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3-Azabicyclo[3.3.1]nonane Derivatives: III.* Synthesis of 3-Substituted 9-Acetonyl-1,5-dinitro-3-azabicyclo[3.3.1]-non-6-en-8-ones by Mannich Condensation of the Janovsky σ-Adduct of 2,4-Dinitrophenol with Acetonide Ion

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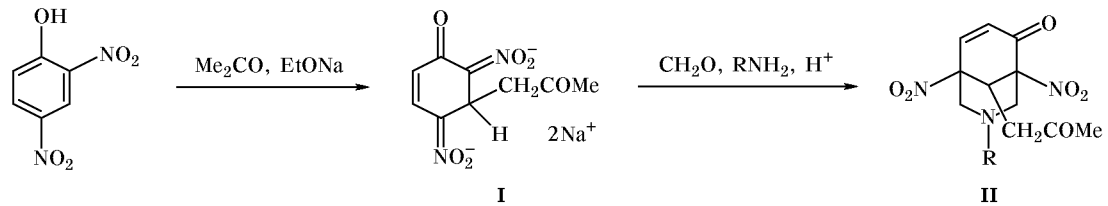
Abstract—A number of 9-acetonyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-one derivatives were synthesized by Mannich condensation of 3-acetonyl-2,4-bis(*aci*-nitro)cyclohex-5-en-1-one disodium salt with formaldehyde and primary amines.

Heteroanalogs of bicyclo[3.3.1]nonanes attract interest primarily as biologically active substances [2] and also as convenient models for conformational analysis [3]. In continuation of our studies on 3-azabicyclo[3.3.1]nonane derivatives [1, 4] we have examined the condensation of 5-acetonyl-4,6-bis(*aci*-nitro)-2-cyclohexenone disodium salt (**I**) with formaldehyde and primary amines (Scheme 1). Severin and Temme [5] described the synthesis of compound **IIa** by this scheme which attracted our attention due to the possibility of introducing acetonyl group into position *9* of the bicyclononane system. The acetonyl group is very promising from the viewpoint of further finctionalization. An obvious advantage of the developed procedure is the possibility for variation of the amine component in the second stage, which opens the way to a series of 3-substituted azabicyclo[3.3.1]-nonanes. The present communication reports on the results of our study of the Mannich condensation of salt **I** with a number of primary amines.

5-Acetonyl-4,6-bis(*aci*-nitro)-2-cyclohexenone disodium salt (**I**) was synthesized according to the procedure described in [6], by reaction of sodium ethoxide with 2,4-dinitrophenol in acetone. The structure of salt **I** follows from its ^{1}H NMR spectrum in DMSO-d_6 in which signals from the olefinic 2-H and 3-H protons appear as doublets (^3J = 9.5 Hz) at 7.28 and 5.08 ppm, respectively. The 5-H proton and 5-CH_2 methylene protons give a triplet and a doublet at 4.91 and 2.44 ppm, respectively (^3J = 5.6 Hz).

Scheme 1.



I **II**

R = CH_3 (**a**), C_2H_5 (**b**), C_4H_9 (**c**), $CH_2C_6H_5$ (**d**), $(CH_2)_2Br$ (**e**), $(CH_2)_2OH$ (**f**), CH_2COOH (**g**), $(CH_2)_2COOH$ (**h**).

* For communication II, see [1].

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Table 1. Yields, melting points, R_f values, and elemental analyses of 3-substituted 9-acetonyl-1,5-dinitro-3-azabicyclo-[3.3.1]non-6-en-8-ones **IIa**–**IIi**

Comp. no.	Yield, %	mp, °C	R_f	Found, %			Formula	Calculated, %		
				C	H	N (Br)		C	H	N (Br)
IIa	64	177–178 (decomp.)	0.57	48.37 48.21	5.07 5.05	14.20 13.87 14.22	$C_{12}H_{15}N_3O_6$	48.48	5.08	14.14
IIb	30	144–146 (decomp.)	0.63	50.76 50.89	5.63 5.54	13.12 13.27	$C_{13}H_{17}N_3O_6$	50.16	5.50	13.50
IIc	39	103–105	0.73	53.05 53.28	6.22 6.23	12.09 12.26	$C_{15}H_{21}N_3O_6$	53.09	6.23	12.38
IId	28	169–171 (decomp.)	0.68	58.16 58.18	5.30 5.42	10.90 10.76	$C_{18}H_{19}N_3O_6$	57.90	5.09	11.25
IIe	26	118–120	0.65	40.23 40.03	4.23 4.17	10.70 (18.73) 11.12 (18.66)	$C_{13}H_{16}BrN_3O_6$	40.02	4.13	10.77 (20.51)
IIf	32	127–129 (decomp.)	0.27	47.71 48.02	5.37 5.08	13.16 13.06	$C_{13}H_{17}N_3O_7$	47.7	5.23	12.83
IIg	38	172–174 (decomp.)	0.69	45.68 45.44	4.42 4.40	12.27 11.99	$C_{13}H_{15}N_3O_8$	45.75	4.43	12.31
IIh	37	181–183 (decomp.)	0.50	47.58 47.78	4.91 5.05	11.70 11.98	$C_{14}H_{17}N_3O_8$	47.30	4.82	11.82
IIi	8	184–186 (decomp.)	0.58							

