One-step synthesis of substituted 3,5-dinitropiperidines and 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes from 1,3-dinitropropanes

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1,5-Dinitro-3,7-diazabicyclo[3.3.1]nonane derivatives were synthesized in up to 83% yields by the Mannich reaction of 1,3-dinitropropanes with excess formaldehyde and primary amines. In some cases, for instance, when 2,2-dimethyl-1,3-dinitropropane and benzylamine or monoethanolamine are used, the reaction occurs with low yields or stops at the step of formation of 3,5-dinitropiperidines. The influence of the structure of the starting compounds and reaction conditions on the yields of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes and 3,5-dinitropiperidines was studied.

Key words: 1,3-dinitropropanes, formaldehyde, primary amines, Mannich reaction, 3,5-dinitropiperidines, 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes.

High biological activity (antitumor,[1] antiarrhythmic,[2] and insecticide[3]) of compounds containing the 3,7-diazabicyclo[3.3.1]nonane fragment stimulates the development of new methods for their syntheses, as well as the synthesis of unknown compounds of this type by the Mannich reaction of aliphatic CH acids[4—6] with primary amines and formaldehydes. One-pot methods for straightforward syntheses of these heterocycles by multiple condensation without isolation of intermediate products are of special interest. In the previous report,[7] we described a new convenient method for the one-step synthesis of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes by the fourfold condensation of 1,3-dinitro-2-phenylpropane with formaldehyde and methylamine or monoethanolamine under the Mannich reaction conditions. In this work, we studied the syntheses of a wide scope of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes and the influence of the structure of the starting reagents and reaction conditions on the yield and composition of the products formed by the reactions of 1,3-dinitropropanes with primary amines and formaldehyde.

We used 1,3-dinitropropane (**1a**), 1,3-dinitro-2-phenyl- (**1b**), 2-(4-bromophenyl)-1,3-dinitro- (**1c**), 1,3-dinitro-2-(2,4-dichlorophenyl)- (**1d**), and 2,2-dimethyl-1,3-dinitropropanes (**1e**) as dinitro compounds and methyl- (**2a**), benzyl- (**2b**), monoethanol- (**2c**), and cyclopropylamines (**2d**) as amines.

Experiments were carried out for 4 h at 20 °C with the molar ratio 1,3-dinitropropane : formaldehyde : amine = 1 : 10 : 5. Using the condensation of 1,3-dinitro-2-phenylpropane (**1b**) with methylamine (**2a**) and formaldehyde as an example, we found that chloroform is the best solvent in which the yield of the corresponding 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane **3d** reaches 83% (Scheme 1). The use of more polar solvents decreases considerably the yield of compound **3d** (Table 1).

Scheme 1

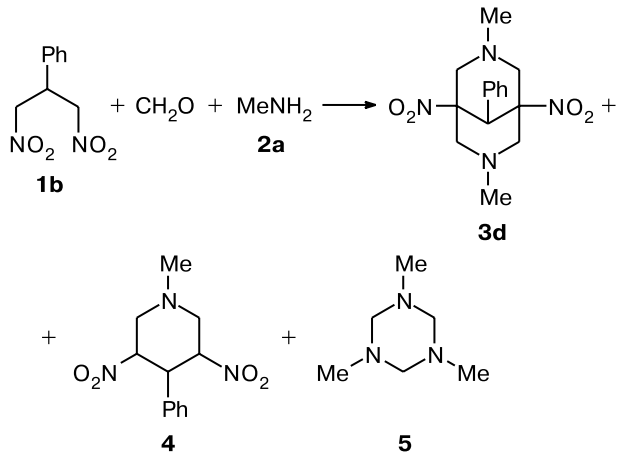

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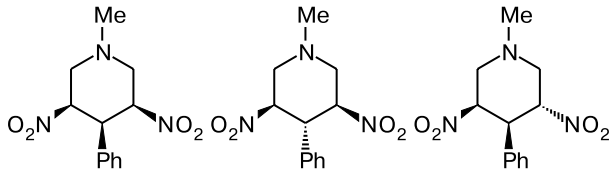
Table 1. Influence of the solvent nature on the composition and yield of the reaction products of 1,3-dinitropropane **1b** with formaldehyde and methylamine (molar ratio **1b** : CH_2O : $MeNH_2$ = 1 : 10 : 5, 4 h, 20 °C)

Solvent	Yield* (%)		
	3d	**4**	**5**
$CHCl_3$	83	3	5
$CHCl_3$—EtOH (5 : 1)	82	4	4
$CHCl_3$—AcOH (1 : 1)	42	34	4
EtOH	20	13	41
DMSO	18	16	41
THF—H_2O (1 : 1)	9	56	4

* Calculated to the isolated product.

In this reaction, monocyclic heterocycles, *viz.*, stereoisomeric 1-methyl-3,5-dinitro-4-phenylpiperidines **4**, **4′**, and **4″** and 1,3,5-trimethylhexahydrotriazine (**5**), are formed along with bicyclic compound **3d**. When a THF—H_2O (1 : 1) mixture is used as a solvent, the overall yield of piperidines **4**, **4′**, and **4″** is 56% and their ratio is ~3 : 1.3 : 1, respectively. It should be mentioned that the reaction medium contains predominantly isomer **4″** after 2 h of reaction in $CHCl_3$.



4 **4′** **4″**

The change in the molar ratio of reagents **1b** : CH_2O : $MeNH_2$ from 1 : 10 : 5 to 1 : 2 : 1 decreases the yield of diazabicyclononane **3d** with a simultaneous increase in the overall yield of 3,5-dinitropiperidines **4** (Table 2).

