Tetrahedron Vol. 47, No 37, pp 7845-7852, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

N-Dealkylation-N-nitrosation of Tertiary Aromatic Amines by n-Butyl Nitrite

Giancarlo Verardo, Angelo G. Giumanini* and Paolo Strazzolini

Department of Chemistry, University of Udine, I-33100 Udine, Italy

(*Received in UK 24 June* 1991)

Key Words·
Nitrosamines; N-Dealkylation; N-Nitrosation; C-Nitration; Alkyl nitrite.

Abstract. *N,N-Dialkyl aromatic amines with a variety of ring substituents are N-dealkylated and N-nitrosated efficiently by n-butyl nitrite/ammonium chloride/water at reflux temperature Ring nitrosation was never observed, but minor amounts of m- and p-nitro amines and/or nitrosamines were formed in some cases Ring nitration is rather a reaction of the initial substrate than a process occurring on formed nitrosamines. The leaving propensities of the initial N-substituents to yield nitrosamines were in the order benzyl >> methyl >> alkyl*

In a previous paper[1] we have reported the reactivity of the systems made up by mixing alkyl nitrites and N,N-dimethyl-aromatic amines Two experimental aspects were worth of peculiar attention: the prompt reactivity and the exceptional variability of the reaction outcome upon seemingly minor changes of the conditions of the experiments It also appeared that the time necessary for the disappearance of the original amine was essentially the same at reflux temperature, given an identical concentration of reactants, independently of wide variations in the nature of substituents However, only if the reaction was prolonged much longer than the time just necessary for the disappearance of the starting amines, further processes set in to transform some products into others.

On the basis of our previous experimental results and some mechanistic considerations, it was possible to set up a procedure for the rapid and efficient N-dealkylation-N-nitrosation of tertiary aromatic amines (1) by n-butyl nitrite The new route to N-nitrosamines (2) avoids the handling of large volumes of aqueous solutions required for the classical N-nitrosation of secondary amines with "HNO_2", the careful operations of temperature, pH and amounts of reagents necessary and the incursion of unwanted side reactions

Results and Discussion

We observed that for N-dealkylation-N-nitrosation of tertiary aromatic amines (1) by n-butyl nitrite (BN) excellent conditions were a fourfold molecular equivalent (m.e.) of BN, one m e. of water and one tenth m.e of ammonium chloride at reflux temperature The results are summarized in Table 1. The individual experiments were monitored by GC-MS and terminated as soon as the starting amine 1 was fully consumed this duration afforded the highest yield of N-nitrosamines 2 in all cases

The yields of N-nitrosamines 2 varied usually from good to almost quantitative although no optimization was attempted It should be noticed that

1 amines with bulky groups either in 2 6-positions of the ring (1qa and 1ha) or at the N-position (1ad, 1ae, 1af and 1fd) did not exert any significant effect on the reaction times and yields of 2,

2 N-benzylamines (1aq, 1bq and 1cq), reacted consistently faster than N-alkyl-amines with another N-substituent of comparable or smaller size; the N-benzyl group was lost exclusively, confirming a previous observation in the reaction of tertiary amines with nitrous acid,[2] however, a further, more extensive report[3] was unable to establish such a

clearcut propensity;

3 with the exception of the N-benzyl group, the smaller N-alkyl substituent was lost preferentially, but this propensity was less prominent as the alkyl chain became longer (compare **1af** with **1ab**, **1ac** with **1ae**). This observation is in agreement with analogous experiments carried out with "HNO_2", with the exception of an ambigous report on N-ethyl-N-methyl-4-nitrobenzeneamine (**1fb**);[4]

4 branching, as in **1ad** and **1fd**, did not influence the propensity of the smaller group to be lost preferentially,

5 any substituent in a key location, like the *para* position with respect to the amino function (see **1ba**, **1bq**, **1cq**, **1fa**, **1fb**, and **1fd**), did not affect the yields of **2** at all: only the rate was slightly reduced by electron withdrawing substituents;

6 as previously shown,[1] seemingly small changes of the reaction catalyst caused dramatic variations in the reaction outcome;

7 side products were aromatic nitro compounds and eventually their N-dealkylation-N-nitrosation products, but when the rate of the disappearance of the amine was high, these processes did not set in Ring nitrations, when they occurred, preceded any eventual N-nitrosation;

8 electron releasing groups in *ortho*- and *para*-position seemed to accelerate the reaction, the latter induced some *ortho*-nitration of the substrate, which was also eventually efficiently N-nitrosated,

9 C-nitrosation products were never detected.

Preparative N-dealkylation-N-nitrosation of aromatic tertiary amines using acidified sodium nitrite has been described, but the procedure has the obvious limitation of the applicability only to some 2,4,6-trisubstituted[5] and nitrosubstituted[6] benzeneamines, because of the occurrence of ring reactions.

