2, i.e., the C_1,C_2 base catalyzed elimination of HNO_2 from BN.

From these findings we can draw a number of safe conclusions: the production of a few chemical species appearing in the previous mechanistic schemes is definitively established in the course of the actual reactions; water may be also formed during the reaction from a

C_1,O-elimination reaction, perhaps induced by base catalysis, from BN



yielding "HNO"; n-butylformate (28) yields an evidence for the reaction between BN and the intermedite aminoether 6b



In a few cases (e.g.: 2a and 2c) N-nitroso-o- and p-nitroderivatives were detected in our reactions: it is likely that these were the products of N-dealkylation-N-nitrosation of the o- and p-nitro-N,N-dialkylderivative.

Experimental Part

Materials and Equipment - All common reagents and solvents, for which the preparation is not described here, were available commercially and were purified according to the specific necessities. All the amine and alkyl nitrite samples were purified immediately before use. AM and BN,[28] 4-nitroso-N,N-dimethylbenzeneamine (10),[28] chloromethylbuthylether [29], di(n-butoxy)methane (16)[30] and tri(n-butoxy)methane (24)[31] were prepared according to described methods.

All the reactions involving any form of nitrite or its possible formation were run in an oxygen-free atmosphere. The intact reaction mixtures were usually analyzed directly by GC-MS without preliminary workup; a control analysis was usually carried out after reduced pressure removal of reactive material. Thermal stability of AN and BN alone at the various operating temperatures and reaction times were checked. Under the below described GC-MS conditions, N-nitroso-N-methylamines were found to be unstable and to yield mostly the corresponding N-methylamine besides variable but small amounts of N-methyleneamine.

GC analyses were performed with a fused silica column (30 m long, 0.32 mm i.d., Supelchem^{R} SE-54, film thichness 0.25 μm) assembled on a Perkin Elmer Sigma 10 gas chromatograph, using the ion source of the mass spectrometer as a detector. Single ion chromatogram would therefore be recorded at any time for selective monitoring. Less demanding GC analyses were performed using pached columns (glass, 2 m long, 3 mm i.d., JXR 3% on Chromosorb W; steel, 2 m long, 2 mm i.d., Carbowax 20M-KOH). GC quantitative determinations were performed by means of suitable internal standards after independent determinations of area/weight calibration factors. In the cases where authentic and pure specimen could not be obtained, an approximate quantitative determination was secured by the use of a reasonably appropriate standard using a unity calibration factor.

Mass spectra in the electron impact positive ions mode were obtained with a Finnigan 1020 mass spectrometer equipped with a conventional ion source operating at 70 eV, a quadrupole filter and detector of ions, data system and library. A preliminary identification of every GC peak was obtained whenever possible by comparison with the spectral library or by interpretation of the recorded spectral pattern. Separated solid products were directly admitted to the ion source; occasionally, some spectra were recorded via GC or the direct inlet with an LKB 9000 mass spectrometer. All identifications were checked whenever possible against authentic specimens also as to their GC properties. The five most intense peaks with bracketed relative intensities and the parent ion are reported for never before reported spectra or uncommon compounds.

IR spectra were recorded on intact mixtures in order to check them against separated materials to rule out post reaction artefacts and on purified homogeneous products to ensure positive identification both by interpretation of the spectral characteristics and identity with spectra of the Aldrich[32] library or any other source of authentic spectra. The KBr technique was used for solids. The equipment used was a JASCO Infrared Spectrometer mod. DS-702G.

^{1}H-NMR Spectra were obtained from a Bruker WP-80 SY spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as solvent; the spectrum of 6b was secured from the kind cooperation of Dr. P. Ferrari and Dr. J. Kettenring of Lepetit Research Center, Varese (Bruker AM-500 equipped with an Aspect 3000 computer).

UV spectra were recorded with a JASCO digital spectrophotometer UV-visible UVIDEC-505 equipped with a derivative scanner mod. DER-1, using isooctane as solvent.

Voltammetric measurements were performed in an EG&G PARC 303A three-electrode cell connected to an EG&G PARC model 273 potentiostat driven by an EG&G PARC model 270 software installed on a IBM system/2 computer. In these experiments, an SME and Pt wire were used as the working and counter electrode respectively, whereas an Ag/0.1 M Ag^{+} electrode was the reference. The medium employed was 0.1 M tetrabutylammonium perchlorate solution in dry acetonitrile.

N,N-Dimethylbenzeneamine (2a) and alkyl nitrites

A.- BN (excess) and 2a (reflux) - The direct reaction of the two compounds in 1:5 molar ratio at reflux temperature during 15 min caused the complete disappearance of 2a and the production of both N-(n-butoxymethyl)-N-methylbenzeneamine (6a) and N,N-di(n-butoxymethyl)-benzeneamine (7a). The amount of 3a formed was detected by GC as being 49.7%. Small amounts of 4-nitro-N,N-dimethylbenzeneamine (8), 2-nitro-N,N-dimethylbenzeneamine (9) and N-formyl--N-methylbenzeneamine (29a).

The nitrosamine 3a could be separated from the mixture by preliminary hydrolysis of 6a and 7a with diluted hydrochloric acid at room temperature and conventional distillation or absorption chromatography on alumina (BDH, Grade I, neutral) using a concentration gradient of ether in hexane (from 0 to 20% vol/vol). The two ethers 6a and 7a are extremely sensitive to moisture, which causes their immediate and complete hydrolysis to N-methylbenzeneamine (17a) and benzeneamine (30a), respectively. Their quantitative analysis exploited the hydrolysis reaction and was performed on the resulting amines. Conventional distillation of the intact mixture did not allow to separate the two ethers in a pure state. Upon opening the argon blanketed reaction apparatus, the colorless gases acquired a deep brown color, due to the instant oxidation of nitrogen monoxide to dioxide.