When the reaction time increases from 1 to 4 h, the yield of diazabicyclononane **3d** increases from 54 to 83%.

Table 2. Influence of the ratio of the starting reagents on the composition and yields of the reaction products of 1,3-dinitropropane **1b** with formaldehyde and methylamine ($CHCl_3$, 4 h, 20 °C)

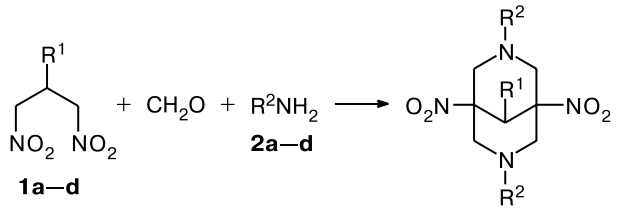
Ratio **1b** : CH_2O : $MeNH_2$	Yield (%)		
	3d	**4**	**5**
1 : 2 : 1	12	55	—*
1 : 4 : 2	42	33	—*
1 : 8 : 4	78	16	—*
1 : 10 : 5	83	3	5
1 : 20 : 10	83	3	10

* Traces.

In this case, the yield of piperidines **4** achieves ~40% after 2 h of the reaction and decreases to ~3% at the end after 4 h. The results obtained indicate that a molecule of diazabicyclononanes is formed through the step of formation of substituted piperidines.

The study of the influence of the nature of the starting reagents on the reaction course revealed that the structure of the amine component is a substantial factor. For example, similarly to 2-phenyldinitropropane **1b**, the condensation of 1,3-dinitropropanes **1a,c,d** with formaldehyde and methylamine under the chosen conditions (ratio 1 : 10 : 5, $CHCl_3$) affords the corresponding 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes **3a,h,i** in rather high yields (64—77%) (Scheme 2). However, on going from methylamine (**2a**) to monoethanolamine (**2c**) or benzylamine (**2b**), their yield decreases remarkably or the reaction ceases at the step of piperidine formation. In the reactions of dinitropropanes **1a,b** with CH_2O and benzylamine (**2b**) and in the reaction of compound **1a** with CH_2O and monoethanolamine (**2c**), the yields of the corresponding diazabicyclononanes **3b,c,f** are only 10—16% (see Scheme 2).

Scheme 2



1a—d **3a—i**

1: R^1 = H (**a**), Ph (**b**), 4-BrC_6H_4 (**c**), 2,4-$Cl_2C_6H_3$ (**d**)
2: R^2 = Me (**a**), $PhCH_2$ (**b**), CH_2CH_2OH (**c**), *cyclo*-C_3H_5 (**d**)

3	R^1	R^2	Yield (%)
a	H	Me	64
b	H	$PhCH_2$	10
c	H	CH_2CH_2OH	16
d	Ph	Me	83
e	Ph	*cyclo*-C_3H_5	60
f	Ph	$PhCH_2$	16
g	Ph	CH_2CH_2OH	75
h	4-BrC_6H_4	Me	77
i	2,4-$Cl_2C_6H_3$	Me	75

The structures of all synthesized compounds were confirmed by the ^1H and ^{13}C NMR spectra. The structures of diazabicyclo[3.3.1]nonanes were interpreted and signals of the H and C atoms of the methylene fragments were assigned, in some cases, using the {C,H} correlation procedure and NOEDIFF experiments. The C(1), C(5), and C(9) atoms are unambiguously determined from the multiplicity and chemical shifts of signals in the ^{13}C NMR spectra. The C(2), C(4), C(6), and C(8) atoms of un-

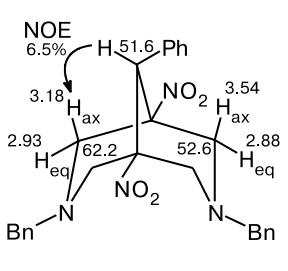
substituted bicyclononanes **3a—c** are chemically equivalent and appear in a region of δ_C 58—61, and the same C atoms of their substituted analogs are pairwise nonequivalent due to the effect of the aryl substituent and appear as signals at δ_C 52—55 and 63—65, the C atoms at the same side with the aryl substituent being the most screened (Table 3). A similar regularity was observed earlier for the same C atoms in the ^{13}C NMR spectrum of 3,7-dibenzyl-9-hydroxy-1,5-bis(methoxycarbonyl)-3,7-diazabicyclo[3.3.1]nonane (δ_C 53.4 and 59.6).[8]

Table 3. ^1H and ^{13}C NMR spectra of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes **3a—i** ($CDCl_3$)