A final consideration pertains to the usefulness of the reaction Besides offering a prompt route to N-nitrosamines, starting from relatively cheap and readily available chemicals, like N-permethylated amines, with recyclable effluents (n-butanol and BN) in small amounts and easily separated by conventional distillation from the reaction mixture, the products themselves are convenient precursor of N-dealkylated amines in many cases (by well known procedures[3,4,7]), 1,1-disubstituted hydrazines (by reductions with a number of reagents[8]) and 4-nitroso aromatic secondary amines (by Fischer-Hepp rearrangement[9] of the 4-unsubstituted **2**) The synthetic scope of N-nitrosamines has also been recently widened by their umpolung[10] In most cases the present route to **2** appears by far and many means more convenient than N-nitrosation of a secondary amine The interest for N-dealkylation, at the same time, is well documented by a number of recent publications, introducing more or less efficient, economic, general and handy procedures,[11] often not at all amenable to large scale preparations

We have consistently used n-butyl nitrite in our experiments, as a convenient reagent which is commercially available and may be easily prepared in the laboratory[12] Optimizations were not carried out, they might obviously involve also the change of the alkyl moiety of the ester

Identification of all the compounds prepared according to this unprecedented procedure was performed by comparison of known chemicals and by careful studies of their spectral and MS properties with supplemental information from thermal degradation (reductive N-denitrosation and "HNO" elimination in the case of N-nitrosamines **2**)[1] in the GC injector and from GC properties[13] Amine **1qa** gave a product **2k**, which was identified on the basis of comparison with authentic 2,6-diisopropyl-N-methyl-3-nitro-N-nitroso-benzeneamine (**2ka**), as 2,6-diisopropyl-N-methyl-4-nitro-N-nitrosobenzeneamine (**2k**) The reaction of BN with N,N,4-trimethylbenzeneamine (**1ba**) gave a C-nitro-N-nitroso derivative (**2i**), which was identified as the 2-isomer by comparison (mp, mixed mp, GC properties, MS, IR, ^1H NMR) with the 3-isomer (**2ia**), namely N,4-dimethyl-3-nitro-N-nitrosobenzeneamine[14]

Experimental Part

WARNING - Anybody wishing to repeat these experiments or carry out similar reactions should be well aware of the known inherent or potential toxicological dangers in handling most of the chemicals used or produced in this work. Thus, safe working conditions are required and decrease of the toxic potential of mixtures and products (before transportation) should be ensured for final disposal

Table 1. Reactions of Tertiary Aromatic Amines (1) with n-Butyl Nitrite (BN)