N-(n-Butoxymethyl)-N-methylbenzeneamine (6a). 31.3% (GC); MS m/z 120 (100), 193 (M^+, 22), 77 (20), 57 (19), 106 (14), 104 (12), 136 (6).

N,N-Di(n-butoxymethyl)benzeneamine (7a). 2.9% (GC); MS m/z 57 (100), 105 (99), 120 (80), 106 (43), 192 (30), 265 (M^+, 14).

N-Formyl-N-methylbenzeneamine (29a). MS m/z 106 (100), 135 (M^+, 72), 77 (36), 94 (20), 51 (18).

In order to monitor the kinetic of the disappearance of 2a and the appearance of 3a and 6a conveniently by GC-MS, a reaction between 2a (2.48 mmol) and BN (13.64 mmol) in the presence of the suitable internal standard diphenylmethane was carried out at 65°C. The result are collected in the fig. 1.

Analogously, a mixture of 2a and freshly distilled alcohol free ($CaCl_2$) AN were kept at 100°C in a flow of nitrogen during 1 h. Only at the very beginning nitrogen monoxide was formed as evidenced by the characteristic coloration upon contact with air. The starting material was completely consumed (TLC, GC), 17a and dimeric material were also absent. The yield of 3a was 45.5%.

When iso-amyl nitrite was used under the same conditions, a complete GC-MS analysis allowed to detect, beside 3a (34.3%), the aminoethers N-(3-methyl-1-butoxy)methyl-N-methylbenzeneamine and di-[N,N-(3-methyl-1-butoxy)methyl]benzeneamine together with trace amount of 8, 9 and 29a.

N-(3-Methyl-1-butoxy)methyl-N-methylbenzeneamine. 47.5% (GC); MS m/z 120 (100), 43 (29), 207 (M^+, 28), 77 (23), 106 (16), 104 (13), 136 (7).

Di[N,N-(3-methyl-1-butoxy)methyl]benzeneamine. 3.2% (GC); MS m/z 120 (100), 105 (99), 43 (70), 106 (47), 206 (30), 293 (M^+, 9).

B.- AN (excess) and 2a - AN and the amine were contacted in a molar ratio 5:1 at room temperature under nitrogen without any exotherm but with the instant formation of a green color. After one week standing in inert atmosphere, the mixture contained 30% 3a (GC). The mixture was then chromatographed on silica gel (Merck, silica gel 60-120 mesh, a 25 cm long glass column) eluting with hexane, hexane-benzene (1:1) and benzene with an ether gradient (from 10 to 100% vol/vol) and finally ether-ethanol (from 5:1 to pure alcohol): from a fraction (crude yield 30%) a pure (TLC, GC) yellow solid, i.e. N,4-dinitroso-N-methylbenzeneamine (22), was obtained from repeated recrystallization from hexane-ether.

N,4-Dinitroso-N-methylbenzeneamine (22). m.p. 154-55°C; NMR δ 3.11 (s, 3H), AA'XX' multitiplet, 4H, divided into two separate specular multiplet simulating a quartet, centered at 6.64 and 8.08; MS m/z 165 (M^+, 100), 119 (30), 42 (27), 77 (23), 136 (21), 120 (16), 105 (15).

C.- BN and 2a (excess, reflux)[33] - The reagents were admixed in 1:5 molar ratio (theor. ratio 2:3) and refluxed during 30 min, although the reaction appeared practically complete after 9 min. GC-MS qualitative and quantitative analysis of the intact reaction mixture revealed the formation of 3a (74.5%), 29a (trace), 9 (trace), 6a (trace), 4-dimethylaminobenzaldehyde (trace), 4-nitro-N-nitroso-n-methylbenzeneamine (12, 1.9%, calc'd as mol 12/mol BN), 8 (trace), 2,4'-(dimethylamino)diphenylmethane (15), 2'-(methylamino)-4-(dimethylamino)diphenylmethane, 4-(methylamino)-4'-(dimethylamino)diphenylmethane and 4,4'-bis(dimethylamino)diphenylmethane (14) Excess 2a recovered amounted to 56%, less than the theoretical 69%.

4-Dimethylaminobenzaldehyde. MS m/z 148 (100), 149 (M^+, 83), 77 (15), 132 (8), 105 (6).

2,4'-(Dimethylamino)diphenylmethane (15). 4.8% (GC); MS[34] m/z 134 (100), 254 (M^+, 70), 118 (67), 239 (43), 91 (34).

2'-(Methylamino)-4-(dimethylamino)diphenylmethane. 4.3% (GC); MS[34] m/z 240 (M^+, 100), 121 (87), 225 (50), 120 (39), 118 (36).

4-(Methylamino)-4-(dimethylamino)diphenylmethane. 4.5% (GC); MS[34] m/z 240 (M^+, 100), 239 (75), 120 (27), 134 (24), 195 (19).

4,4'-Bis(dimethylamino)diphenylmethane (14). 78.8% (GC); MS[34] m/z 254 (M^+, 100), 253 (90), 210 (35), 134 (32), 126 (30).