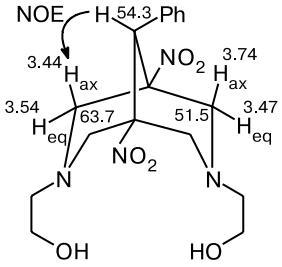
Compound	δ_H (*J*/Hz)						δ_C				
	$H_{ax}(2)$, $H_{ax}(4)$ (d)	$H_{eq}(2)$, $H_{eq}(4)$ (d)	$H_{ax}(6)$, $H_{ax}(8)$ (d)	$H_{eq}(6)$, $H_{eq}(8)$ (d)	H(9) (s)	Other H atoms	C(1), C(5)	C(2), C(4)	C(6), C(8)	C(9)	Other C atoms
3a [a]	2.48 (12.0)	2.28 (12.0)	2.48 (12.0)	2.28 (12.0)	2.18	1.90 (s, 2 Me)	84.8	60.9	60.9	34.9	44.1 (2 Me)
3b	3.00 (11.3)	2.86 (11.3)	3.00 (11.3)	2.86 (11.3)	2.77	3.70 (s, 2 CH_2); 7.25—7.39 (2 Ph)	84.6	58.5	58.5	35.5	60.6 (2 CH_2); 127.7 (p-C_{Ph}); 128.7, 128.9 (o-C_{Ph}, m-C_{Ph}); 136.2 (i-C_{Ph})
3c	3.45 (11.2)	2.88 (11.2)	3.45 (11.2)	2.88 (11.2)	2.68	2.67 (t, NCH_2, J = 5.2); 3.65 (t, OCH_2, J = 5.2); 4.15 (br.s, 2 OH)	83.9	58.1	58.1	38.5	58.3 (NCH_2); 58.5 (OCH_2)
3d	3.45 (12.0)	2.87 (12.0)	3.10 (12.0)	2.87 (12.0)	4.44	2.34, 2.49 (both s, 2 Me); 7.05—7.36 (m, Ph)	88.1	54.7	64.6	51.1	44.1, 44.8 (2 Me); 128.5, 128.8, 130.6, 131.6 (o-C_{Ph}, m-C_{Ph}, i-C_{Ph}, p-C_{Ph})
3e	3.77 (12.1)	3.05 (12.1)	3.40 (11.3)	2.98 (11.3)	4.51	0.44—0.66 (m, 2 CH_2CH_2); 1.86 (m, 2 CH); 7.18—7.40 (m, Ph)	87.4	52.7	62.3	50.8	7.1, 7.3 (CH_2CH_2); 35.6, 36.0 (2 CH); 128.3 (p-C_{Ph}); 128.6 (o-C_{Ph}); 131.3 (m-C_{Ph}); 131.6 (i-C_{Ph})
3f	3.54 (11.1)	2.88 (11.1)	3.18 (12.0)	2.93 (12.0)	4.60	3.70, 3.82 (both s, 2 CH_2); 7.05—7.36 (m, 3 Ph)	88.2	52.6	62.2	51.6	60.6, 61.6 (2 CH_2); 128.7, 128.8, 128.9, 129.3 (o-C_{Ph}, m-C_{Ph}, o-C_{Bn}, m-C_{Bn}, p-C_{Bn}); 131.5 (p-C_{Ph}); 131.6 (i-C_{Ph}); 136.3, 136.4 (i-C_{Bn})
3g	3.74 [b] (12.2, 2.3)	3.47 (12.2)	3.44 [b] (10.8, 2.3)	3.54 (10.8)	4.33 [c]	2.76 (t, N(3)CH_2, J = 5.2); 3.02 (t, N(7)CH_2, J = 5.4); 3.68 (t, OCH_2, J = 5.2); 3.84 (t, OCH_2, J = 5.4); 7.10—7.34 (m, Ph)	87.0	51.5	63.7	54.3	58.0 (N(3)CH_2); 58.1 (N(7)CH_2); 58.3, 58.7 (2 OCH_2); 128.9 (o-C_{Ph}); 129.2 (m-C_{Ph}); 130.8 (i-C_{Ph}); 131.0 (p-C_{Ph})
3h	3.58 (12.1)	2.96 (12.1)	3.18 (10.9)	2.98 (10.9)	4.45	2.45, 2.58 (both s, 2 Me); 7.23—7.42 (m, H arom.)	88.1	54.7	64.8	51.3	44.2, 44.7 (2 Me); 123.4, 130.8, 131.8, 133.3 (p-C_{Ph}, i-C_{Ph}, o-C_{Ph}, m-C_{Ph})
3i	3.65 (12.3)	2.95 (12.3)	3.14 (10.8)	3.05 (10.8)	5.12	2.50, 2.57 (both s, 2 Me); 7.16 (dd, H(5′), J = 8.7, J = 2.3); 7.40 (d, H(3′), J = 2.3); 7.98 (d, H(6′), J = 8.7)	88.1	55.2	65.6	46.9	44.0, 44.5 (2 Me); 127.1 C(5′); 128.9 C(2′); 130.4 C(3′); 132.5 C(6′); 134.9 C(1′); 139.0 C(4′)

[a] The ^1H and ^{13}C NMR spectra correspond to published data.[5]
[b] Dd.
[c] Br.s.

It seems more difficult to assign signals of nonequivalent methylenic protons of the heterocycles, whose positions in the ^{1}H NMR spectra can be affected by a conformational equilibrium in solutions of the corresponding diazabicyclo[3.3.1]nonanes (chair—chair or chair—boat). In particular, the 1D NOEDIFF experiments for compound **3f** showed that the protons with δ 3.54 are localized at the side of the phenyl substituent, and irradiation at the resonance frequency H—C(9) increases the intensity of signals of the downfield protons with δ 3.18 at the C(6) and C(8) atoms. In both cases, this indicates that the axial protons at both the C(2), C(4) and C(6), C(8) atoms appear in a low field compared to the equatorial protons. Similar changes in chemical shifts of the protons and C atoms were observed for compound **3d** with the methyl substituents at the N atoms.