Starting Amine (compd)	Reaction time, min	Reaction products (compd, yield[a] %)
Ph-NMe_2 (1aa)[1]	20	Ph-NNOMe, (2aa, 87)[13g,22,23,24]; 4-NO_2-Ph-NNOMe (2fa, 8.7)
Ph-NMeEt (1ab)	20	Ph-NNOMe, (2aa, 7 5); Ph-NNOEt, (2ab, 72 4)[13g,22,23,24]; 4-NO_2-Ph-NNOMe, (2fa, 1); 4-NO_2-Ph-NNOEt (2fb, 4 8)
Ph-NMePr (1ac)	20	Ph-NNOMe, (2aa, 14 3); Ph-NNOPr, (2ac, 70.2)[23,24]; 4-NO_2-Ph-NNOMe, (2fa, 1); 4-NO_2-Ph-NNOPr, (2fc, 2 8); 4-NO_2-Ph-NMePr (1fc, 3 3)
Ph-NMe(i-Pr) (1ad)	20	Ph-NNO(i-Pr), (2ad, 86 1)[13c,13f]; 4-NO_2-PhNMe(i-Pr) (1fd, 3 5)
Ph-NMeBu (1ae)	18	Ph-NNOMe, (2aa, 18 3); Ph-NNOBu, (2ae, 68 5)[23,25]; 4-NO_2-Ph-NNOMe, (2fa, 0 5); 4-NO_2-Ph-NMeBu (2fe, 1 2); 4-NO_2-Ph-NNOBu (1fe, 4 2)
Ph-NMeHex (1af)	20	Ph-NNOMe, (2aa, 11); Ph-NNOHex, (2af, 58)[26]; 4-NO_2-Ph-NMeHex (1ff, 17)
Ph-NMeBn (1ag)	5	Ph-NNOMe (2aa, 94)
4-Me-Ph-NMe_2 (1ba)	10	4-Me-Ph-NNOMe, (2ba, 81)[4,13g,22,27]; 4-Me-2-NO_2-Ph-NNOMe (2i, 6 8)
4-Me-Ph-NMeBn (1bg)	4	4-Me-Ph-NNOMe (2ba, 93)
4-Me-Ph-NEtBn (1cg)	4	4-Me-Ph-NNOEt (2cb, 91)[28]
4-MeO-Ph-NMe_2 (1da)[1,b]	5	4-MeO-Ph-NNOMe, (2da, 85.5); 4-MeO-2-NO_2-Ph-NNOMe (2j, 11 4)
4-Br-Ph-NMe_2 (1ea)[1]	15	4-Br-Ph-NNOMe (2ea, 88)
4-NO_2-Ph-NMe_2 (1fa)	25	4-NO_2-Ph-NNOMe (2fa, 91 7)[6]
4-NO^2-Ph-NMeEt (1fb)	25	4-NO_2-Ph-NNOMe, (2fa, 24); 4-NO_2-Ph-NNOEt (2fb, 67)[29]
4-NO_2-Ph-NMe(i-Pr) (1fd)	25	4-NO_2-Ph-NNO(i-Pr) (2fd, 91)
2,6-$(i\text{-Pr})_2$-Ph-NMe_2 (1ga)	17	2,6-$(i\text{-Pr})_2$-Ph-NNOMe, (2ga, 89 7); 2,6-$(i\text{-Pr})_2$-4-NO_2-Ph-NNOMe (2k, 3 2)
2,4,6-$(Me)_3$-Ph-NMe_2 (1ha)	10	2,4,6-$(Me)_3$-Ph-NNOMe (2ha, 93)[5a,30]

[a]Isolated yield [b]Twice the usual amount of NH_4Cl was used in order to optimize the yield of 2da. Under the usual conditions, the time for the consumption of 1da was 10 min.

Table 2. Properties of Some Amines (1) and N-Nitrosamines (2)

Compd	mp[a] (°C) or bp/P[a] (°C/Pa)	IR[b] (cm^{-1})	^1H NMR[c] (δ, ppm, J, Hz)	MS[d] (m/z; rel%)
1fc	58	2940, 1590, 1520, 1473, 1386, 1305, 1285, 1210, 1190, 1105, 1097, 960, 818, 750	0.96(t, 3H, J=7.34), 1.42-1.90 (m, 2H), 6.58(d, 2H, J=9.53), 8.09(d, 2H, J=9 53)	165(100), 119(75), 194 (M^+, 57), 77(18), 42 (18), 149(11), 91(11)
1fd	51	2940, 2900, 1600, 1571, 1505, 1468, 1386, 1320, 1295, 1195, 1160, 1105, 1038, 818, 750	1.24(d, 6H, J=6 35), 2.87(s, 1H), 4.22(septet, 1H, J=6.35), 6.65(d, 2H, J=9.53), 8 09(d, 2H, J=9.53)	179(100), 133(77), 194 (M^+, 55), 77(19), 117 (13), 105(13), 163(12)
1fe	77	2920, 2900, 2840, 1592, 1515, 1473, 1385, 1290, 1205, 1190, 1100, 989, 815, 748	0.78-1.89(m,7H), 3.07(s,3H), 3.43 (t, 2H, J=7.40), 6.58(d, 2H, J=9.53), 8.10(d, 2H, J=9.53)	165(100), 119(59), 208 (M^+, 28), 77(2), 104(1), 91(1)
1ff	72	2920, 2900, 2830, 1595, 1520, 1475, 1456, 1378, 1277, 1190, 1100, 985, 819, 750	0.72-1 82(m, 11H), 3.06(s, 3H), 3.42(t, 2H, J=7.40), 6.57(d, 2H, J=9 53), 8 09(d, 2H, J=9.53)	165(100), 119(64), 236 (M^+, 39), 149(8), 77(8), 105(6), 91(6)
2fc	112	1595, 1518, 1490, 1437, 1415, 1338, 1315, 1303, 1167, 1082, 978, 850, 750, 686	0.93(t, 3H, J=7.15), 1.34-1 87 (m, 2H), 4 03(pseudo t, 2H), 7 76(d, 2H, J=9 35), 8.36(d, 2H, J=9 35)	179(100), 133(88), 105 (53), 151(46), 209(M^+, 31), 77(29), 120(17)
2fd	57	3030, 1520, 1460, 1445, 1370, 1335, 1316, 1130, 1270, 892, 850, 750, 727, 688	two separate d, 6H, centered at 1.30 and 1.54, J=6.84, 5.16(m, 1H), 7.62(d, 2H, J=9.28), 8.37(d 2H, J=9.28)	133(100), 179(93), 117 (52), 76(49), 149(44), 91(30), 50(30), 209(M^+, 27)
2fe	87	3040, 2920, 2840, 1591, 1510, 1465, 1338, 1300, 1165, 1078, 1003, 842, 746, 680	0.59-2.02(m, 7H), 4 06(t, 2H, J=7.32), 7.76(d, 2H, J=9.28), 8.35(d, 2H, J=9 28)	151(100), 193(94), 105 (72), 43(70), 134(44), 223(M^+, 34)