AN and 2a (excess, reflux) - In one experiment 2a (8.2 mmol) and AN (1.9 mmol) were kept at 100°C during 4 h (although the reaction appeared complete after 15 min; a colorless liquid gently refluxed). At the beginning some nitrogen monoxide developed; the mixture was red-brown. Quantitative GC, using n-tetradecane as internal standard, was used to determine the yield of 14 (64%). In this experiment 3a was produced in 42% yield, accompanied by some 15% (calc'd as mol 2a/mol AN) 17a.

In another experiment AN (60 mmol) was slowly added to 2a (260 mmol) stirred at 100°C; the reaction mixture was then kept at 115°C during 2 h. A colorless liquid gently refluxed at the begining. The intact reaction mixture has been fractionally distilled obtaining: n-pentanol (ca. 100%, calc'd as mol alcohol/mol AN), 2a (66% left over, theor. 66%), 3a (52%) (all distilled in the range 52-122°C at ca. 3066 Pa and identified by spectroscopic properties, GC, MS and elemental analyses) and 14 (ca. 66%, bp 150-155°C at 160 Pa, crude material), recrystallized from hexane-ethanol and methanol, mp 86-7°C, lit.[34] 88-90°C, correctly analyzing for 14 and having the spectroscopic and GC properties expected for it. An undistillable residue amounted to ca. 2 g.

The yield of 3a is lower than that of the dimeric condensation product 14 because the latter is a product preceding the formation of the former in the complex reaction sequence, and, unless all the reaction following the initial event were to be "instantaneous" - an obviously unlike event - it is expected that formation of dimers of type 14 would usually exceed the yield of 3a.

D.- Protic catalyses of the reaction between 2a and BN (excess, reflux) - In one experiment 2a (8.50 mmol), BN (42.3 mmol) and water (25.4 mmol) were refluxed during 20 min, a time sufficient for causing the total disappearance of the amine, obtaining 3a (37%), 4-nitro-N,N-dimethylbenzeneamine (8, 27.5%) and 2-nitro-N,N-dimethylbenzeneamine (9, 20.2%).

In another experiment water was replaced by PTSA (0.85 mmol) obtaining 3a (36.4%), 8 (27.5%) and 9 (21.3%) under the exactly same conditions.

In a third experiment water was used in equivalent amount to 2a and ammonium chloride (0.85 mmol) was added, obtaining 3a (87%) and 4-nitro-N-nitroso-N-methylbenzeneamine (12, 8.7%) under exactly the same conditions. The latter product was separated, after evaporation under low pressure (1 torr) of any more volatile fraction from the intact mixture, by absorption chromatography on alumina (hexane-ether from 100:0 to 80:20 vol/vol).

4-Nitro-N-nitroso-N-methylbenzeneamine (12). m.p. 105-6°C, lit[35] m.p. 104°C; IR (KBr) 3095w, 1610m, 1595m, 1510m, 1463m, 1395m, 1338s, 1300s, 1203m, 1175m, 1073s, 943m, 847m, 810m, 745m, 680w cm^{-1}; NMR δ 3.47 (s, 3H), AA'XX' multiplet, 4H, divided into two separate specular multiplet simulating a quartet, centered at 7.75 and 8.36; MS (direct inlet) m/z 105 (100), 151 (96), 181 (M+, 32), 104 (30), 63 (17), 90 (15).

Ammonium chloride added without water to the above mixture was inactive, the reaction replicating the results given uder heading A.

4-Bromo-N,N-dimethylbenzeneamine(2b) and BN

A.- BN (excess) and 2b (reflux) - The amine (2b, 7.89 mmol) and freshly prepared, essentially butanol-free, BN (47.8 mmol) were refluxed during 3 h, i.e. the time just necessary for the complete disappearance of 2b as monitored by GC and TLC (alumina, elution with hexane-ether 1.5:1 vol/vol) under dry nitrogen. The whole brown reaction mixture was freed from volatile material by a preliminary distillation at ca. 3333 Pa and a final evaporation at 133 Pa (oil bath at 95°C, residual material 2.15 g) taken up with dry hexane (2 mL) and deep frozen by immersion of the reaction flask into liquid nitrogen, which caused its complete solidification. Upon reaching room temperature, the solution had separated pale yellow crystals of practically pure 4-bromo-N-methyl-N-nitrosobenzeneamine (3b), which is no more present (TLC) in the mother liquor. This solution (1.73 g of product) contained 4-bromo-N-(n-butoxymethyl)-N-methylbenzeneamine (6b, 68.8%) and 4-bromo-N,N-di(n-butoxymethyl)benzeneamine (7b, 0.92%), as determined directly by GC for 7b and by GC, after hydrolysis to 4-bromo-N-methylbenzeneamine (17b, see infra), for 6b. Conventional distillation gave pure 6b.

4-Bromo-N-methyl-N-nitrosobenzeneamine (3b). m.p. 73°C, lit[36] m.p. 74; IR 3100w, 1490s, 1445vs, 1387vs, 1302s, 1280s, 1195vs, 1175s, 1085vs, 1005s, 960s, 947s, 820vs, 520s, 485m cm^{-1}; NMR δ 3.42 (s, 3H), A_2B_2 multiplet, 4H, centered at 7.51; MS (direct inlet) m/z 184 (100), 186 (97), 105 (81), 104 (81), 63 (43), 77 (41), 155 (40), 157 (38), 214 (M$^+$, 16), 216 (M$^+$, 15).

