New *N*-nitrosoamines
1. Synthesis and nitrosative cleavage of the Mannich bases derived from nitrogen-containing heterocycles and primary aliphatic amines

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The reactions of isatin, benzotriazole, and succinimide with formaldehyde and methylamine yield monoamines $RCH_2N(Me)CH_2R$ and methylenediamines $RCH_2N(Me)CH_2N(Me)CH_2R$. The use of ethylenediamine as the amino component affords *N*,*N*′-disubstituted imidazolidines, while the reactions with 3-aminopropan-1-ol give *N*-substituted tetrahydro-1,3-oxazines. $RCH_2NBu^i_2$ was obtained from succinimide, formaldehyde, and diisobutylamine. Nitrosative cleavage of the amines obtained was studied; it was shown that monoamines and methylenediamines give *N*-nitrosoamines $RCH_2N(NO)Me$, which were structurally characterized by X-ray diffraction analysis. $RCH_2NBu^i_2$ affords diisobutylnitrosamine, while imidazolidines transform into dinitroso compounds $RCH_2N(NO)CH_2CH_2N(NO)CH_2R$.

Key words: aminomethylation, nitrogen-containing heterocycles, primary aliphatic amines, nitrosative cleavage of tertiary amines, *N*-nitrosoamines, X-ray diffraction analysis, ^{1}H NMR and IR spectroscopy.

N-nitrosoamines possessing unusual chemical and biological properties[1] have long attracted the attention of many specialists.

As a rule, *N*-nitrosoamines are obtained by nitrosation of secondary amines[2—7] or nitrosative cleavage of tertiary amines.[8—11]

In our opinion, secondary or tertiary amines containing different heterocyclic fragments are especially attractive as the starting compounds since the latter are parts of various drugs. The present work is devoted to the synthesis of new tertiary amines containing heterocyclic fragments, study of their nitrosative cleavage, and elucidation of structures of the *N*-nitrosoamines obtained.

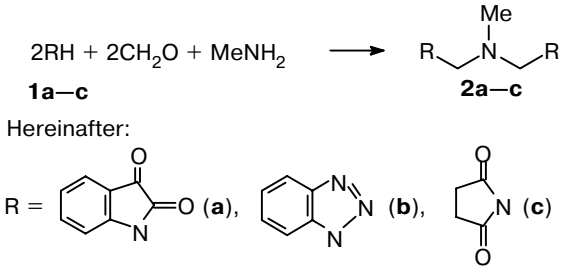
Results and Discussion

The starting amines were synthesized by aminomethylation (the Mannich reaction). The substrates to be aminomethylated were nitrogen-containing heterocycles with a mobile hydrogen atom at the N atom (NH acids), namely, isatin (**1a**), benzotriazole (**1b**), and succinimide (**1c**). The amino components were primary aliphatic amines (methylamine, ethylenediamine, and 3-aminopropan-1-ol).

Tertiary monoamines. Aminomethylation of NH acids by primary aliphatic amines is studied to a lesser extent than that by secondary amines. Nevertheless, it was established that the reactions with primary alkylamines mostly yield tertiary amines, *i.e.,* an NH acid, formaldehyde, and an alkylamine react in the molar ratio 2 : 2 : 1.[12,13]

We found that the reactions of benzotriazole **1b** and succinimide **1c** with formaldehyde and methylamine in the ratio 2 : 2 : 1 smoothly occur in Pr^iOH at ambient temperature, giving tertiary amines **2b** and **2c** in 80—82% yields (Scheme 1). Heating was required for poorly soluble isatin **1a**, and tertiary amine **2a** was obtained in moderate yield (see Scheme 1).

Scheme 1



The reaction of succinimide **1c** with formaldehyde and diisobutylamine affords amine **3** (Scheme 2).

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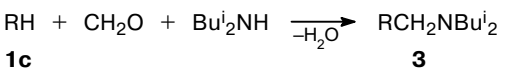
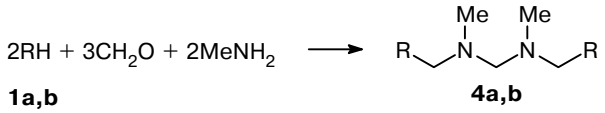
Scheme 2



Tertiary diamines. The compositions and structures of the Mannich reaction products are known to depend on the ratio of the starting reagents.[13] Thus the reaction of isatin **1a** with formaldehyde and methylamine in the ratio 2 : 4 : 2.9 gave diamine **4a** as the major product (Scheme 3), while benzotriazole **1b** reacts with formaldehyde and methylamine in the ratio 2 : 5 : 11 to form diamine **4b** (Scheme 3).

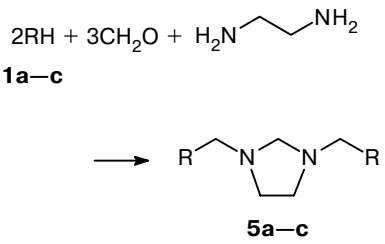
Scheme 3



No similar diamine was obtained from succinimide **1c**; with a fivefold excess of methylamine, aminolysis occurred, while a decrease in its excess results only in monoamine **2c**.

The use of ethylenediamine as the amino component in the Mannich reactions with compounds **1a—c** afforded a group of cyclic tertiary diamines, namely, imidazolidines **5a—c** (Scheme 4).

Scheme 4



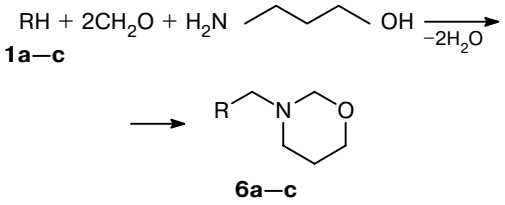
The reactions are carried out, as in the synthesis of **4a,b**, in Pr^{i}OH at room temperature or with moderate heating; compounds **5a—c** were isolated in high yields.

***N*-Substituted tetrahydro-1,3-oxazines.** The reactions with 3-aminopropan-1-ol gave *N*-substituted tetrahydro-1,3-oxazines **6a—c** (Scheme 5)*.