The methyl group signal is a singlet at δ 2.14 ppm. The IR spectrum of the 2,4-dinitrophenol adduct with acetonide ion contains strong absorption bands from the *aci*-nitro groups at 1476 cm^{-1} ($\nu_{as}NO_2$) and 1250, 1279, and 1322 cm^{-1} (ν_sNO_2) and a doublet peak from the carbonyl group at 1689/1701 cm^{-1}.

Salt **I** was then brought into reaction with formaldehyde and primary amines. As a result, a number of 3-substituted 9-acetonyl-1,5-dinitro-3-azabicyclo-[3.3.1]non-6-en-8-one derivatives **II** were obtained. The structure of product **II** was proved by the IR and ^{1}H NMR spectra and elemental analyses (Tables 1–3). In the IR spectra of Mannich bases **II** (Table 2) we observed absorption bands in the regions 1320–1380 and 1540–1555 cm^{-1}, which belong to symmetric and antisymmetric stretching vibrations of the nitro groups, and a double band at 1690–1720 cm^{-1} due to carbonyl stretching vibrations.

The ^{1}H NMR data (Table 3, Fig. 1) are consistent with the proposed structures; they suggest *chair* conformation of the piperidine fragment in **II**, in keeping with the results of X-ray diffraction study of analogous 3-azabicyclo[3.3.1]nonane derivatives [1, 4, 7] and molecular-mechanics simulation of the structure of molecule **IIa** (Fig. 2). The downfield region of the ^{1}H NMR spectra (δ 7.5–7.6 ppm) contains the 8-H proton signal as a doublet of doublets due to coupling with 7-H (J = 10.6 Hz) and 9-H (J = 2.5 Hz). The 7-H signal is a doublet in the region 6.4–6.6 ppm. The narrow range of chemical shifts of the olefinic protons indicates that in all compounds **II** the substituent on the nitrogen atom is oriented *exo* with respect to the double bond plane. The acetonyl residue occupies axial position in the piperidine ring, and the carbonyl group is coplanar to the plane formed by the C^1, C^2, C^4, and C^5 atoms. The latter conclusion follows from the fact that the α- and β-methylene protons are nonequivalent owing to their asymmetric arangement relative to the equatorial plane. Signals from these protons are split into doublets due to coupling with each other (J = 18.7 Hz) and are additionally split into doublets of doublets

Table 2. IR spectra of 3-substituted 9-acetonyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-ones **IIa**–**IIi**, cm^{-1}

Compound no.	$\nu_{as}NO_2$	$\nu_s NO_2$	νCH_{aliph}	δCH_{aliph}	$\nu C=C$	$\nu C=O$	Other bands
IIa	1552	1356	2828, 2871,	1419	1615	1701	
			2908, 2936,	1452		1695	
		1373	2961, 3069	1467		1717	
IIb			2845, 2875,	1424		1699	
	1539	1339	2900, 2915,	1457	1624		
	1550	1376	2938, 2972,	1472		1717	
			3070				
IIc		1335	2827, 2869,	1422		1696	
	1546	1350	2933, 2957,	1457	1619		
		1369	3078	1467		1720	
IId	1545	1320	–	–	1605	1708	
						1699	
IIe	1539	1332	2830, 2930,	1419		1716	
		1340	2950, 3065	1450	1616		
	1550	1350		1463		1700	
IIf		1333	2790, 2880,	1422		1690	
	1548	1352	2926, 2960,	1452	1615		3234 (νOH)
		1374	3074	1465		1711	
IIg		1326	2880, 2910,	1415		1700	
	1548	1348	2960, 3070		1605	1710	3000–2500 (νOH)
		1380		1470		1740	
IIh		1325	2843	1424			
	1529	1345	2940		1617	1702	
		1373	3067	1463			