3f

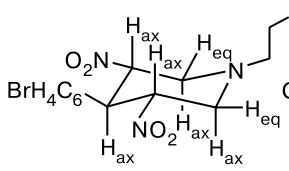


3g

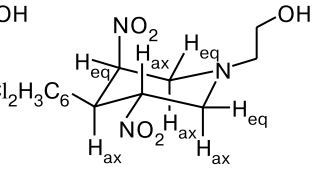
It should be noted that these results are only in part similar to the data for 3,7-dibenzyl-9-hydroxy-1,5-bis(methoxycarbonyl)-3,7-diazabicyclo[3.3.1]nonane.[8] In fact, the axial protons from the side of the substituent have a downfield shift compared to the equatorial protons, whereas an opposite tendency is observed for the protons at the C(6) and C(8) atoms ($\delta_{H_{eq}} - \delta_{H_{ax}} < 0$ for **3d,f** and $\delta_{H_{eq}} - \delta_{H_{ax}} = 0.14$ for the corresponding hydroxy derivative). Among 3,7-diazabicyclo[3.3.1]nonanes synthesized here, only *N*-hydroxyethyl substituted compound **3g** exhibits a similar regularity in the ^{1}H NMR spectrum (see Table 3). The 1D NOEDIFF experiment for this compound exhibited an interaction between the proton at the C(9) atom and the proton giving a signal at δ 3.44. In addition, this is the case of compound **3g** when the ^{1}H NMR spectrum contains the far-range spin-spin coupling (SSC) constant between the H(2), H(8) and H(4), H(6) axial protons, respectively (J = 2.3 Hz), which is likely related to their specific W arrangement. It should be mentioned that the structure of compound **3g** was also confirmed by the encounter synthesis from 2,4-dinitrophenol using a known method[9]; however, its yield was only ~1%.

The chemical shift and SSC constant values were also used for the assignment of signals of protons of isomeric piperidines **4**. For isomers **4** and **4′**, the most probable is a chair-like conformation of the heterocycle with the diequatorially arranged nitro groups (δ_H 4.79 and 4.96) and different *cis*- or *trans*-arrangements of the phenyl substituent. In this case, signals of the protons at the C(4) atom appear as triplets at δ 4.34 and 3.88 with the SSC constants ^3J = 7.5 Hz and ^3J = 11.2 Hz. Taking into account published data[10] for piperidine-2,3,4,5-tetracarboxylates, we can assign them to isomers **4** and **4′**, respectively. In isomer **4″**, the H(3) and H(5) protons at the nitro groups also appear as one signal, whose downfield shift (δ_H 6.10) indicates their *trans*-arrangement and, probably, fast ring inversion. In the ^{13}C NMR spectra of isomers **4** and **4′**, signals of the C atoms containing the nitro groups are observed at δ ~86, while in isomer **4″** they appear at δ 81.2.

The condensation of formaldehyde and monoethanolamine (**2c**) with 2-aryl-1,3-dinitropropanes **1c,d** proceeds poorly and ceases at the step of formation of 3,5-dinitropiperidines. In the case of dinitropropane **1c**, only 4-(4-bromophenyl)-1-(2-hydroxyethyl)-3,5-dinitropiperidine (**6**) was isolated in 13% yield. The chemical shifts and SSC constants of signals from the protons of the heterocycle in the ^{1}H NMR spectrum of this compound are very close to similar signals of compounds **4′** and correspond to the isomer with diequatorial arrangement of both nitro groups. The repeated introduction of dinitropiperidine **6** into the reaction with formaldehyde and methylamine does not furnish the expected unsymmetrically substituted diazabicyclo[3.3.1]nonane, and the starting piperidine **6** returns unchanged.



6

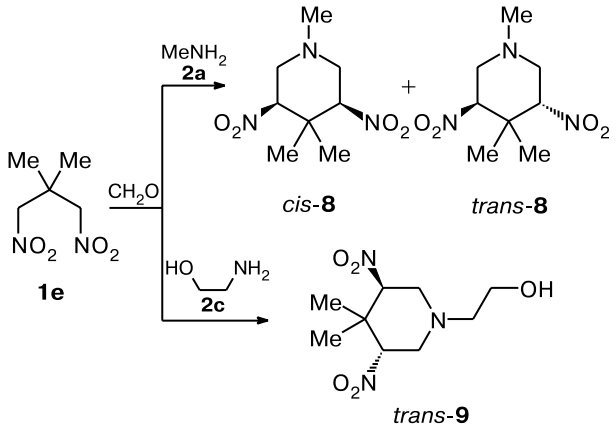


7

Unlike dinitropropane **1c**, the use in this reaction of 2-(2,4-dichlorophenyl)-1,3-dinitropropane (**1d**) containing the Cl atom in the *ortho*-position of the benzene ring leads to 3,5-dinitropiperidine **7** in 49% yield. This compound has the equatorial/axial nitro groups. In the ^{1}H NMR spectrum of compound **7**, all protons of the heterocycle are nonequivalent and have equal integral intensities, whereas the signals of the C(2), C(6) and C(3), C(4) atoms in the ^{13}C NMR spectrum are also pairwise nonequivalent. The spin-spin proton decoupling at the C(4) atom ($^3J_{3_{eq},4_{ax}}$ = 3.0 Hz, $^3J_{4_{ax},5_{ax}}$ = 11.4 Hz) and chemical shifts of the methinic protons at the C(5) (δ 6.00) and C(3) (δ 5.20) atoms indicate their axial and equatorial arrangement. These data along with the absence of doubled signals of the hydroxyethyl substituent indicate that heterocycle **7** in solution has a retarded chair-like conformation with equatorial arrangement of the aryl substituent.