As in the synthesis of imidazolidines **5a—c**, the process includes two consecutive aminomethylation reactions. Unlike the formation of **5a—c** through two *N*-aminomethylation reactions, *N*- and *O*-aminomethylations are involved in the latter case. In both cases, the intramolecular cyclization provides high yields of products with the stoichiometric ratio of the starting reagents.

* For details see Ref. 14.

Scheme 5

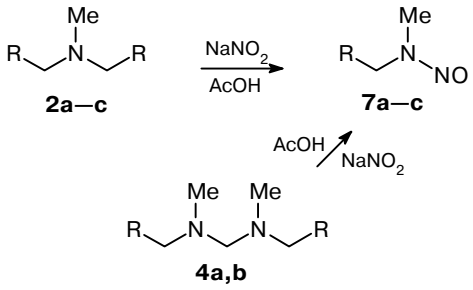


The structures of the tertiary amines obtained were established by elemental analysis and ^{1}H NMR and IR spectroscopy (Table 1). The ^{1}H NMR spectrum of methylenediamine **4a** could not be recorded because of its low solubility in available deuterated solvents.

Nitrosative cleavage of tertiary mono- and diamines. The nitrosative cleavage is usually performed by heating a mixture of an amine and sodium nitrite in aqueous acetic acid for a long time.[8,9] Nitrosamines were also prepared by treating tertiary amines with nitric acid in acetic anhydride[10] or with nitrogen dioxide.[11] Drastic reaction conditions and a complicated isolation procedure often preclude the preparation of nitrosamines in high yields.

Although we found no examples of the application of this reaction for the synthesis of nitrosamines from the Mannich bases, one could expect that these would undergo such a cleavage under milder conditions and more smoothly, considering the lability of the N_{amine}—C bonds. In fact, monoamines **2a—c** and diamines **4a,b** underwent nitrosative cleavage when treated with a mixture of anhydrous acetic acid and sodium nitrite at ambient or even reduced temperature to form nitrosamines **7a—c** (Scheme 6).

Scheme 6



The products were isolated by simply diluting the reaction mixture with water and separating the resulting precipitate. (Nitrosamine **7c**, which is well soluble in aqueous acetic acid, is isolated by extraction with CH_2Cl_2).

It should be noted that the nitrosative cleavage of monoamines **2a—c** is accompanied by the loss of a substituent containing the heterocyclic fragment, while methylenediamines **4a,b** undergo the cleavage of the

Table 1. Characteristics of the Mannich bases

Compound	Molecular formula	Found / Calculated (%)			^{1}H NMR (solvent), δ (*J*/Hz)	IR (KBr), ν/cm^{-1}
		C	H	N		
2a	$C_{19}H_{15}N_3O_4$	65.12 65.32	4.59 4.33	11.78 12.03	($CDCl_3$): 2.52 (s, 3 H, CH_3N); 4.70 (s, 4 H, NCH_2N); 7.04, 7.62 (both d, 2 H each, H(4,7), *J* = 8.0); 7.15, 7.56 (both t, 2 H each, H(5,6), *J* = 8.0)	2940, 2830, 1360 (CH_3, CH_2); 1735 (C=O); 1610, 1470, 765 (Ar); 1330, 1310, 1255 (C—N)
2b*	$C_{15}H_{15}N_7$	61.30 61.42	5.20 5.15	33.45 33.43	($CDCl_3$): 2.53 (s, CH, CH_3N); 5.60 (s, 4 H, NCH_2N); 7.40, 7.52 (both t, 2 H each, H(5,6), *J* = 8.0); 7.67, 8.09 (both d, 2 H each, H(4,7), *J* = 8.0)	3061, 3000, 1610, 1590, 1495, 1455, 790, 780, 745 (Ar); 2961, 2876, 2831, 1435, 1425, 1400, 1370 (CH_3, CH_2); 1325, 1310, 1280, 1270 (C—N)
2c	$C_{11}H_{15}N_3O_4$	52.02 52.17	5.91 5.97	16.70 16.59	($CDCl_3$): 2.36 (s, 3 H, CH_3N); 2.70 (s, 8 H, $CH_2C(O)$); 4.42 (s, 4 H, NCH_2N)	2985, 2945, 2860, 2810, 1455, 1410, 1356 (CH_3, CH_2); 1756, 1700 (C=O); 1285, 1265, 1250, 1175, 1155, 1070, 1045 (C—N, C—C)
3	$C_{13}H_{24}N_2O_2$	64.77 64.97	10.16 10.06	11.75 11.66		2960, 2865, 1350 (CH_2); 1775, 1705 (C=O); 1285, 1235, 1150, 1090, 1050 (C—N, C—C)
4a	$C_{21}H_{20}N_4O_4$	64.37 64.28	5.00 5.14	14.06 14.28		2960, 2865, 1435, 1355 (CH_3, CH_2); 1725 (C=O); 1605, 1465, 765 (Ar); 1330, 1305, 1240 (C—N)
4b	$C_{17}H_{20}N_8$	60.89 60.70	5.77 5.99	33.30 33.31	($CDCl_3$): 2.46 (s, 6 H, CH_3N); 3.28 (s, 2 H, CH_2); 5.69 (s, 4 H, NCH_2N); 7.37, 7.50 (both t, 2 H each, H(5,6), *J* = 8.0); 7.69, 8.08 (both d, 2 H each, H(4,7), *J* = 8.0)	2975, 2956, 2940, 2876, 2845, 2815, 1430, 1385, 1370 (CH_3, CH_2); 3087, 3060, 3021, 1610, 1490, 1450, 775, 765, 755, 745 (Ar); 1325, 1305, 1290, 1280 (C—N)
5a	$C_{21}H_{18}N_4O_4$	64.34 64.61	4.80 4.65	14.42 14.35	(DMSO-d_6): 2.90 (s, 4 H, NCH_2); 3.63 (s, 2 H, NCH_2N); 4.57 (s, 4 H, $CH_2NC(O)$); 7.14, 7.64 (both t, 2 H each, H(5,6), *J* = 7.6); 7.25, 7.55 (both d, 2 H each, H(4,7), *J* = 7.6)	2930, 2845, 1385, 1366, 1350 (CH_2); 1735 (C=O); 1615, 1470, 765 (Ar); 1255, 1050 (ring)
5b	$C_{17}H_{18}N_8$	60.96 61.06	5.37 5.43	33.82 33.51	(CD_3CN): 2.90 (s, 4 H, NCH_2CH_2N); 3.82 (s, 2 H, NCH_2); 5.50 (s, 4 H, NCH=N); 7.40, 7.50 (t, 2 H each, H(5,6), *J* = 7.7); 7.65, 7.99 (both d, 2 H each, H(4,7), *J* = 7.7)	3056, 1613, 1496, 1451, 797, 767, 743 (Ar); 2939, 2870, 2840, 1435, 1388, 1370 (CH_2); 1196, 1061 (ring)
5c	$C_{13}H_{18}N_4O_4$	53.08 53.05	6.26 6.16	19.36 19.04	($CDCl_3$): 2.70 (s, 8 H, $CH_2C(O)$); 2.87 (s, 42 H, NCH_2CH_2N); 3.58 (s, 2 H, NCH_2); 4.30 (s, 4 H, NCH_2N)	2950, 2930, 2900, 2850, 1435, 1405, 1345 (CH_2); 1770, 1695 (C=O); 1230, 1080 (ring)
6a	$C_{13}H_{14}N_2O_3$	63.53 63.40	5.59 5.73	11.10 11.37	(CD_3CN): 1.60 (quint, 2 H, $CH_2\underline{CH_2}CH_2$, *J* = 5.0); 2.98 (t, 2 H, $N\underline{CH_2}CH_2$, *J* = 5.0); 3.70 (t, 2 H, $O\underline{CH_2}CH_2$, *J* = 5.0); 4.41 (s, 2 H, NCH_2O); 5.63 (s, 2 H, NCH_2N); 7.41, 7.55 (both dd, 1 H each, H(6), *J* = 8.0, H(5), *J* = 8.0); 7.75, 8.00 (both d, 1 H each, H(7), *J* = 8.0, H(4), *J* = 8.0)	3062, 3029, 1616, 1496, 1454, 800, 743 (Ar); 2973, 2951, 2930, 2870, 2837, 1382, 1367, 1340 (CH_2); 1205, 1181, 1046, 1001, 1205, 1181, 1046, 1001, 977, 950, 884 (oxazine)