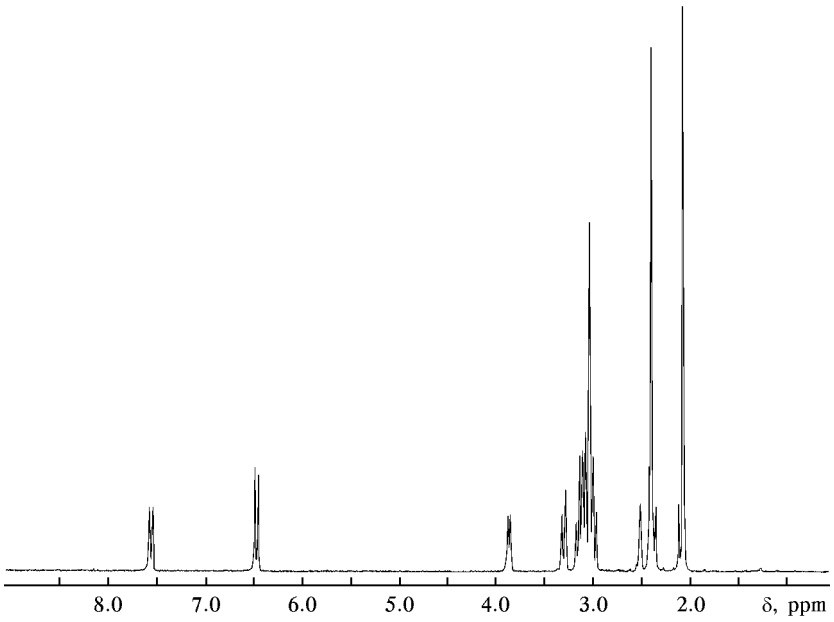


Fig. 1. ^1H NMR spectrum of 9-acetonyl-3-methyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-one (**IIa**).

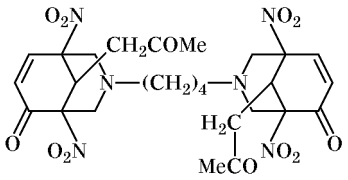
Table 3. ^{1}H NMR spectra of 3-substituted 9-acetonyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-ones **IIa**–**IIh**

Compound no.	Chemical shifts δ, ppm (coupling constants *J*, Hz)						
	6-H	7-H	9-H	2-H$_{eq}$	2-H$_{ax}$	4-H$_{eq}$	4-H$_{ax}$
IIa	7.55 d.d (10.59, 2.49)	6.47 d (10.59)	3.85 d.d.d (8.09, 2.49, 1.86)	3.29 d (10.59)	3.12 d (10.59)	3.08 d (11.22)	2.98 d (11.22)
IIb	7.54 d.d (10.59, 2.49)	6.43 d (10.59)	3.86 d.d.d (8.09, 2.49, 1.89)	3.38 d (10.59)	3.13 d (10.59)	3.13 d (10.59)	3.03 d (10.59)
IIc	7.54 d.d (10.59, 2.49)	6.46 d (10.59)	3.86 d.d.d (8.09, 2.49, 1.80)	3.33 d (10.59)	3.12 d (10.59)	3.10 d (11.21)	3.02 d (11.21)
IId	7.56 d.d (10.58, 2.49)	6.56 d (10.58)	3.89 d.d.d (8.10, 2.49, 1.86)	3.33 d (10.59)	3.17 d (10.59)	3.09 d (11.22)	3.13 d (11.22)
IIe	7.53 d.d (10.59, 2.49)	6.47 d (10.59)	3.89 d.d.d (8.10, 2.49, 1.86)	3.44 d (10.59)	3.38 d (10.59)	3.28 d (11.22)	3.21 d (11.21)
IIf	7.53 d.d (10.59, 2.49)	6.46 d (10.59)	3.84 d.d.d (8.10, 2.49, 1.86)	3.44 d (10.59)	3.34 d (10.59)	3.25 d (11.21)	3.18 d (11.21)
IIg	7.55 d.d (10.58, 2.49)	6.48 d (10.58)	3.82 d.d.d (8.10, 2.49, 1.86)	3.57 d (10.59)	3.47 d (10.59)	3.50 d (11.21)	3.19 d (11.21)
IIh	7.50 d.d (10.59, 2.49)	6.43 d (10.59)	3.86 d.d.d (8.10, 2.49, 1.86)	3.36 d (10.59)	3.25 d (10.59)	3.12 d (11.21)	3.16 d (11.21)