(continued)

Table 2. (continuation)

Compd	mp[a] (°C) or bp/P[a] (°C/Pa)	IR[b] (cm^{-1})	^1H NMR[c] (δ, ppm, J, Hz)	MS[d] (m/z; rel%)
2ga	98	2940, 2900, 2840, 1585, 1455, 1428, 1380, 1360, 1213, 1065, 1048, 1016, 803, 688	1.16(d, 6H, J=6.97), 1.22(d, 6H, J=6.97), 2 31-2.93(m, 2H), 3.36 (s, 3H), 7 18-7.62(m, 3H)	190(100), 175(88), 160 (86), 132(45), 91(45), 118(42), 220(M^+, 1)
2k	124	3020, 2940, 1523, 1440, 1345, 1200, 1072, 1005, 947, 893, 752	1 22-1 47(complex pattern, 12H), 2 51-3.18(m, 2H), 3 39(s, 3H), 7 57(d, 1H, J=1 83), 7 76(d, 1H, J=1.83)	235(100), 201(59), 172 (44), 144(37), 185(35), 158(33), 187(30),132 (28), 265(M^+, 1)

[a]Melting and boiling points are uncorrected [b]Spectra were recorded on neat liquids and in KBr for solids [c]Spectra recorded in $CDCl_3$ solutions using TMS as internal standard [d]Spectra recorded via GC inlet for all amines with background substraction between 35 and 450 u N-Nitrosamine spectra were recorded on very pure specimens by vaporization into the ion source from a solid probe between room temperature and 100°C as suitable. These compounds do not usually withstand the high temperatures of the GC injector, yielding imines (by loss of HNO) and, in larger proportions, the denitrosated amines by a radical cleavage and subsequent hydrogen abstraction from solvent.

Analytical equipment and procedures used during this work were described here.[1]

Materials – n-Butyl nitrite (BN) was prepared as described[12,15] and its purity was gained by IR. BN could be stored without loss of purity at −20°C in the dark for ca. week For longer storage times, the compound was redistilled before use. Simple tic amines (**1aa**, **1ab**, **1ba** and **1ea**) were commercially available. N,N,4-Trimethyl-3-benzeneamine (**1ia**) was prepared as described.[16] N,N-Dimethylarylamine **1fa** was ously described by us,[17] **1da**, **1qa** and **1ha** were prepared after the reported dure[17] Mono-N-alkylations of primary amines 4-nitrobenzeneamine (**3**) and hylbenzeneamine (**4**) were performed to obtain N-ethyl-4-nitrobenzeneamine (**3b**), propyl-4-nitrobenzeneamine (**3d**) and N-benzyl-4-methylbenzeneamine (**4q**), ctively, using a modification[18] of the N-permethylation procedure ($NaBH_4$ – RR'CO –).[17] Mono-N-alkylations of secondary amines **3b**, **3d**, **4q** and N-methylbenzeneamine were performed by an extension of the N-permethylation procedure[17] obtaining **1fb**, **bq**, **1cq**, **1ac**, **1ad**, **1ae**, **1af** and **1aq**, respectively