(*to be continued*)

Table 1 (*continued*)

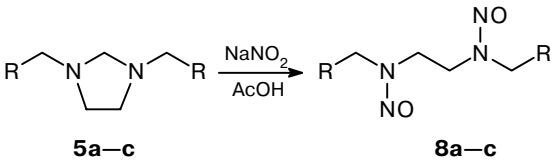
Compound	Molecular formula	Found / Calculated (%) C	H	N	^{1}H NMR (solvent), δ (*J*/Hz)	IR (KBr), ν/cm^{-1}
6b	$C_{11}H_{14}N_4O$	60.32 60.54	6.32 6.47	26.01 25.67	(CD_3CN): 1.60 (quint, 2 H, $CH_2\underline{CH_2}CH_2$, *J* = 5.0); 2.98 (t, 2 H, $N\underline{CH_2}CH_2$, *J* = 5.0); 3.70 (t, 2 H, $OCH_2\underline{CH_2}$, *J* = 5.0); 4.41 (s, 2 H, NCH_2O); 5.63 (s, 2 H, NCH_2N); 7.41, 7.55 (both d, 1 H each, H(6), *J* = 8.0, H(5), *J* = 8.0); 7.75, 8.00 (both d, 1 H each, H(7), *J* = 8.0, H(4), *J* = 8.0)	3098, 3032, 2993, 1613, 1508, 1466, 728, 713 (Ar); 2960, 2924, 2876, 2870, 2837, 1382, 1367, 1340, (CH_2); 1205, 1181, 1046, 1001, 977, 950, 884 (oxazine)
6c	$C_9H_{14}N_2O_3$	54.24 54.53	6.92 7.12	14.40 14.13	(CD_2Cl_2): 1.11 (quint, 2 H, $CH_2\underline{CH_2}CH_2$, *J* = 5.1, 4.8); 2.68 (s, 4 H, $CH_2C(O)$); 2.92 (t, 2 H, NCH_2CH_2, *J* = 5.1); 3.73 (t, 2 H, $CH_2\underline{CH_2}O$, *J* = 4.8); 4.28 (s, 2 H, NCH_2O); 4.42 (s, 2 H, NCH_2N)	2987, 2969, 2954, 2924, 2864, 2810, 2750, 2726, 1442, 1418, 1409, 1388, 1367, 1349 (CH_2); 1763, 1697 (C=O); 1223, 1058, 983, 899 (oxazine)

* See Ref. 13.

N—C bonds of the methylenediamine fragment and no loss of the heterocycle takes place.

Cyclic diamines **5a—c** undergo a similar cleavage to give bisnitrosamines **8a—c** (Scheme 7).

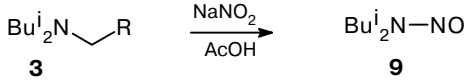
Scheme 7



5a—c **8a—c**

The nitrosative cleavage of amine **3** occurs with the splitting of the heterocyclic fragment to yield the known[15,16] diisobutylnitrosamine **9** (Scheme 8).

Scheme 8



3 **9**

In the reactions studied, all tertiary amines derived from isatin and succinimide give the corresponding nitrosamines in high yields. Benzotriazole derivatives **2b** and **4b** afford nitrosamine **7b** in but moderate yield. Bisnitrosamine **8b** could be obtained from cyclic diamine **5b** in very low yield. The low yields of nitrosamines **7b** and **8b** may be attributed to the known fact[17] of hydrolytic instability of aminomethylated benzotriazoles. To reduce the contribution from the hydrolytic transformations of these amines during their nitrosative cleavage, we carried out the reaction in a mixture of AcOH with Ac_2O and changed the order of mixing the reagents.