The reaction of 2,2-dimethyl-1,3-dinitropropane (**1e**) with formaldehyde and methylamine (**2a**) or monoethylamine (**2c**) also ceases at the step of formation of the corresponding 3,5-dinitropiperidines **8** and **9** (Scheme 3), and the repeated introduction of the latter into condensation with methylamine and formaldehyde does not provide the expected unsymmetrical 3,7-diazabicyclo[3.3.1]nonane. In this case, 1,4,4-trimethyl-3,5-dinitropiperidine (**8**) is synthesized as a mixture of *trans*- and *cis*-isomers (~1 : 1.5) with an overall yield of 51%, while 1-(2-hydroxyethyl)-4,4-dimethyl-3,5-dinitropiperidine (**9**) was isolated as the single *trans*-isomer (~20% yield).

Scheme 3



In the spectrum of isomer *cis*-**8**, the signal assigned to the protons at the C(3) and C(5) atoms is a doublet of doublets with the SSC constants $^3J_{ax,ax}$ = 11.4 Hz and $^3J_{ax,eq}$ = 4.0 Hz. The methyl substituents at the C(4) atoms are chemically nonequivalent and appear as signals at δ 1.08 and 1.37. Therefore, in this compound both nitro groups are equatorial, and the conformational equilibrium is strongly shifted toward the predomination of the chair-like isomer. In the ^{1}H NMR spectrum of isomer *trans*-**8**, protons at the C(3) and C(5) atoms appear as a triplet with ^3J = 5.4 Hz, and the methyl substituents at the C(4) atom are equivalent and have a chemical shift at δ 1.23, indicating (in the case of *trans*-arranged nitro groups as in piperidine **4″**) an averaged conformational state in a $CDCl_3$ solution at room temperature. Signals of the protons in the ^{1}H NMR spectrum of piperidine **9**, which also has the *trans*-configuration of two nitro groups, appear similarly and, moreover, they are broadened due to the conformational mobility of the heterocycle.

It should be noted that 1,3-dinitro-2-phenylpropane (**1b**) does not react with formaldehyde and 2-amino-2-(hydroxymethyl)-1,3-propanediol or aminotrimethoxymethane (unlike monoethanolamine) and returns unchanged from the reaction mixture.

Thus, we have developed the one-step methods for the synthesis of substituted 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes and the corresponding 3,5-dinitropiperidines by the reaction of 1,3-dinitropropanes with formaldehyde and primary amines. The reaction direction depends on the structure of the starting reagents and reaction conditions.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ using Me_4Si as the internal standard. IR spectra were obtained on a Specord M-80 instrument in thin layer or Nujol. Mass spectra were recorded on an MX-1300 spectrometer with a temperature of the supply cylinder of 100 °C and an ionizing voltage of 12 and 70 eV. GLC analysis was carried out on a Chrom-5 chromatograph with a flame-ionization detector (column 1200×5 mm with 5% SE-30 on Inerton N-AW DMCS (0.125—0.160 mm), helium as carrier gas). TLC analysis was carried out on Silufol chromatographic plates (Merck), and preparative separation was performed by column chromatography on silica gel.

1,3-Dinitropropane (**1a**)[11] and aryl-substituted 1,3-dinitropropanes **1b—d** [12] and 2,2-dimethyl-1,3-dinitropropane (**1e**)[13] were synthesized according to described procedures. The physicochemical constants of compounds **3a** [5] (eluent petroleum ether—$CHCl_3$, 1 : 3), **3d** [7] (eluent $CHCl_3$—Pr^iOH, 7 : 3), **3g** [7] (eluent $CHCl_3$—Pr^iOH, 9 : 1), and **5** [14] (eluent $CHCl_3$—Pr^iOH, 1 : 9) coincided with published data.

Reaction of 1,3-dinitropropanes 1a—d with formaldehyde and amines (general procedure). A mixture of 26% aqueous formaldehyde (2.58 g, 22 mmol) and the corresponding primary amine **2a—d** (11 mmol) were added to a solution of 1,3-dinitropropane **1a—d** (2.2 mmol) in $CHCl_3$ (15 mL) at 0—10 °C, and the resulting mixture was kept for 4 h at 20 °C. The reaction mixture was washed with water (3×5 mL) and dried with Na_2SO_4. After the solvent was removed under reduced pressure, the residue was chromatographed on a column packed with SiO_2. To study the influence of the reaction conditions on the yields of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes and 3,5-dinitropiperidines, we changed the solvent nature and ratio of the starting reagents (see Tables 1 and 2). The ^{1}H and ^{13}C NMR spectra of dinitrodiazabicyclononanes **3a—i** are presented in Table 3.

3,7-Dibenzyl-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (3b). Dinitropropane **1a** (0.29 g), amine **2c** (1.20 g), and formaldehyde (22 mmol) gave 0.09 g (10%) of compound **3b** as an oily liquid, R_f 0.67 (eluent $CHCl_3$—MeOH, 7 : 3). Found (%): C, 63.75; H, 6.05; N, 14.17. $C_{21}H_{24}N_4O_4$. Calculated (%): C, 63.62; H, 6.10; N, 14.14. MS, *m/z*: 396 $[M]^+$. IR, ν/cm^{-1}: 704, 816, 1364 (Ph); 1376, 1544 (NO_2).