4-Bromo-N-(n-butoxymethyl)-N-methylbenzeneamine (6b). b.p. 125°C (45 Pa); IR (neat) 2960s, 2930s, 2880s, 1590m, 1495vs, 1430m, 1375m, 1355s, 1315m, 1290m, 1270m, 1255m, 1220m, 1185m, 1115m, 1075vs, 1055s, 1035m, 960m, 810s, 755w cm^{-1}; NMR δ 0.89 (t, 3H, J = 7.34 Hz), 1.35 (pseudo sext, 2H), 1.54 (pseudo q, 2H), 3.04 (s, 3H), 3.39 (t, 2H, J = 6.50 Hz), 4.72 (s, 2H), A_2X_2 pseudo q, 4H, resulting from two doublets centered at 6.72 and 7.30; MS m/z 200 (100), 198 (100), 57 (35), 118 (15), 185 (13), 273 (M$^+$, 10), 271 (M$^+$, 10).

When the original mixture was refluxed for the time just necessary for the complete disappearance of 6b (60 h), the following compounds were produced:

di(n-butoxy)methane (16, ca. 30%), isolable by distillation, identical with an authentic specimen, after evaporation of BN and, upon addition of toluene, azeotropic distillation of formed BuOH;

formaldehyde, condensing as paraformaldehyde on the flask condenser during the reaction, identified by IR and traditional methods;

tri(n-butoxy)methane (24, ca. 7%), identified by comparison with authentic specimen;

4-bromo-N-methyl-N-nitrosobenzeneamine (3b), 78% (isolated yield), obtained as above described;

4-bromo-N,N-di(n-butoxymethyl)benzeneamine (7b), 10% (GC), which could be isolated by distillation, b.p. 146°C (7 Pa), IR (neat) 2960s, 2940s, 2880s, 1597m, 1497vs, 1465m, 1380s, 1365s, 1325m, 1280m, 1260m, 1205m, 1080vs, 1040vs, 1010s, 990m, 930w, 820m cm^{-1}; NMR δ 0.92 (pseudo t, 6H), 1.10-1.93 (m, 8H), 3.45 (t, 4H, J = 6.65 Hz), 4.83 (s, 4H), A_2B_2 multiplet, 4H, centered at 7.18, MS m/z 57 (100), 183 (39), 185 (38), 87 (22), 200 (18), 198 (18), 272 (5), 270 (5), 345 (M$^+$, 2), 343 (M$^+$, 2);

1,3,5,7,-tetra(4-bromophenyl)-1,3,5,7-tetrazocine (31, separated yield ca. 7%), identified by comparison with an authentic specimen, prepared according to a described method.[37]

Minor concentrations of the following compounds were detected and identified by GC-MS analysis of the intact mixture (listed in order of elution):

4-bromo-N-methylenebenzeneamine (32b, from thermal decomposition of 31 and 3b) MS m/z 185 (M$^+$, 100), 183 (M$^+$, 100), 184 (63), 182 (60), 157 (40), 155 (40), 50 (33);

2,4-dibromo-N,N-dimethylbenzeneamine (33), MS[38] m/z 278 (100), 279 (M$^+$, 72), 280 (44), 276 (42), 281 (M$^+$, 21), 277 (M$^+$, 33), 75 (27), 118 (24);

4-bromo-N-formyl-N-methylbenzeneamine (29b, from 24 and 17b), MS m/z 186 (100), 184 (100), 215 (M$^+$, 72), 213 (M$^+$, 72), 172 (57), 174 (52), 105 (43);

4-bromo-2-nitro-N,N-dimethylbenzeneamine (34), MS[38] m/z 118 (100), 171 (80), 169 (80), 185 (42), 184 (42), 199 (39), 182 (37), 183 (36), 227 (35), 229 (33), 246 (M$^+$, 25), 244 (M$^+$, 25).

B.- Protic catalyses of the reaction between 2b and BN (excess, reflux) - The amine (2b, 1.095 mmol), ammonium chloride (0.1 mmol), water (1.1 mmol) and BN (4.6 mmol) were refluxed under inert atmosphere during 15 min; all the volatile material was distilled off (residual pressure 133 Pa, max bath temperature 95°C), the brown solid residue was taken up with hexane and water, the organic layer was dried over Na_2SO_4, reduced to a small volume, completely solidified by immersion into liquid nitrogen and allowed to warm up to room temperature. Solid 3b (88%, separated yield) was obtained. The mixture before work up contained also a large amount of di(n-butoxy)methane (16).

The reaction had essentially the same outcome if ammonium chloride was replaced by PTSA in the same stoichiometric ratio.

The conditions of the reaction with ammonium chloride were reproduced except that water was not admitted into the system. After 15 min, ca. 10% of the starting material was still present. Under these conditions ammonium chloride appeared insoluble. The products were 16 (4%), 3b (20%) and 6b (55%).

In another experiment the amine (2b, 5 mmol), water (15 mmol) and BN (25 mmol) were refluxed 15 min under nitrogen: GC-MS analysis of the reaction mixture showed the complete disappearance of the starting substrate and the namely formed 3b (56.7%), 2,4-dibromo-N,N-dimethylbenzeneamine (33, 6.4%), 4-bromo-2-nitro-N,N-dimethylbenzeneamine (34, 27%) and 4-nitro-N,N-dimethylbenzeneamine (8, 6.9%), which were separated by absorption chromatography on silica gel (BDH, silica gel 60-120 mesh), using hexane with a gradient of CH_2Cl_2 (from 0 to 50% vol/vol) as eluant obtaining the separate yield shown in brackets.