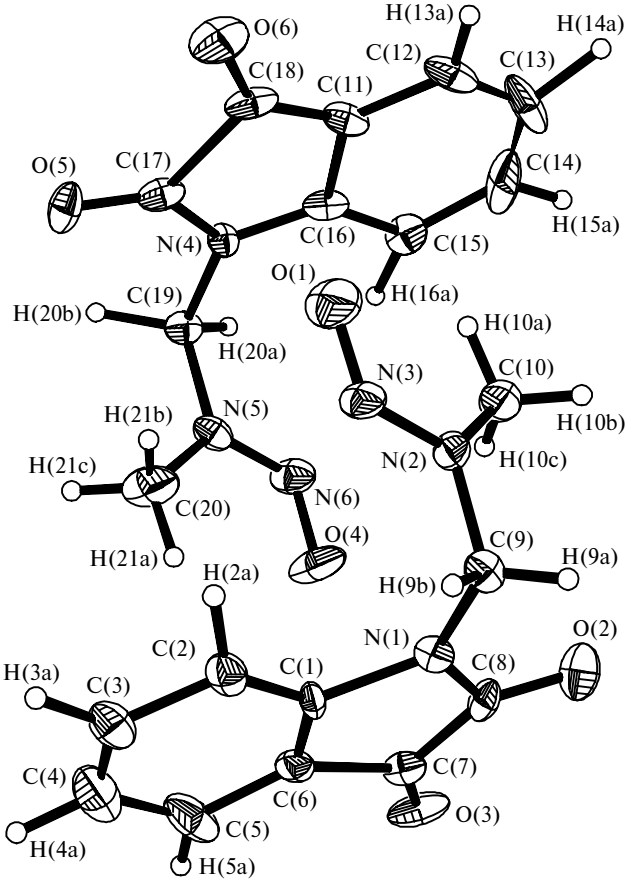


Fig. 1. Structures of two independent molecules in compound **7a**.

Table 2. Characteristics of *N*-nitrosoamines

Compound	Molecular formula	Found / Calculated (%)			^{1}H NMR (solvent), δ (*J*/Hz)	IR (KBr), ν/cm^{-1}
		C	H	N		
7a	$C_{10}H_9N_3O_3$	54.95 54.79	4.42 4.14	19.05 19.17	(CD_2Cl_2): 3.07 (s, 3 H, CH_3N); 6.10 (s, 2 H, NCH_2N); 7.16, 7.68 (both d, 1 H each, H(4,7), *J* = 7.3); 7.23, 7.67 (both t, 1 H each, H(5,6), *J* = 7.3)	3030, 1615, 1470, 760 (Ar); 2920, 2705, 1445, 1345 (CH_3, CH_2); 1745, 1735 (C=O); 1430, 1035 (N—N=O)
7b	$C_8H_9N_5O$	50.48 50.26	5.11 4.74	36.82 36.63	(CD_3CN): 3.00 (s, 3 H, CH_3N); 7.02 (s, 2 H, NCH_2N); 7.43, 7.58 (both t, 1 H each, H(5,6)); 7.74, 8.05 (both d, 1 H each, H(4,7))	3090, 3066, 3021, 1614, 1492, 1454, 785, 760, 751 (Ar); 2936, 1422, 1367 (CH_3, CH_2); 1459, 1031 (N—N=O)
7c	$C_6H_9N_3O_3$	42.19 42.10	5.12 5.30	25.04 24.55	(CD_3CN): 2.73 (s, 4 H, $CH_2C(O)$); 3.00 (s, 3 H, CH_3N); 5.77 (s, 2 H, NCH_2N)	3015, 2935, 1420, 1400, 1350 (CH_3, CH_2); 1775, 1715 (C=O); 1445, 1025 (N—N=O); 1285, 1255, 1165, 1070 (C—N)
8a	$C_{20}H_{16}N_6O_6$	55.52 55.05	5.12 3.69	19.05 19.26		3013, 1610, 1470, 760 (Ar); 2925, 2849, 1420, 1340 (CH_2); 1735 (C=O); 1465, 1035, 1010 (N—N=O); 1300, 1250 (C—N)
8b	$C_{16}H_{16}N_{10}O_2$	49.95 50.52	4.12 4.24	37.00 36.82		3070, 3020, 1613, 1492, 1453 sh, 790, 746 (Ar); 2930, 2854, 1428, 1371, 1351, 1341 (CH_2); 1467, 965 (N—N=O); 1230, 1194 (C—N)
8c	$C_{12}H_{16}N_6O_6$	42.74 42.35	4.56 4.74	37.00 24.70		2945, 1415, 1350 (CH_2); 1775, 1707 (C=O); 1455, 1060 (N−N=O); 1300, 1280, 1175, 1125 (C—N, C—C)

Our attempts to perform nitrosative cleavage of tetrahydro-1,3-oxazines **6a—c** failed; the expected *N*-nitroso derivatives were not isolated from the resulting mixtures. This may partly be due to the hydrolysis of the nitrite group formed upon *O*-nitrosation when the reaction mixture is diluted with water. (These investigations are in progress and their results will be published elsewhere.)

All the nitrosamines obtained were identified by elemental analysis and IR spectroscopy (Table 2). The structures of mononitrosamines **7a—c** were also confirmed by ^{1}H NMR spectroscopic data. The ^{1}H NMR spectra of bisnitrosamines **8a,c** could not be recorded because of their low solubilities in available deuterated solvents.

Nitrosamines **7a,b** were structurally characterized by X-ray diffraction analysis (Figs. 1, 2). The N(NO)Me fragments in both molecules are geometrically similar (Tables 3, 4). For example, the NNO group is nonlinear (the N—N—O angle is 111.0(4)° and 117.9(4)° in **7a** for two independent molecules and 114.3(2)° in **7b**), which is not surprising since the nitroso N atom has a free lone electron pair not involved formally in bonding. The second N atom virtually lies in the plane containing the neighboring C atoms and the N atom (the deviations of the N(2) and N(5) atoms in **7a** (see Fig. 1) or the N(2) atom in **7b** (see Fig. 2) are 0.0105 and 0.0566 Å in **7a**

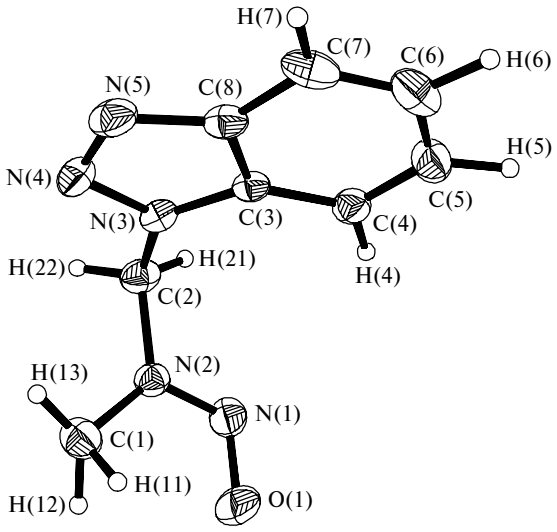


Fig. 2. Structure of **7b**.