3,7-Di(2-hydroxyethyl)-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (3c). Dinitropropane **1a** (0.29 g), amine **2c** (0.67 g), and formaldehyde (22 mmol) gave 0.09 g (16%) of compound **3c** as an oily liquid, R_f 0.65 (eluent $CHCl_3$—MeOH, 7 : 3). Found (%): C, 48.55; H, 7.46; N, 20.67. $C_{11}H_{20}N_4O_4$. Calculated (%): C, 48.53; H, 7.39; N, 20.59. IR, ν/cm^{-1}: 1376, 1544 (NO_2); 3400 (OH). MS, *m/z*: 304 $[M^+]$.

3,7-Dicyclopropyl-1,5-dinitro-9-phenyl-3,7-diazabicyclo[3.3.1]nonane (3e). Dinitropropane **1b** (0.29 g), amine **2d**

(0.63 g), and formaldehyde (22 mmol) gave 0.49 g (60%) of compound **3e** as colorless crystals, m.p. 164—166 °C (from hexane), R_f 0.66 (eluent $CHCl_3$). Found (%): C, 60.86; H, 6.51; N, 14.92. $C_{19}H_{24}N_4O_4$. Calculated (%): C, 61.29; H, 6.48; N, 15.05. MS, *m/z*: 372 $[M]^+$. IR, ν/cm^{-1}: 840, 3020, 3080, 3100 (Ar); 1360, 1555 (NO_2).

3,7-Dibenzyl-1,5-dinitro-9-phenyl-3,7-diazabicyclo[3.3.1]nonane (3f). Dinitropropane **1b** (0.46 g), amine **2b** (1.20 g), and formaldehyde (22 mmol) gave 0.16 g (16%) of compound **3f** as colorless crystals, m.p. 179—180 °C, R_f 0.75 (eluent $CHCl_3$—MeOH, 7 : 3). Found (%): C, 68.75; H, 6.05; N, 11.97. $C_{27}H_{28}N_4O_4$. Calculated (%): C, 68.64; H, 5.97; N, 11.86. MS, *m/z*: 472 $[M]^+$. IR, ν/cm^{-1}: 704, 816, 1364 (Ph); 1376, 1544 (NO_2).

9-(4-Bromophenyl)-3,7-dimethyl-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (3h). Dinitropropane **1c** (0.64 g), amine **2a** (1.40 g), and formaldehyde (22 mmol) gave 0.56 g (64%) of compound **3h** as colorless crystals, m.p. 196—197 °C, R_f 0.80 (eluent $CHCl_3$—MeOH, 7 : 3). Found (%): C, 45.50; H, 4.55; Br, 20.25; N, 13.94. $C_{15}H_{19}BrN_4O_4$. Calculated (%): C, 45.13; H, 4.80; Br, 20.01; N, 14.03. MS, *m/z*: 380 $[M]^+$. IR, ν/cm^{-1}: 680 (Br); 704, 816, 1364 (Ar); 1376, 1544 (NO_2).

3,7-Dimethyl-9-(2,4-dichlorophenyl)-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (3i). Dinitropropane **1d** (0.80 g), amine **2a** (1.40 g), and formaldehyde (22 mmol) gave 0.85 g (77%) of compound **3i** as colorless crystals, m.p. 151—152 °C, R_f 0.77 (eluent $CHCl_3$—MeOH, 7 : 3). Found (%): C, 46.65; H, 4.65; Cl, 18.10; N, 14.57. $C_{15}H_{18}Cl_2N_4O_4$. Calculated (%): C, 46.27; H, 4.66; Cl, 18.22; N, 14.40. MS, *m/z*: 389 $[M]^+$. IR, ν/cm^{-1}: 816, 1348, 3056 (Ar); 1376, 1544 (NO_2).

1-Methyl-3*r*,5*c*-dinitro-4*c*-phenyl- (4), 1-methyl-3*r*,5*c*-dinitro-4*t*-phenyl- (4′), and 1-methyl-3*r*,5*t*-dinitro-4*c*-phenylpiperidines (4″). According to the general procedure, a yellowish viscous liquid, being a mixture of isomeric compounds **4**, **4′**, and **4″** in a ratio of 3 : 1.3 : 1, was obtained from dinitropropane **1b** (0.46 g, 2.2 mmol), a 25% solution of methylamine (**2a**) (1.36 g, 11 mmol), and 26% aqueous formaldehyde (2.58 g, 22 mmol) in a THF—H_2O (1 : 1) mixture. Found (%): C, 54.55; H, 5.46; N, 15.97. $C_{12}H_{15}N_3O_4$. Calculated (%): C, 54.33; H, 5.70; N, 15.84. The isomers were characterized in mixture by NMR spectroscopy, and their quantitative composition was determined from the ratio of surface areas of signals from the methinic protons at the C(4) atom. For all isomers, signals of the protons of the phenyl substituent in the ^{1}H NMR spectrum appear at δ 7.21—7.56. In the ^{13}C NMR spectrum, signals of proton-containing C atoms are observed at δ 127.4—130.0, while the signals of quaternary C atoms lie at δ 133.1, 133.3, and 134.0.

Isomer 4. ^{1}H NMR, δ: 2.42 (s, 3 H, MeN); 2.56 (t, 2 H, $H_{ax}(2)$, $H_{ax}(6)$, $^2J = {}^3J_{ax,ax}$ = 10.4 Hz); 3.60 (dd, 2 H, $H_{eq}(2)$, $H_{eq}(6)$, ^2J = 10.4 Hz, $^3J_{ax,eq}$ = 3.1 Hz); 4.34 (t, 1 H, H(4), ^3J = 7.5 Hz); 4.79 (ddd, 2 H, H(3), H(5), $^3J_{ax,eq}$ = 7.5 Hz, $^3J_{ax,ax}$ = 10.4 Hz, $^3J_{ax,eq}$ = 3.1 Hz). ^{13}C NMR, δ: 45.3 (MeN); 45.9 (C(4)); 58.0 (C(2), C(6)); 86.4 (C(3), C(5)).