',6-Diisopropyl-3-nitrobenzeneamine (**6**) was prepared according to a reported dure[19] 2,6-Diisopropyl-N-methyl-3-nitrobenzeneamine (**6a**) was prepared by the methylation procedure[17] using a 1·1 equivalent of formaldehyde· the reaction re containing **6**, **6a** and 2,6-diisopropropropyl-N,N-dimethyl-3-nitrobenzeneamine (**6aa**) in pproximate ratios (GC–peak areas ratios) 1.8.4 was treated with nitrous acid[15] to the N-nitrosoderivative **2ka** of **6a**, whose GC properties and thermolysis-GC-MS rties were definitively different from those of **2k** the only observable product was both cases the corresponding N-denitrosation-N-hydrogenation derivative iisopropyl-N-methyl-3-nitrobenzeneamine **6a** and 2,6-diisopropyl-N-methyl-4-nitro-neamine **7a**, respectively) with distinct GC[20] and MS[21]

N-Dealkylation-N-nitrosation General Procedure – A mixture of the amine **1** (4 28 , BN (21 40 mmol), water (4 28 mmol) and ammonium chloride (0 428 mmol) was ed under an inert atmosphere for the time necessary for the complete pearance of the amine (< 1%) as monitored by GC Volatile material was then rated in vacuo (ca 2660 Pa) and the residue was purified by column atography on alumina (BDH, Grade I, neutral) using hexane–ether mixtures and/or ents of appropriate concentrations The yields reported in Table 1 refer to pure ated products Table 2 enlists the physical properties, IR, NMR and MS of all the osamines as well as those of side products prepared for the first time by us, the s were identical with autentic specimen prepared according with literature

Acknowledgements – This work was supported in part by grants to AGG (CNR 49 03, CNR 89 03765 03, MPI 1987–1989 40% and 60%) and to GV (MPI 1987 60% and 40%). The authors are grateful to Miss. G. Favret for helpful assistance in many s of the work during the course of her thesis work for a degree in Food Sciences is institution, Mr P Polese for technical assistance and Mr P Padovani for expert imental maintenance

erences and Notes

Verardo, G , Giumanini, A G , Strazzolini, P *Tetrahedron*, **1990**, *46*, 4303
Wegler R , Frank, W *Ber Dtsch Chem Ges* **1936**, *69*, 2071
Smith, P A S , Leoppky, R. N *J Am Chem Soc* **1967**, *89*, 1147
Crowley, G P , Milton, G J G , Reade, T H , Todd, W M. *J Chem Soc* **1940**, 1286.
a) Emerson, W S *J Am Chem Soc* **1941**, *63*, 2023 (b) Glaser, H , Moller, F , Pieper, G , Schroter, R , Spielberger, G , Soll, H In *Methoden der Organischen Chemie* (Houben-Weyl), 4th ed , Muller, E , Ed , G Thieme Verlag Stuttgart, 1957, Vol XI/1, pp 979–980 and references cited therein
Macmillan, W G , Reade, T H *J Chem Soc* **1929**, 2863
a) Enders, D , Hassel, T., Pieter, R , Renger, B , Seebach, D *Synthesis* **1976**, 548 b) Thompson, J T , Williams, D L H *J Chem Soc , Perkin Trans 2* **1977**, 1932 (c) Hallett, G , Johal, S , Meyer, T A , Williams, D L H In *N-Nitroso Compounds Analysis, Formation and Occurrence*, Walker, E A , Griciute, L , Castegnaro, M , Borzsonyi, M , Eds , IARC Scientific Publications Lyon (France), 1980, Vol 31, pp 31–41 (d) Kano, S , Tanaka, Y , Sugino, E , Shibuya, S , Hibino, S *Synthesis* **1980**, 741 (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 1179–1183 and 1191–1194 (f) Walters, C

L.; Eisenbrand, G. In *Environmental Carcinogens. Selected Methods of Analysis*; Egan, H., Ed.; IARC Scientific Publications: Lyon (France), 1983; Vol. 45, pp 467–490 (g) Williams, D. L. H. In *Advances in Physical Organic Chemistry*; Golden, V., Bethell, D., Eds.; Academic Press: New York, 1983; Vol. 19, pp 407–413. (h) Lunn, G., Sansone, E. B. *J. Org. Chem.* **1984**, *49*, 3470. (i) Lunn, G.; Sansone, E. B. *Synthesis* **1985**, 1104 (j) Ohta, T., Kojima, K., Takitani, S. *Chem. Pharm. Bull.* **1987**, *35*, 3943. (k) Williams, D. L. H. In *Nitrosation*, Cambridge University Press: New York, 1988, pp 128–141.