2,4-Dibromo-N,N-dimethylbenzeneamine (33). b.p. 100°C (107 Pa), lit[39] 275°C (98.6 kPa); IR (neat) 2915s, 2840m, 2800m, 2760m, 1475vs, 1445s, 1425s, 1365m, 1315m, 1182m, 1155s, 1130m, 1090m, 1045m, 1028s, 940m, 862m, 810s, 775s, 660m, 592m, 555m cm^{-1}; NMR[38] δ 2.77 (s, 6H), 6.93 (d, 1H, J = 8.55 Hz), 7.36 (d of d, 1H, J = 8.55 Hz, J_m = 2.22 Hz), 7.68 (d, J_m = 2.22 Hz).

4-Bromo-2-nitro-N,N-dimethylbenzeneamine (34). m.p. 65°C, lit[35] 66°C; IR (KBr) 2920w, 2860w, 2790w, 1600s, 1590s, 1505vs, 1430s, 1380s, 1268s, 1210m, 1150m, 1060m, 953w, 870m, 805m, 762m cm^{-1}; NMR[38] δ 2.88 (s, 6H), 6.89 (d, 1H, J = 8.93 Hz), 7.47 (d of d, 1H, J = 8.93 Hz, J_m = 2.48 Hz), 7.88 (d, 1H, J_m = 8.93 Hz).

4-Bromo-N,N-dimethylbenzeneamine (2b) and "nitrous acid"

A solution of trichloroacetic acid (6.64 mmol) in $CHCl_3$ (13 mL) was added slowly to a slurry of finely divided sodium nitrite (6.64 mmol) in $CHCl_3$ (10 mL) at -30°C under nitrogen and the mixture stirred at this temperature during 50 min. The amine (2b, 5 mmol) in $CHCl_3$ (10 mL) was slowly added under nitrogen, turning the mixture into a bright orange color. At the end of the addition, the temperature was allowed to rise to ambient during 1 h. The mixture was finally diluted with ether and washed with water. The yield of 3b was 19% (isolated). The starting amine survived to the extent of 64%, while some 7% ended up as 4-bromo-2-nitro-N,N-dimethylbenzeneamine (34). A minor amount of 2,4-dibromo-N,N-dimethylbenzeneamine (33) was also detected.

4-Methoxy-N,N-dimethylbenzeneamine (2c) and BN

A.- BN (excess) and 2c (reflux) - The amine (2c, 1.35 mmol) and BN (6.8 mmol) were refluxed during 18 min: after this time no starting amine was left. GC-MS analysis revealed the presence of the following compounds: 4-methoxy-N-methyl-N-nitrosobenzeneamine (3c, 40%), 4-methoxy-2-nitro-N,N-dimethylbenzeneamine (26, 30.1%), 4-methoxy-N-(n-butoxymethyl)-N-methylbenzeneamine (6c, 23%) and 4-methoxy-N,N-di(n-butoxymethyl)benzeneamine (7c, 3.3%), which were eluted in this order. The GC quantitative analysis has been performed by the internal standard technique on a hydrolysed sample, as described above. The products were identified by their mass spectra and GC properties, which for 3c and 26 were identical with those of the analogous products isolated in the experiments given under heading B (see below).

4-Methoxy-N-(n-butoxymethyl)-N-methylbenzeneamine (6c). MS m/z 150 (100), 223 (M^+, 15), 136 (9), 135 (9), 122 (9), 120 (8).

4-Methoxy-N,N-di(n-butoxymethyl)benzeneamine (7c). MS m/z 135 (100), 57 (73), 15 (71), 12120 (32), 122 (16), 222 (14), 295 (M^+, 9).

B.- Protic catalyses of the reaction between 2c and BN (excess) - The amine (2c, 4.97 mmol), BN (20.0 mmol), ammonium chloride (1.5 mmol) and water (4.97 mmol) were refluxed 5 min, a time sufficient for the complete disappearance of 2c. The volatile products were evaporated in vacuo and the higher boiling material was separated into two major components by absorption chromatography on alumina (hexane-ether from 100:0 to 40:60 vol/vol): 3c and 4-methoxy-2-nitro-N-methyl-N-nitrosobenzeneamine (27).

4-Methoxy-N-methyl-N-nitrosobenzeneamine (3c). m.p. 46°C, lit[24] 47°C; IR (KBr) 2930w, 2880w, 2815w, 1608m, 1590m, 1507s, 1435vs, 1417vs, 1384s, 1311s, 1242vs, 1208vs, 1090vs, 1028vs, 955s, 835vs, 811vs, 615s, 530s cm^{-1}; NMR δ 3.43 (s, 3H), 3.85 (s, 3H), A_2X_2 multiplet, 4H, divided into two separate specular multiplets simulating a quartet, centered at 6.94 and 7.44; MS m/z 136 (100), 121 (59), 108 (58), 77 (40), 93 (36), 67 (35), 166 (M^+, 7).

4-Methoxy-2-nitro-N-methyl-N-nitrosobenzeneamine (27). m.p. 49°C; IR (KBr) 1612m, 1522vs, 1451s, 1358s, 1300s, 1278s, 1245s, 1185s, 1120s, 1053m, 1013vs, 955s, 860s, 835s, 797s, 587m, 552m cm^{-1}; NMR δ 3.38 (s, 3H), 3.94 (s, 3H), 7.25-7.70 (m, 3H); MS m/z 181 (100), 164 (74), 123 (50), 120 (45), 108 (38), 92 (32), 134 (25), 211 (M^+, 1).