Table 3. Selected geometrical parameters of compound **7a**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
		Molecule A			
N(1)—C(1)	1.482(4)	N(1)—C(8)	1.3904)	N(1)—C(9)	1.412(4)
N(2)—N(3)	1.376(5)	N(2)—C(9)	1.463(6)	N(2)—C(10)	1.374(6)
N(3)—O(1)	1.223(6)	O(2)—C(8)	1.249(5)	O(3)—C(7)	1.216(5)
C(1)—C(2)	1.369(5)	C(1)—C(6)	1.340(5)	C(2)—C(3)	1.406(5)
C(3)—C(4)	1.363(7)	C(4)—C(5)	1.509(7)	C(5)—C(6)	1.406(5)
C(6)—C(7)	1.530(5)	C(7)—C(8)	1.453(5)		
		Molecule B			
N(4)—C(17)	1.341(5)	N(4)—C(18)	1.363(5)	N(4)—C(20)	1.462(5)
N(5)—N(6)	1.2325)	N(5)—C(20)	1.449(5)	N(5)—C(21)	1.518(6)
N(6)—O(4)	1.234(5)	O(5)—C(18)	1.182(5)	O(6)—C(19)	1.211(5)
C(12)—C(13)	1.366(5)	C(12)—C(17)	1.447(5)	C(12)—C(19)	1.359(5)
C(13)—C(14)	1.266(6)	C(14)—C(15)	1.344(7)	C(15)—C(16)	1.413(6)
C(16)—C(17)	1.402(5)	C(18)—C(19)	1.656(5)		

Angle	ω/deg	Angle	ω/deg
	Molecule A		
C(1)—N(1)—C(8)	106.9(2)	C(1)—N(1)—C(9)	126.1(2)
C(8)—N(1)—C(9)	127.0(3)	N(3)—N(2)—C(9)	111.3(3)
N(3)—N(2)—C(10)	126.6(4)	C(9)—N(2)—C(10)	122.0(3)
N(2)—N(3)—O(1)	111.0(4)	N(1)—C(1)—C(2)	124.6(3)
N(1)—C(1)—C(6)	110.9(3)	C(2)—C(1)—C(6)	124.5(3)
C(1)—C(2)—C(3)	118.0(4)	C(2)—C(3)—C(4)	119.3(4)
C(3)—C(4)—C(5)	123.3(4)	C(4)—C(5)—C(6)	112.1(4)
C(1)—C(6)—C(5)	122.9(4)	C(1)—C(6)—C(7)	107.4(3)
C(5)—C(6)—C(7)	129.7(4)	O(3)—C(7)—C(6)	128.1(4)
O(3)—C(7)—C(8)	126.9(4)	C(6)—C(7)—C(8)	104.9(3)
N(1)—C(8)—O(2)	122.8(3)	N(1)—C(8)—C(7)	109.9(3)
O(2)—C(8)—C(7)	126.8(4)	N(1)—C(9)—N(2)	111.0(3)
	Molecule B		
C(17)—N(4)—C(18)	114.3(3)	C(17)—N(4)—C(20)	123.8(3)
C(18)—N(4)—C(20)	121.1(3)	N(6)—N(5)—C(20)	121.3(4)
N(6)—N(5)—C(21)	118.0(4)	C(20)—N(5)—C(21)	120.2(3)
N(5)—N(6)—O(4)	117.9(4)	C(13)—C(12)—C(17)	117.9(3)
C(13)—C(12)—C(19)	133.1(4)	C(17)—C(12)—C(19)	108.9(3)
C(12)—C(13)—C(14)	124.5(4)	C(13)—C(14)—C(15)	118.4(4)
C(14)—C(15)—C(16)	126.2(4)	C(15)—C(16)—C(17)	113.4(4)
N(4)—C(17)—C(12)	110.0(3)	N(4)—C(17)—C(16)	130.4(3)
C(12)—C(17)—C(16)	119.6(3)	N(4)—C(18)—O(5)	130.5(4)
N(4)—C(18)—C(19)	101.5(3)	O(5)—C(18)—C(19)	127.9(4)
O(6)—C(19)—C(12)	136.8(4)	O(6)—C(19)—C(18)	118.0(3)
C(12)—C(19)—C(18)	105.2(3)	N(4)—C(20)—N(5)	112.9(3)

and by 0.0082 Å in **7b**). Although the geometrical parameters of the N(NO)Me fragment in two independent molecules of compound **7a** are somewhat nonequivalent (see Table 3) (probably, because of packing effects, which redistribute the electron density in this fragment), the angular conformation of the NNO fragment in both nitroso compounds is typical of such organic derivatives,[18] sharply differing from the linear one characteristic of metal nitrosyl complexes where the lone electron pair of the N atom is involved in bonding to the metal center, which makes the N—O and M—N distances significantly shorter.[19]

Thus, a route to new *N*-nitrosoamines *via* the aminomethylation of heterocyclic NH acids followed by the nitrosative cleavage of the resulting Mannich bases is proposed.

Experimental

The starting high-purity NH acids and amines (≥98%) were used without additional purification. Solvents for reaction and recrystallization purposes were reagent and analytical grades.

^{1}H NMR spectra were recorded on an NMR spectrometer with a superconducting magnet (294 MHz) (the instrument was designed and manufactured at the Institute of Problems of Chemical Physics, Russian Academy of Sciences). IR spectra (KBr) were recorded on a Specord M82 spectrophotometer.