Isomer 4′. ^{1}H NMR, δ: 2.50 (s, 3 H, MeN); 2.72 (t, 2 H, $H_{ax}(2)$, $H_{ax}(6)$, $^2J = {}^3J_{ax,ax}$ = 10.8 Hz); 3.45 (dd, 2 H, $H_{eq}(2)$, $H_{eq}(6)$, ^2J = 10.8 Hz, $^3J_{ax,eq}$ = 4.1 Hz); 4.96 (ddd, 2 H, H(3), H(5), $^3J_{ax,ax}$ = 11.2 Hz, $^3J_{ax,ax}$ = 10.8 Hz, $^3J_{ax,eq}$ = 4.1 Hz); 3.88 (t, 1 H, H(4), ^3J = 11.2 Hz). ^{13}C NMR, δ: 45.3 (MeN); 48.8 (C(4)); 58.8 (C(2), C(6)); 85.8 (C(3), C(5)).

Isomer 4″. ^{1}H NMR, δ: 2.47 (s, 3 H, MeN); 2.79 (dd, 2 H, $H_{ax}(2)$, $H_{ax}(6)$, $^2J = {}^3J_{ax,ax}$ = 11.5 Hz); 3.70 (dd, 2 H, $H_{eq}(2)$, $H_{eq}(6)$, ^2J = 11.5 Hz, $^3J_{ax,eq}$ = 4.5 Hz); 5.05 (t, 1 H, H(4), ^3J = 10.1 Hz); 6.10 (ddd, 2 H, H(3), H(5), ^3J = 4.5 Hz, ^3J = 10.1 Hz, ^3J = 11.5 Hz). ^{13}C NMR, δ: 45.3 (MeN); 45.9 (C(4)); 58.2 (C(2), C(6)); 81.2 (C(3), C(5)).

4*t*-(4-Bromophenyl)-1-(2-hydroxyethyl)-3*r*,5*c*-dinitropiperidine (6). Dinitropropane **1c** (0.64 g), amine **2b** (0.67 g), and formaldehyde (22 mmol) gave 0.11 g (13%) of compound **6** as colorless crystals, m.p. 139—140 °C (from hexane), R_f 0.50 (eluent $CHCl_3$—Pr^iOH, 7 : 3). Found (%): C, 41.85; H, 4.28; Br, 21.45; N, 11.29. $C_{13}H_{16}BrN_3O_5$. Calculated (%): C, 41.73; H, 4.31; Br, 21.35; N, 11.23. MS, *m/z*: 374 $[M]^+$. IR, ν/cm^{-1}: 680, 816, 1348, 1376, 1544, 3600. ^{1}H NMR, δ: 2.81 (t, 2 H, CH_2N, ^3J = 4.4 Hz); 2.86 (dd, 2 H, $H_{ax}(2)$, $H_{ax}(6)$, ^2J = 11.1 Hz, $^3J_{ax,ax}$ = 11.5 Hz); 3.58 (dd, 2 H, $H_{eq}(2)$, $H_{eq}(6)$, ^2J = 11.1 Hz, $^3J_{ax,eq}$ = 4.2 Hz); 3.75 (t, 2 H, CH_2O, ^3J = 4.4 Hz); 3.90 (t, 1 H, H(4), $^3J_{ax,ax}$ = 11.5 Hz); 4.91 (td, 2 H, H(3), H(5), $^3J_{ax,ax}$ = 11.5 Hz, $^3J_{ax,ax}$ = 11.1 Hz, $^3J_{ax,eq}$ = 4.2 Hz); 7.13 (d, 2 H, *o*-H arom., *J* = 8.4 Hz); 7.50 (d, 2 H, *m*-H arom., *J* = 8.4 Hz). ^{13}C NMR, δ: 48.7 (C(4)); 56.2 (C(2), C(6)); 58.7 (CH_2N); 58.9 (CH_2O); 85.6 (C(3), C(5)); 123.5 (*p*-C arom.); 130.9 (*o*-C arom.); 132.4 (*i*-C arom.); 132.7 (*m*-C arom.).