In another experiment a homogeneous solution of the amine (2c, 4.07 mmol), PTSA (5.53 mmol) and BN (29.9 mmol) was kept under nitrogen during 3 days at room temperature. A precipitate formed after one day. At the end of the preset reaction time, residual BN and volatile products were distilled off at ca. 667 Pa and 30-40°C. The residual paste was washed with diluted sodium hydroxyde, extracted with ether and dried over Na_2SO_4. Absorption chromatography on alumina (hexane-ether from 100:0 to 50:50 vol/vol) gave 4-methoxy-3-nitro-N,N-dimethylbenzeneamine (26, 84%) and 4-methoxy-2-nitro-N-methyl-N-nitrosobenzeneamine (27, ca. 2%). GC-MS of the original mixture allowed to identify also: di(n-butoxy)methane (16), a tiny amount of N-methyl-N-nitrosobenzeneamine (3c) and a peak for 4-methoxy-x,y-dinitro-N,N-dimethylbenzeneamine (in a concentration comparable with that of 27).

4-Methoxy-2-nitro-N,N-dimethylbenzeneamine (26). m.p. 15°C, lit [24] 14°C; IR (neat) 2920 m, 2870m, 2820m, 2775m, 1515vs, 1432s, 1340s, 1250vs, 1238s, 1195s, 1160s, 1035vs, 952m, 918m, 905m, 800s cm^{-1}; NMR δ 2.79 (s, 6H), 3.79 (s, 3H), 7.03-7.42 (m, 3H); MS m/z 120 (100), 135 (80), 134 (79), 121 (71), 196 (M^+, 59), 151 (42), 179 (39).

4-Methoxy-x,y-dinitro-N,N-dimethylbenzeneamine. MS m/z 224 (100), 121 (73), 241 (M^+, 64), 149 (58), 77 (51), 148 (50), 134 (44).

In a third experiment a mixture of the amine (2c, 4.67 mmol), water (4.67 mmol) and BN

(27.9 mmol) was stirred during 3 days at room temperature under nitrogen. Usual workup and purifications yielded 3c (68%) and 27 (28%). The GC-MS trace of the whole mixture showed a large amount of tri(n-butoxy)methane (24) and minor amounts of di(n-butoxy)methane (16) and 4-methoxy-N-methylenebenzeneamine (32c, formed by thermal decomposition of 3c in the injector of the gc apparatus).

4-Methoxy-N-methylenebenzeneamine (32c). MS m/z 120 (100), 135 (M+, 87), 92 (23), 65 (22), 77 (8), 51 (6).

Stability of 3

These nitrosamines, prepared by the action of sodium nitrite and hydrochloric acid on 17[28] were found to be thermally and hydrolytically unstable under the GC conditions normally employed (dilution with commercial solvents, fused silica columns, injector temperature: 300°C). The thermal decomposition, which is usually a minor reaction led to the imines (Ar-N=CH_2, 32), whereas the hydrolysis, which liberates HNO_2, gave the corresponding N-methylbenzeneamine (17). The nitrosamine is quite stable under TLC conditions using alumina (hexane-ether) and silica gel (hexane-CH_2Cl_2). The other N-nitrosamines encountered in this study behaved similarly.

Injection of a solution of pure 3b in commercial ether into the GC apparatus (injector 150-300°C) invariably yielded variable amounts of N,N'-dimethyl-N,N'-di(4-bromophenyl)-hydrazine, identified by MS and 4-bromo-N-methylbenzeneamine (17b) accompanied by traces of 4-bromo-N-methylenebenzeneamine (32b). We believe this to be the results of both pyrolysis and (in part) hydrolysis (by traces of water in the solvent) of 3b. In the higher injector temperature range 17b and 32b were the only products observed. Similar behaviour was observed with other N-nitrosamines. Low GC injector temperature (below 150°C, whenever feasible) analysis of a few N-nitrosamines using glass columns prevented the degradation of the compounds.

N,N'-Dimethyl-N,N'-di(4-bromophenyl)benzeneamine. MS m/z 185 (100), 184 (93), 187 (78), 186 (78), 105 (40), 77 (22), 104 (20), 157 (12), 155 (12), 370 (M+, 3), 372 (M+, 1), 368 (M+, 1).

Stability of 4-bromo-N-(n-butoxymethyl)-N-methyl- and 4-bromo-di(n-butoxymethyl)benzeneamine (6b and 7b respectively)

Both compounds gave with aqueous HCl at room temperature (15 min) respectively the amines 17b and 30b. If the compounds are not stored in a moisture free ambient, they formed di(4-bromo-N-methylbenzeneamino)methane and 1,3,5,7-tetra(4-bromophenyl)-1,3,5,7-tetrazocine (31) respectively. TLC on alumina or silica gel lead to their prompt decomposition. Aminoether 7b underwent partial decomposition to 4-bromo-N-methylenebenzeneamine (32b) when injected into a GC apparatus (200-300°C). Aminoether 6b was found to be quite sensitive to traces of moisture when injected into a gaschromatograph, producing amounts of 17b.

4-Bromo-N-(n-butoxymethyl)-N-methylbenzeneamine (6b)

4-Bromo-N-methylbenzeneamine (17b, 5.4 mmol) in hexane (20mL) was treated with butyllithium (8 mmol) in hexane at -30°C during 1 h and subsequently with chloromethylbutylether (8 mmol) and the solution was kept 30 min at this temperature. GC-MS analysis revealed a good advancement of the reaction (> 70%) to the desired product 17b, which was not isolated.

Electrochemical reduction of BN

The reduction potential of BN has been determined by linear sweep voltammetry measurements. BN turned out to undergo to an irreversible reduction process characterized by a peak potential of -1.68±0.01 V.