***N,N*-Bis[(isatin-1-yl)methyl]methylamine (2a).** A mixture of isatin **1a** (1.47 g, 10 mmol), Pr^{i}OH (12 mL), and 34%

Table 4. Selected geometrical parameters of compound **7b**

Bond	*d*/Å	Bond	*d*/Å	Bond	*d*/Å
O(1)—N(1)	1.231(3)	N(1)—N(2)	1.309(3)	N(2)—C(1)	1.441(4)
N(2)—C(2)	1.450(3)	N(3)—N(4)	1.368(3)	N(3)—C(2)	1.440(3)
N(3)—C(3)	1.361(3)	N(4)—N (5)	1.296(3)	N(5)—C(8)	1.367(3)
C(3)—C(4)	1.393(3)	C(3)—C(8)	1.391(2)	C(4)—C(5)	1.365(4)
C(5)—C(6)	1.393(4)	C(6)—C(7)	1.356(5)	C(7)—C(8)	1.402(4)

Angle	ω/deg	Angle	ω/deg
O(1)—N(1)—N(2)	114.3(2)	N(1)—N(2)—C(1)	123.1(2)
N(1)—N(2)—C(2)	115.3(2)	C(1)—N(2)—C(2)	121.6(2)
N(4)—N(3)—C(2)	120.1(2)	N(4)—N(3)—C(3)	110.4(2)
C(2)—N(3)—C(3)	129.5(2)	N(3)—N(4)—N(5)	107.8(2)
N(4)—N(5)—C(8)	109.4(2)	N(2)—C(2)—N(3)	111.3(2)
N(3)—C(3)—C(4)	133.5(2)	N(3)—C(3)—C(8)	104.0(2)
C(4)—C(3)—C(8)	122.5(2)	C(3)—C(4)—C(5)	115.7(2)
C(4)—C(5)—C(6)	122.3(3)	C(5)—C(4)—C(7)	122.3(3)
C(5)—C(4)—C(8)	116.8(2)	N(5)—C(8)—C(3)	108.4(2)
N(5)—C(8)—C(7)	131.3(2)	C(3)—C(8)—C(7)	120.3(2)

formalin (0.88 g, 10 mmol of CH_2O) was stirred at 70 °C for 2 h. Then a mixture of a 25.9% aqueous solution of $MeNH_2$ (0.6 g, 5 mmol) and Pr^iOH (12 mL) was added dropwise over 30 min. The reaction mixture was stirred at 70 °C for 30 min and without heating for 1 h and left overnight. The precipitate that formed was filtered off, washed with Pr^iOH and MeOH, and dried. The yield of the crude product was 0.9 g (51.6%), m.p. 173—176 °C (decomp.). This product was used for subsequent reactions without additional purification. An analytical sample (m.p. 180—182 °C, decomp.) was obtained by stirring the product in a mixture of MeOH with MeCN (1 : 1, 6 mL of the mixture per gram) at ~20 °C for 1 h. The solid precipitate was filtered off, washed with MeOH, and dried.

***N,N*-Bis[(benzotriazol-1-yl)methyl]methylamine (2b).** A 25.9% aqueous solution of $MeNH_2$ (3 g, 25 mmol) was added with stirring to a solution of benzotriazole (**1b**) (5.95 g, 50 mmol) in 20 mL of Pr^iOH. Then a solution of formalin (4.5 g, 51 mmol of CH_2O) in 10 mL of water was added dropwise. The reaction mixture was stirred at ~20 °C for 4 h, and water (10 mL) was added dropwise. The resulting solution was stirred for 1 h and left without stirring overnight. The precipitate that formed was filtered off, washed with Pr^iOH—water (1 : 1), and dried. The yield of **2b** was 6 g (82%), m.p. 96—99 °C. After recrystallization from acetone, m.p. 101—103 °C (*cf.* Ref. 13: m.p. 88—90 °C).

***N,N*-Bis(succinimidomethyl)methylamine (2c).** A 25.9% aqueous solution of $MeNH_2$ (1.31 g, 11 mmol) was added with stirring to a mixture of succinimide **1c** (1.98 g, 20 mmol) and Pr^iOH (7 mL). After 10 min, formalin (1.85 g, 21 mmol of CH_2O) was added, and the reaction mixture was stirred for 4 h and cooled to 10 °C. The precipitate that formed was filtered off, washed with cold Pr^iOH (−15 °C), and dried. The yield of **2c** was 2.05 g (81%), m.p. 173—177 °C. After recrystallization from $CHCl_3$—CCl_4, m.p. 175—177 °C.

***N*-(Succinimidomethyl)diisobutylamine (3).** Formalin (0.97 g, 11 mmol of CH_2O), diisobutylamine hydrochloride (1.82 g, 11 mmol), and succinimide (**1c**) (0.99 g, 10 mmol) were added with stirring to a solution of $KHCO_3$ (1.1 g, 11 mmol) in 15 mL of water. The reaction mixture was kept at 50 °C for 0.5 h and then cooled to 10 °C. The precipitate that formed was filtered off, washed with cold water, and dried. The yield of **3** was 1.85 g (77%), m.p. 80—82 °C. After recrystallization from Pr^iOH—water, m.p. 83—84 °C.

1,5-Bis(isatin-1-yl)-2,4-dimethyl-2,4-diazapentane (4a). A mixture of a 25.9% aqueous solution of $MeNH_2$ (3 g, 25 mmol), Pr^iOH (30 mL), formalin (3.5 g, 40 mmol of CH_2O), and isatin (**1a**) (2.94 g, 20 mmol) was stirred at 50 °C for 1.5 h. After 45 min, an aqueous solution of $MeNH_2$ (0.5 g, 4 mmol) was added, and the reaction mixture was left without stirring at ~20 °C overnight. The precipitate that formed was filtered off, washed with MeOH, and dried. The yield of crude diamine **4a** was 3.3 g (84%), m.p. 168—172 °C (decomp.). This product was used for subsequent reactions without additional purification. An analytical sample (m.p. 174—176 °C, decomp.) was obtained as described for **2a** (20 mL of the solvent per gram, stirring for 6 h).