1-(2-Hydroxyethyl)-3*r*,5*t*-dinitro-4*c*-(2,4-dichlorophenyl)piperidine (7). Dinitropropane **1d** (0.80 g), amine **2b** (0.67 g), and formaldehyde (22 mmol) gave 0.49 g (49%) of compound **7** as colorless crystals, m.p. 108—109 °C (from hexane), R_f 0.51 (eluent $CHCl_3$—Pr^iOH, 7 : 3). Found (%): C, 42.69; H, 4.10; Cl, 19.55; N, 11.59. $C_{13}H_{15}Cl_2N_3O_5$. Calculated (%): C, 42.87; H, 4.15; Cl, 19.47; N, 11.54. MS, *m/z*: 364 $[M]^+$. IR, ν/cm^{-1}: 816, 1348, 3056, 1376, 1544, 3600. ^{1}H NMR, δ: 2.75 (t, 2 H, H_2CN, ^3J = 5.8 Hz); 2.82 (t, 1 H, $H_{ax}(6)$, $^2J = {}^3J_{ax,ax}$ = 11.4 Hz); 3.00 (dd, 1 H, $H_{ax}(2)$, ^2J = 11.5 Hz, $^3J_{ax,eq}$ = 2.7 Hz); 3.62 (dd, 1 H, $H_{eq}(6)$, ^2J = 11.4 Hz, $^3J_{ax,eq}$ = 3.9 Hz); 3.65 (t, 2 H, H_2CO, ^3J = 5.8 Hz); 3.75 (dd, 1 H, $H_{ax}(4)$, $^3J_{ax,ax}$ = 11.4 Hz, $^3J_{ax,eq}$ = 3.0 Hz); 4.18 (dd, 1 H, $H_{eq}(2)$, ^2J = 11.5 Hz, $^3J_{eq,eq}$ = 3.9 Hz); 5.20 (ddd, 1 H, $H_{eq}(3)$, $^3J_{eq,eq}$ = 3.9 Hz, $^3J_{ax,eq}$ = 2.7 Hz, $^3J_{ax,eq}$ = 3.0 Hz); 6.00 (td, 1 H, $H_{ax}(5)$, $^3J_{ax,ax}$ = 11.4 Hz, $^3J_{ax,eq}$ = 3.9 Hz); 7.27—7.30, 7.39—7.45 (m, 3 H, H arom.). ^{13}C NMR, δ: 42.7 (C(4)); 56.2 (C(6)); 56.9 (C(2)); 58.3 (CH_2N); 58.8 (CH_2OH); 80.7 (C(5)); 83.3 (C(3)); 128.1 (C arom.); 129.5 (C arom.); 130.3 (C arom.); 129.9 (C arom.); 134.8 (C arom.); 135.5 (C arom.).

1,4,4-Trimethyl-*trans*- and 1,4,4-trimethyl-*cis*-3,5-dinitropiperidines (8). Dinitropropane **1e** (0.36 g), amine **2a** (1.40 g), and formaldehyde (22 mmol) gave 0.24 g (51%) of isomeric piperidines **8** (*trans* : *cis* ≈ 1 : 1.5) as colorless crystals, m.p. 55—56 °C (from hexane), R_f 0.68 (eluent $CHCl_3$). Found (%): C, 44.38; H, 7.00; N, 19.24. $C_8H_{15}N_3O_4$. Calculated (%): C, 44.23; H, 6.96; N, 19.34. MS, *m/z*: 217 $[M]^+$. IR, ν/cm^{-1}: 1184, 1200 (Me); 1376, 1552 (NO_2). Isomer *cis*-**8**. ^{1}H NMR, δ: 1.08, 1.37 (s, 6 H, 2 Me); 2.42 (s, 3 H, MeN); 2.84 (t, 2 H, $H_{ax}(2)$, $H_{ax}(6)$, $^2J = {}^3J_{ax,ax}$ = 11.4 Hz); 3.30 (dd, 2 H, $H_{eq}(2)$, $H_{eq}(6)$, ^2J = 11.4 Hz, $^3J_{ax,eq}$ = 4.0 Hz); 4.50 (dd, 2 H, $H_{ax}(3)$, $H_{ax}(5)$, $^3J_{ax,ax}$ = 11.4 Hz, $^3J_{ax,eq}$ = 4.0 Hz). ^{13}C NMR, δ: 14.5, 25.4 ($Me_2C(4)$); 35.0 (C(4)); 45.4 (MeN); 53.0 (C(2), C(6)); 88.7 (C(3), C(5)). Isomer *trans*-**8**. ^{1}H NMR, δ: 1.23 (s, 6 H, $Me_2C(4)$); 2.36 (s, 3 H, MeN); 2.95 (d, 4 H, $H_2C(2)$, $H_2C(6)$, ^3J = 5.0 Hz); 4.99 (t, 2 H, H(3), H(5), ^3J = 5.0 Hz). ^{13}C NMR, δ: 22.4 ($Me_2C(4)$); 35.1 (C(4)); 45.4 (MeN); 53.5 (C(2), C(6)); 87.6 (C(3), C(5)).

1-(2-Hydroxyethyl)-4,4-dimethyl-*trans*-3,5-dinitropiperidine (9). Dinitropropane **1e** (0.36 g), amine **2b** (0.67 g), and formal-

dehyde (22 mmol) gave compound **9** (0.11 g, 20%) as colorless crystals, m.p. 81—82 °C (from hexane), R_f 0.47 (eluent $CHCl_3$—Pr^iOH, 7 : 3). Found (%): C, 43.85; H, 6.99; N, 17.37. $C_9H_{17}N_3O_5$. Calculated (%): C, 43.72; H, 6.93; N, 17.00. MS, *m/z*: 247 $[M]^+$. IR, ν/cm^{-1}: 1192, 1204, 1376, 1544, 3600. ^{1}H NMR, δ: 1.22 (s, 6 H, 2 Me); 2.44 (br.s, 1 H, OH); 2.65 (m, 2 H, H_2CN); 3.08 (d, 4 H, $H_2C(2)$, $H_2C(6)$, ^3J = 5.1 Hz); 3.57 (br.s, 2 H, H_2CO); 4.94 (t, 2 H, H(3), H(5), ^3J = 5.1 Hz). ^{13}C NMR, δ: 22.2 (2 Me); 36.2 (C(4)); 51.1 (CH_2N); 58.1 (C(2), C(6)); 58.2 (CH_2O); 88.2 (C(3), C(5)).

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