8. (a) Enders, E. In *Methoden der Organischen Chemie* (Houben-Weyl), 4th ed., Muller, E., Ed.; G. Thieme Verlag: Stuttgart, 1967; Vol. X/2, Part 2, pp 224–230 (b) See reference 7e, pp 1188–1189.
9. (a) Shine, H. J. In *Aromatic Rearrangements*, Elsevier: Amsterdam, 1967, pp 124–271 (b) 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 (c) See reference 7k, pp 113–125.
10. (a) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15 (b) See reference 7e, pp 1194–1198.
11. (a) Bernardi, L., Bosisio, G. *J. Chem. Soc., Chem. Commun.* **1974**, 690 (b) Montzka, T. A., Matiskella, J. D., Partyka, R. A. *Tetrahedron Lett.* **1974**, *14*, 1325. (c) Murahashi, S. I.; Yano, T. *J. Chem. Soc., Chem. Commun.* **1979**, 270. (d) Dopp, D., Heufer, J. *Tetrahedron Lett.* **1982**, *23*, 1553 (e) Maryanoff, B. E., Molinari, A. J., McComsey, D. F., Maryanoff, C. A. *J. Org. Chem.* **1983**, *48*, 5074. (f) Olofson, R. A., Martz, J. T., Senet, J. P., Piteau, M., Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081 (g) Okazaki, R., Tokitoh, N. *J. Chem. Soc., Chem. Commun.* **1984**, 192 (h) Monkovic, I., Wong, H., Bachand, C. *Synthesis* **1985**, 770.
12. Miller, M. W., Audrieth, L. F. In *Inorganic Syntheses*, Fernelius, W. C., Ed., Robert E. Krieger Publishing Company: New York, 1978, Vol. II, pp 139–140.
13. N-Nitrosamines, due to a π-contribution to the N-N bond, usually have rotational barrier above 20 kcal/mol [(a) Shur, H. In *Anwendungen der Kernmagnetischen Resonanz in der Organischen Chemie*, Bredereck, H., Muller, E., Eds., Spring-Verlag: Berlin, 1965; pp 338–341] Their ^{1}H NMR spectra are therefore expected to show well defined patterns for the possible conformers at equilibrium at room temperature.[13a] On the other hand, steric hindrance may favor a single form [(b) Karabatsos, G. J., Taller, R. A. *J. Am. Chem. Soc.* **1957**, *79*, 6136]. The phenyl ring appeared twisted to a significant extent even in *ortho*-unsubstituted aromatic nitrosamines [(c) D'Agostino, J. T.; Jaffe, H. H. *J. Am. Chem. Soc.* **1970**, *92*, 5160, (d) Caminati, W., Giumanini, A. G. *J. Mol. Struct.* **1987**, *162*, 255] with the result of causing much less steric hindrance to the oxygen than, say, a *tert*-butyl group [(e) D'Agostino, J. T., Jaffé, H. H. *J. Am. Chem. Soc.* **1969**, *91*, 3383]; the N-methyl group always ends up 100% on the oxygen side [(f) D'Agostino, J. T., Jaffé, H. H. *J. Org. Chem.* **1971**, *36*, 992] The situation for an N-isopropyl group is intermediate, as confirmed by our present observations on **2ad** and **2fd**, for which the rotamers ratio was identical, within experimental error, and equal to that found previously[13f] for the former. All of the N-methylnitrosamines exhibited a single peak for the methyl protons, which was a good indication for the presence of a single rotamer [(g) Looney, C. E., Phillips, W. D., Reilly, E. L. *J. Am. Chem. Soc.* **1957**, *79*, 6136], which is believed to be the one with the alkyl group on the same side of the oxygen.[13b,13f] the positions of the peaks were found essentially insensitive to any ring substitution. This fact reaffirms the tenuous conjugation between the ring and the nitrosamino function. A small, but consistent shift to lower field of the methyl proton resonances in $CDCl_3$ with respect to those recorded in CCl_4[13f] reflected the H-bonding properties of the former solvent for the oxygen pole. The closer association of the N-nitrosamines with the solvent might rationalize the total absence of the *anti*-rotamer in our spectra even – and a fortiori – when *ortho*-substituents strongly presented coplanarity of the benzene hexagon with the functional group (steric hindrance to solvation). Space filling molecular models and perhaps electronic considerations (the methyl protons are certainly rather polarized [(h) Haszeldine, R. N., Mattison, B. J. H. *J. Chem. Soc.* **1955**, 4172]) permit to rationalize the absolute preference for *syn* configuration even for molecules presenting the quasi orthogonal position of the phenyl group. The compound **2k**, though, showed additional complications in the ^{1}H NMR pattern for the isopropyl