1,5-Bis(benzotriazol-1-yl)-2,4-dimethyl-2,4-diazapentane (4b). A mixture of a 25.9% aqueous solution of $MeNH_2$ (6.6 g, 55 mmol), Pr^iOH (8 mL), formalin (2.2 g, 25 mmol of CH_2O), and benzotriazole (**1b**) (1.19 g, 10 mmol) was stirred at ~20 °C for 4 h and then poured onto a watch glass. The solvent was evaporated with a flow of air with periodical stirring. The solid residue (1.7 g, theoretical yield 1.68 g) was mixed with 50% aqueous acetone (2 mL) and cooled to −15 °C. The precipitate was filtered off and dried. The yield of **4b** was 1.43 g (85%), m.p. 102—105 °C. After recrystallization from MeCN, m.p. 106—108 °C. A mixture of the product with monoamine **2b** clearly depressed the melting point (83—92 °C).

1,3-Bis[(isatin-1-yl)methyl]imidazolidine (5a). A mixture of a 70% aqueous solution of ethylenediamine (2.57 g, 30 mmol), Pr^iOH (45 mL), formalin (8.4 g, 95 mmol of CH_2O), and isatin (**1a**) (8.82 g, 60 mmol) was stirred at 20 °C for 30 min and then at 50—55 °C for an additional 2.5 h. The reaction mixture was left without stirring at ~20 °C overnight. The precipitate that formed was filtered off, washed with Pr^iOH and MeOH, and dried. The yield of **5a** was 11.5 g (98%), m.p. 163—164 °C (decomp.). The product was used for subsequent reactions without additional purification. An analytical sample (m.p. 166—167 °C, decomp.) was obtained as described for **4a**.

1,3-Bis[(benzotriazol-1-yl)methyl]imidazolidine (5b). A mixture of benzotriazole (**1b**) (9.52 g, 80 mmol), Pr^iOH (68 mL), a 70% aqueous solution of ethylenediamine (3.43 g, 40 mmol),

and formalin (11.12 g, 126 mmol of CH_2O) was stirred at 20 °C for 30 min and then at 50—55 °C for an additional 1 h. The reaction mixture was cooled to 20 °C, and the precipitate that formed was filtered off, washed with Pr^iOH, and dried. The yield of **5b** was 11.7 g (87.4%), m.p. 125—127 °C. After recrystallization from CCl_4—$CHCl_3$, its melting point remained unchanged.

1,3-Bis(succinimidomethyl)imidazolidine (5c). A mixture of a 70% aqueous solution of ethylenediamine (2.14 g, 25 mmol), Pr^iOH (50 mL), formalin (7.15 g, 81 mmol of CH_2O), and succinimide (**1c**) (4.95 g, 50 mmol) was stirred at ~20 °C for 6 h and left without stirring overnight. The reaction mixture was then cooled to −15 °C and kept for 6 h. The precipitate that formed was filtered off, washed with cold Pr^iOH (−15 °C), and dried. The yield of **5c** was 5.7 g (77.5%), m.p. 120—122 °C. After recrystallization from AcOEt, its melting point remained unchanged.

3-[(Isatin-1-yl)methyl]tetrahydro-1,3-oxazine (6a). A mixture of **1a** (2.94 g, 20 mmol), Pr^iOH (29 mL), 3-aminopropan-1-ol (1.5 g, 20 mmol), and formalin (3.53 g, 40 mmol of CH_2O) was stirred at 50 °C for 1 h. Then the reaction mixture was cooled to 15 °C, and the precipitate that formed was filtered off and dried. The yield of **6a** was 3.9 g (79%), m.p. 128—130 °C. After recrystallization from CCl_4, m.p. 130—132 °C.

3-[(Benzotriazol-1-yl)methyl]tetrahydro-1,3-oxazine (6b) was obtained analogously from compound **1b** (11.9 g, 100 mmol). The yield of **6b** was 18.5 g (85%), m.p. 105—107 °C. The product recrystallized from water has the same melting point.

3-(Succinimidomethyl)tetrahydro-1,3-oxazine (6c). A mixture of **1c** (14.85 g, 150 mmol), Pr^iOH (45 mL), 3-aminopropanol (11.25 g, 150 mmol), and formalin (26.5 g, 300 mmol of CH_2O) was stirred at 50 °C for 1 h. The solvent was removed *in vacuo*, and Pr^iOH (30 mL) and *n*-heptane (30 mL) were added to the residue. The mixture was stirred and cooled to 0 °C, the precipitate was filtered off and dried. The yield of **6c** was 22.5 g (76%), m.p. 58—60 °C. After recrystallization from Pr^iOH—*n*-heptane, m.p. 64—66 °C.

N*-[(Isatin-1-yl)methyl]-*N*-nitrosomethylamine (7a).** ***A. Sodium nitrite (1.72 g, 25 mmol) was added portionwise over 1.5 h with stirring and cooling to 15—18 °C to a mixture of amine **2a** (1.05 g, 3 mmol) and glacial AcOH (10 mL). The reaction mixture was kept at ~20 °C for 6 h and poured into 70 mL of cold water. The precipitate was filtered off, washed with water, and dried. The yield of **7a** was 0.59 g (90%), m.p. 167—170 °C. After recrystallization from $CHCl_3$—CCl_4, m.p. 171—173 °C.

B. The above procedure was used to obtain compound **7a** from diamine **4a** (0.98 g, 2.5 mmol), AcOH (15 mL), and $NaNO_2$ (2.59 g). The yield of **7a** was 0.94 g (86%), m.p. 166—169 °C. After recrystallization from $CHCl_3$—CCl_4, m.p. 171—173 °C.

The IR and ^1H NMR spectra of both samples are identical.