Acknowledgements - This work was supported in part by grants to AGG (CNR 86.01649.03, MPI 1987-1989 40% and 60%) and to GV (MPI 1987 60%). The authors are grateful to Dr. M. Poiana for helpful assistance in many phases of the work, prof. G. Bontempelli of this department for advice in the electrochemical work, mr. P. Polese for laboratory help and mr. P. Padovani for expert instrumental maintenance and assistance.

References and Notes

1. (a) Saavedra, J.E. *Org. Prep. Prod. Inc.* 1987, *19*, 83-159 (review). (b) Boyer, J.H.; Kumar, G.; Pillai, T.P. *J. Chem. Soc., Perkin Trans. 1* 1986, 1751. (c) Boyer, J.H.; Pillai, T.P. *J. Chem. Soc., Perkin Trans. 1* 1985, 1661. (d) Boyer, J.H.; Pillai, T.P.; Ramakrishnan, V.T. *Synthesis* 1985, 677. (e) Challis, B.C.; Challis, J.A. in *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Supplement F, Part 2, pp 1170-1172. (f) Horner, L.; Hübenett, F. *Chem. Ber.* 1953, *86*, 193.
2. (a) Williams, D.L.H. in *Nitrosation*; Cambridge University Press: New York, 1988; p 98. (b) See ref. 1e. (c) Sandler, S.R.; Karo, W. in *Organic Functional Group Preparations*; Academic Press: New York, 1971; Vol. II, pp 432-434. (d) Challis, B.C.; Butler, A.R. in *The Chemistry of the Amino Group*; Patai, S., Ed.; Interscience Publishers: New York, 1968; pp 319-320. (e) Smith, P.A.S.; Loeppky, R.N. *J. Am. Chem. Soc.* 1967, *89*, 1147. (f) Hein, G.E. *J. Chem. Ed.* 1963, *40*, 181. (g) Turney, T.A.; Wright, G.A. *Chem. Rev.* 1959, *59*, 497.
3. Sitka, A.; Rolfes, H. *Ber.* 1920, *53*, 1242.
4. Giumanini, A.G.; Caboni, M.F.; Galletti, G.C. *Gazz. Chim. It.* 1981, *111*, 515.
5. (a) Casado, J.; Lorenzo, F.M.; Mosquera, M.; Prieto, M.F.R. *Can. J. Chem.* 1984, *62*, 136. (b) Loeppky, R.N.; Tomasik, W.; Millard, T.G. in *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer*; O'Neill, I.K., von Borstel, R.C., Miller, C.T., Long, J., Bartsh, H., Eds.; IARC Scientific Publications: Lyon (France), 1984; Vol. 57, pp 353-364. (c) Aldred, S.E.; Williams, D.L.H. *J. Chem. Soc., Perkin Trans. 2* 1981, 1021. (d) Kurechi, T.; Kikugawa, K.; Kato, T. *Fd. Cosmet. Toxicol.* 1980, *18*, 581. (e) Oae, S., Asai, N.; Fujimori, K. *J. Chem. Soc., Perkin Trans. 2* 1978, 1124.
6. (a) Dabora, R.; Molina, M.; Ng, V.; Wishnok, J.S.; Tannenbaum, S.R. in *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer*; O'Neill, I.K., von Borstel, R.C., Miller, C.T., Long, J., Bartsh, H., Eds.; IARC Scientific Publications: Lyon (France), 1984; Vol. 57, pp 311-316. (b) See ref. 5b. (c) Doyle, M.P.; Terpstra, J.W.; Pickering, R.A., LePoire, D.M. *J. Org. Chem.* 1983, *48*, 3379. (d) See ref. 1e, pp 1168-1169. (e) Aldred, S.E.; Williams, D.L.H. *Fd. Chem. Toxicol.* 1982, *20*, 79. (f) See

ref. 4. (g) Challis, B.C.; Shuker, D.E.G. *J. Chem. Soc., Chem. Commun.* 1979, 315. (h) Gutierrez Rios, E.; Rodriguez, A.; Santos, A. *Anales Real Soc. Españ. Fis. Quim.* 1967, *63*, 297. (i) Clark, R.D.; Helmkamp, G.K. *J. Org. Chem.* 1964, *29*, 1316.