resonances perhaps due to some different rather frozen populations of rotamers or, better, the non identity of the isopropyl groups, due to a twisted ring in a configuration frozen by the action of resonance between part of the sp^2 lone pair of the amine nitrogen and the strongly conjugating nitro group. The latter hypothesis was confirmed by the pair doublets for the non equivalent aromatic protons. Minor concentrations of *anti* rotamers were evidenced from the spread α-methylene resonance in the spectra of higher homologues from ethyl upword.

14. (a) Pinnow, J. *Ber. Dtsch. Chem Ges.* **1895**, *28*, 3039. (b) Vorländer, D.; Siebert, E. J. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 283.
15. Vogel, A. In *Vogel's Textbook of Practical Organic Chemistry, including Quantitative Organic Analysis*, 4th ed.; revised by Furniss, B. S., Hannaford, A. J., Roger, V., Smith, P. W. G., Tatchell, A. R.; Longman: New York, 1978.
16. Crocker, H. P.; Jones, B. *J. Chem. Soc.* **1959**, 1808. IR (KBr) 3000, 2940, 2900, 2870, 2785, 1628, 1510, 1445, 1421, 1403, 1380, 1350, 1237, 1220, 1064, 880, 830, 807, 760, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) 2.44(s, 3H), 2.96(s, 6H), 6.70–7.62(m, 3H); MS (70 eV) m/z 180(M^+, 100), 91(70), 134(57), 133(56), 163(55), 118(50), 135(44), 77(28), 132 (24); mp 38°C.
17. (a) Giumanini, A. G.; Verardo, G.; Gei, M. H.; Lassiani, L. *J Labelled Comp. Radiopharm.* **1987**, *24*, 255. (b) Giumanini, A. G.; Verardo, G.; Poiana, M. *Boll. Chim. Farm* **1987**, *126*, 129.
18. Verardo, G.; Giumanini, A. G.; Poiana, M.; Strazzolini, P. in course of publication.
19 Giumanini, A. G.; Verardo, G.; Poiana, M. *J. Prakt. Chem.* **1988**, *330*, 161
20. Elution times: 9' 14" for 6a and 8' 40" for 7a; fused silica column, 30 m long, 0 32 mm i.d., Supelchem^R SE-54, carrier gas helium, flow rate 1 mL min^{-1}.
21. 6a. MS (70 eV) m/z 176(100), 236(M^+, 80), 132(56), 148(54), 146(47), 191(44), 221(41), 160(41); 7a: MS (70 eV) m/z 201(100), 160(85), 158 (29), 236(M^+, 27), 132(24), 221(20), 175(19), 187(16).
22. Schmidt, E.; Fischer, H. *Ber Dtsch, Chem. Ges* **1920**, *53*, 1529.
23. Pensabene, J. W., Fiddler, W.; Dooley, C.; Calvin, J.; Doerr, R. C.; Wasserman, A. E. *J. Agr. Food Chem* **1972**, *20*, 274.
24. Lovejoy, D. J., Vosper, A. J. *J Chem. Soc. A* **1968**, 2325.
25. Frienz-David, H. E.; Blangey, L.; Kaul, H. *Helv. Chim Acta* **1946**, *29*, 1765.
26. Willenz, J. *J. Chem. Soc.* **1955**, 1677
27. Hodgson, H. H.; Kershaw, A. *J. Chem Soc* **1929**, 277
28. Stroh, H. *Chem Ber.* **1958**, *91*, 2645
29. Stoermer, R. *Ber Dtsch. Chem. Ges.* **1898**, *31*, 2523.
30. Horner, L., Hübenett, F. *Justus Liebigs Ann Chem.* **1953**, *579*, 193.