N*-[(Benzotriazol-1-yl)methyl]-*N*-nitrosomethylamine (7b).** ***A. Sodium nitrite (1.38 g, 20 mmol) was added portionwise over 10 min with stirring and cooling to 0—2 °C to a mixture of glacial AcOH (10 mL) and Ac_2O (10 mL). Then a finely ground mixture of amine **2b** (3.37 g, 11.5 mmol) and $NaNO_2$ (3.45 g, 50 mmol) was added over 1.5 h. The reaction mixture was kept at 0—2 °C for 6 h (after 3 h, the thickened mass was diluted with 7 mL of AcOH), poured into 140 mL of water with ice, and stirred for 30 min. The precipitate was filtered off, washed with cold water, and dried. Isopropyl alcohol (2 mL) was added, and the resulting mixture was thoroughly stirred and cooled to −15 °C. The solid precipitate was filtered off, washed with a small amount of cold Pr^iOH (−15 °C), and dried. The yield of **7b** was 1.23 g (56%), m.p. 96—98 °C. After recrystallization from CCl_4 or Pr^iOH—*n*-heptane, m.p. 99—100 °C.

B. The same procedure was used to obtain **7b** from compound **4b** (3.36 g, 10 mmol), AcOH (20 mL), Ac_2O (15 mL), and $NaNO_2$ (6.9 g), but the crude product was not treated with Pr^iOH. The yield of **7b** was 1.88 g (49%), m.p. 95—98 °C. After recrystallization from CCl_4 or Pr^iOH—*n*-heptane, m.p. 99—100 °C.

The ^1H NMR and IR spectra of both samples are identical.

***N*-Nitroso-*N*-(succinimidomethyl)methylamine (7c).** Sodium nitrite (2.9 g, 42 mmol) was added portionwise over 1.5 h with stirring and cooling to 15—18 °C to a mixture of amine **2c** (1.52 g, 6 mmol) and glacial AcOH (22 mL). The reaction mixture was kept at 15 °C for 6 h and poured into 140 mL of cold water. The product was extracted with CH_2Cl_2. The extract was washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo* to give compound **7c** (0.92 g, 89.7%), m.p. 79—83 °C. After recrystallization from AcOEt, m.p. 85—86 °C.

1,6-Bis(isatin-1-yl)-2,5-dinitroso-2,5-diazahexane (8a) was obtained as described for **7a** from imidazolidine **5a** (0.98 g, 2.5 mmol), AcOH (10 mL), and $NaNO_2$ (1.73 g). The yield of **8a** was 0.94 g (86%), decomp. at 251—260 °C. After recrystallization from DMSO, decomp. at 262—267 °C.

1,6-Bis(benzotriazol-1-yl)-2,5-dinitroso-2,5-diazahexane (8b) was synthesized as described for **7b** from imidazolidine **5b** (3.34 g, 10 mmol), glacial AcOH (17 mL), Ac_2O (10 mL), and $NaNO_2$ (4.5 g). The reaction mixture was poured into cold water and left at 0 °C overnight. The product obtained was filtered off, dried, mixed with Pr^iOH (2 mL) and dichloroethane (2 mL), heated to boiling, and cooled to ~20 °C. The precipitate was filtered off and dried. The yield of **8b** was 0.4 g (10.5%), m.p. 150—154 °C. After repeated recrystallization from Pr^iOH—dichloroethane, m.p. 162—164 °C.

2,5-Dinitroso-1,6-bissuccinimido-2,5-diazahexane (8c) was obtained as described for **7a** from imidazolidine **5c** (1.47 g, 5 mmol), glacial AcOH (15 mL), and $NaNO_2$ (3.52 g). The yield of **8c** was 1.36 g (80%), m.p. 228—230 °C (decomp.). After recrystallization from DMF—DMSO, m.p. 230—231 °C (decomp.).

Table 5. Crystallographic parameters of the compounds studied

Parameter	**7a**	**7b**
Molecular formula	$C_{10}H_9N_3O_3$	$C_8H_9N_5O$
Space group	*Pc*	$P2_1/c$
a/Å	10.829 (2)	10.832 (2)
b/Å	8.206 (2)	8.057 (2)
c/Å	11.705 (2)	10.743 (2)
β/deg	96.29	95.36
V/Å^3	1033.8 (5)	933.5 (4)
Z	4*	4
ρ_{calc}/g cm^{-3}	1.408	1.360
Scan range θ—2θ/deg	3—55	2—56
Number of measured reflections	2147	3090
Number of reflections with $I > 4\sigma$	1693	2944
Weighting scheme, w^{-1}	$\sigma^2(F)+0.0010F^2$	$\sigma^2(F)+0.041F^2$
R	0.068	0.051
R_w	0.079	0.074

* The cell contains two independent molecules.

Synthesis of compound 9. Nitrosative cleavage of amine **3** (1.32 g, 5.5 mmol) using glacial AcOH (13 mL) and $NaNO_2$ (2.5 g) was carried out as described for **7a**. The reaction mixture was poured into 70 mL of cold water, and the product was extracted with CH_2Cl_2. The extract was washed with water and dried with $MgSO_4$. The solvent was removed, and the residue was distilled to give compound **9** (0.67 g, 80%), b.p. 86—88 °C (10 Torr), n_D^{20} 1.4439. IR, ν/cm^{-1}: 2965, 2935, 2900, 2875, 1435, 1390, 1370, 1345 (CH_3, CH_2); 1465, 1070 (N—N=O); 1295, 1200 (C—N).

X-ray diffraction analysis. Single crystals of compounds **7a,b** were stuck to a glass rod with fast-drying epoxy resin and transferred to a diffractometer goniometer. Experimental sets of reflections were collected on CAD-4 (**7a**) and Siemens R3/PC (**7b**) four-circle automated diffractometers (λ(Mo-$K\alpha$), λ = 0.71074 Å, T = 22 °C). The unit cell parameters were determined and refined from 24 equivalent reflections with $2\theta < 24—28°$. Three strong reflections with $0 < \chi < 65°$ were measured as standards after every 100 reflections. Because the intensities of these reflections remained unchanged during data collection, no special corrections were applied. Crystallographic parameters and structure refinements are presented in Table 5.

Structures **7a,b** were solved by the direct methods and refined in the full-matrix anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were located from a difference Fourier synthesis and refined isotropically. All calculations were performed using the SHELXTL PLUS program package (PC version).[20] The atomic coordinates in **7a,b** have been deposited with the Cambridge Crystallographic Database. Selected geometrical parameters of the molecules studied are given in Tables 3 and 4.

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