7. (a) Cadogan, J.I.G.; Roy, D.A.; Smith, D.M. *J. Chem. Soc. (C)* 1966, 1249. (b) Friedman, L.; Logullo, F.M. *J. Am. Chem. Soc.* 1963, *85*, 1549. (c) Stiles, M.; Miller, R.G.; Burckhardt, V. *J. Am. Chem. Soc.* 1963, *85*, 1792. (d) McCall, E.B.; Blackman, E.J. *B.P. 929,093* (*Chem. Abs.* 1963, *59*, 12,704). (e) Cadogan, J.I.G. *J. Chem. Soc.* 1962, 4257. (f) Huang, S. *Hua Hsüeh Hsüch Pao* 1959, *25*, 171. (g) Zerweck, W.; Schubert, M.; Flieshhaner, R. *G.P. 905,015* (*Chem. Abs.* 1956, *50*, 12,111).
8. (a) Batt, L. in *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Supplement F, Part 1, pp 417-458. (b) Batt, L.; Robinson, G.N. in *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Supplement F, Part 2, pp 1070-1075.
9. Budzikiewicz, H. *Angew. Chem. Int. Ed. Engl.* 1981, *20*, 624.
10. Singer, G.M. in *N-Nitroso Compounds: Analysis, Formation and Occurrence*; Walker, E.A., Griciute, L., Castegnaro, M., Börzönyi, M., Eds.; IARC Scientific Publications: Lyon (France), 1980; Vol. 31, pp 139-151.
11. (a) Colonna, M.; Greci, L.; Poloni, M. *J. Chem. Soc., Perkin Trans. 2* 1984, 165. (b) Michejda, C.J.; Tipton, T.J.; Campbell, D.H. in *Environmental N-Nitroso Compounds, Analysis and Formation*; Walker, E.A., Bogovski, P., Griciute, L., Eds.; IARC Scientific Publications: Lyon (France), 1976; Vol. 14, pp 255-260.
12. (a) Dvorak, V.; Menec, I.; Zyca, J. *Microchem. J.* 1967, *12*, 99. (b) Seo, E.T.; Nelson, R.F.; Fritsch, J.M.; Marcoux, L.S.; Leedy, O.W.; Adams, R.N. *J. Am. Chem. Soc.* 1966, *88*, 3498. (c) A p,p'-dimerisation-bis-deprotonation product of 19a was observed in the oxidation of 2a with 10% aqueous HNO_3 (Li, J.C.M.; Ritter, D.M. *J. Am. Chem. Soc.* 1953, *75*, 3024).
13. See ref. 2a, pp 162-163.
14. Elliot, G.A.; Kleist, L.L.; Wilkins, F.T.; Webb, H.W. *J. Chem. Soc.* 1926, 1219.
15. Bachman, G.B.; Hokama, T. *J. Am. Chem. Soc.* 1957, *79*, 4370.
16. See ref. 2a, p 162.
17. (a) Loeppky, R.N.; Tomasik, W. *J. Org. Chem. 1983, 48*, 2751. (b) Ohshima, H.; Kawabata, T. in *Environmental Aspects of N-Nitroso Compounds*; Walker, E.A., Castegnaro, M., Griciute, L., Lyle, R.E., Eds.; IARC Scientific Publications: Lyon (France), 1978; Vol. 19, pp 143-153.
18. (a) Al-Omran, F.; Fujiwara, K.; Giffney, J.C.; Ridd, J.H.; Robinson, S.R. *J. Chem. Soc., Perkin Trans. 2* 1981, 518. (b) See ref. 11a.
19. (a) Williams, D.L.H. in *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Supplement F, Part 1, pp 127-153. (b) Shine, H.J. in *Aromatic Rearrangements*; Elsevier: Amsterdam, 1967; pp 124-271.
20. Matzudaira, C. *Ber.* 1887, *20*, 1611.
21. Hughens, E.D.; Ridd, J.H. *J. Chem. Soc.* 1958, 82.
22. This type of reactivity was observed with the 4-iodo-N,N-dimethylbenzeneamine-"HNO_2"

system (Aitken, M.F.; Reade, T.H. *J. Chem. Soc.* 1926, 1826), but more then a century ago on the chloro and bromo analogs by some German chemists: see reff. therein.

23. Eberson, L.; Radner, F. *Acc. Chem. Res.* 1987, *20*, 53 and reff. cited therein.
24. Hodgson, H.H.; Crook, J.H. *J. Chem. Soc.* 1932, 1812.
25. Galliani, G.; Rindone, B. *J. Chem. Soc., Perkin Trans. 1* 1980, 828.
26. Urbansky, T. in *Chemistry and Technology of Explosives*; Pergamon Press: London, 1964; Vol. I, pp 116-120.
27. Giffney, J.C.; Ridd, J.H. *J. Chem. Soc., Perkin Trans. 2* 1979, 618.
28. Vogel, A. in *Vogel's Textbook of Practical Organic Chemistry, including Quantitative Organic Analysis*, forth edition; revised by Furniss, B.S., Hannaford, A.J., Rogers, V., Smith, P.W.G., Tatchell, A.R.; Longman: New York, 1978.
29. Weygand, C.; Gabler, R.; Bircan, N. *J. prakt. Chem.*, 1941, *158*, 266.
30. Ghysels, M. *Bull. soc. chim. Belg.* 1924, *33*, 57.
31. Sah, P.P.T.; Ma, T.S. *J. Am. Chem. Soc.* 1932, *54*, 2964.
32. Pouchert, C.S. in *The Aldrich Library of Infrared Spectra* third edition; Aldrich Chemical Company, Inc.: Milwaukee (Wisconsin), 1981.
33. The yields of products and the percentles of disappearance of $\underline{2a}$ were calculated on the basis of the stoichiometric equation

$$6\ \underline{2a} + 4\ \mathrm{BN} \longrightarrow 2\ \underline{14} + 2\ \underline{3a} + N_2O + H_2O$$

for all experiments under this heading unless otherwise stated. The consistently defective balance for $\underline{2a}$ formed in these reactions is to be related to the occurrence of minor products, N-demethylated diphenylmethane derivatives and GC undetected higher polymers, for which different stoichiometries are effective.

34. Giumanini, A.G.; Musiani, M.M. *Z. Naturforsch.* 1977, *32b*, 1314.
35. Macmillan, W.G.; Reade, T.H. *J. Chem. Soc.* 1929, 2863.
36. Votocek, E.; Lukes, R. *Chem. Listy.* 1928, *22*, 217.
37. Giumanini, A.G.; Verardo, G.; Zangrando, E.; Lassiani, L. *J. prakt. Chem.* 1987, *329*, 1087.
38. Doyle, M.P.; Van Lente, M.A.; Mowat, R.; Fobare, W.F. *J. Org. Chem.* 1980, *45*, 2570.
39. Fries, K. *Liebig Ann. Chem.* 1906, *346*, 188.