Compound no.	Chemical shifts δ, ppm (coupling constants *J*, Hz)			
	α-H	β-H	γ-H	R
IIa	3.11 d.d (18.68, 8.09)	2.37 d.d (18.68, 1.86)	2.05 s	2.38 s (CH_3)
IIb	3.11 d.d (19.30, 8.09)	2.40 d.d (19.30, 1.89)	2.05 s	2.62 q (7.22, C**H**$_2$CH$_3$), 0.98 t (7.22, CH$_2$C**H**$_3$)
IIc	3.07 d.d (19.31, 8.09)	2.40 d.d (19.31, 1.80)	2.05 s	2.53 t (6.85, C**H**$_2$CH$_2$CH$_2$CH$_3$,), 1.35 q (6.85, CH$_2$C**H**$_2$CH$_2$CH$_3$), 1.19 sext (7.48, CH$_2$CH$_2$C**H**$_2$CH$_3$), 0.85 t (7.48, CH$_2$CH$_2$CH$_2$C**H**$_3$)
IId	3.12 d.d (19.30, 8.10)	2.39 d.d (19.30, 1.86)	2.05 s	7.22–7.31 m (3H, *m*-H, *p*-H), 7.14 m (2H, *o*-H), 3.75 s (CH_2)
IIe	3.11 d.d (18.68, 8.10)	2.36 d.d (18.68, 1.86)	2.05 s	3.42 t (6.85, CH$_2$C**H**$_2$Br),2.99 t (6.85, C**H**$_2$CH$_2$Br)
IIf	3.10 d.d (18.68, 8.10)	2.35 d.d (18.68, 1.86)	2.05 s	4.34 br.s (OH), 3.46 br.s (CH$_2$C**H**$_2$OH), 2.67 t (5.60, C**H**$_2$CH$_2$OH)
IIg	3.12 d.d (18.68, 8.10)	2.37 d.d (18.68, 1.86)	2.05 s	11.95 br.s (COOH), 3.44 d and 3.58 d (CH$_2$COOH, *J* = 17.44)
IIh	3.09 d.d (19.30, 8.10)	2.35 d.d (19.30, 1.86)	2.04 s	11.94 br.s (COOH), 2.83 t (6.85, C**H**$_2$CH$_2$COOH), 3.00 t (6.85, CH$_2$C**H**$_2$COOH)

due to coupling with 9-H ($J_{9\alpha}$ = 8.1 Hz, $J_{9\beta}$ = 1.9 Hz). Both nitro groups occupy equatorial positions but form different angles with the equatorial plane. The oxygen atom in the 1-NO_2 group appears as close as possible to the 2-H_{eq} proton, whose signal is displaced downfield. The oxygen atom in the 5-NO_2 group is located at a long distance from 4-H_{eq}, for the ONO plane is turned apart due to repulsion between lone electron pairs on the carbonyl and nitro group oxygen atoms. Therefore, the equatorial and axial positions at C^2 and C^4 become nonequivalent: the doublet signals from 2-H_{eq} and 2-H_{ax} ($J_{ax,eq}$ = 10.6 Hz) are located in a weaker field than those from 4-H_{eq} and 4-H_{ax} ($J_{ax,eq}$ = 10.6–11.2 Hz). The substituent on the nitrogen atom has no appreciable effect on the chemical shifts of piperidine ring protons. An exception is compound **IIg** in which oxygen atoms of the carboxy group are located in front of C^2 and C^4. The result is that the corresponding proton signals shift downfield. Also, methylene protons of the $N-CH_2COOH$ group are nonequivalent due to asymmetric arrangement with respect to the C^2NC^4 plane: their signals are split into doublets ^2J = 17.4 Hz.

Following the above procedure and using 1,4-diaminobutane as amine component, we obtained double condensation product **IIi**.



IIi

Thus, the Mannich condensation of 5-acetonyl-4,6-bis(*aci*-nitro)-2-cyclohexenone provides a synthetic route to polyfunctional 3-azabicyclo[3.3.1]nonene derivatives.

EXPERIMENTAL

The IR spectra of crystalline products were obtained on a Specord 75IR spectrophotometer. The ^1H NMR spectra were recorded on a Bruker AC-300 instrument (300.13 MHz) in CCl_4. Silufol UV-254 plates were used for thin-layer chromatography; eluent acetone–toluene–hexane (1 : 4 : 1), detection under UV irradiation. The melting points were determined on a Koefler heating device (Boetius).

3-Substituted 9-acetonyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-ones IIa–IIh (*general procedure***).** Appropriate amine hydrochloride or the corresponding free base, 10 mmol, was dissolved in 10 ml of water. The solution was cooled with ice, and 5 ml of 30% formaldehyde solution (52 mmol) was added. 5-acetonyl-4,6-bis(*aci*-nitro)-2-cyclohexenone disodium salt was dissolved in the resulting mixture, and 10 ml of 50% acetic acid was added. After several minutes, the precipitate was extracted into dichloroethane. The organic phase was repeatedly washed with water, dried over calcium chloride, and evaporated under reduced pressure. The residue was subjected to column chromatography on ASKG silica gel using toluene (compounds **IIa**–**IIe** and **IIi**), toluene–acetone (10 : 1, by volume; compound **IIf**), or toluene–acetone (2 : 1; **IIg**, **IIh**) as eluent. Compounds **IIa** and **IIc** were precipitated from the toluene solution with hexane. Compounds **IIf**–**IIi** were dissolved in toluene on heating, and the solution was treated with charcoal, filtered, and evaporated. Compounds **IIb** and **IIe** were precipitated from acetone (5 ml) with ethanol. Product **IId** was precipitated from acetone (5 ml) with water.

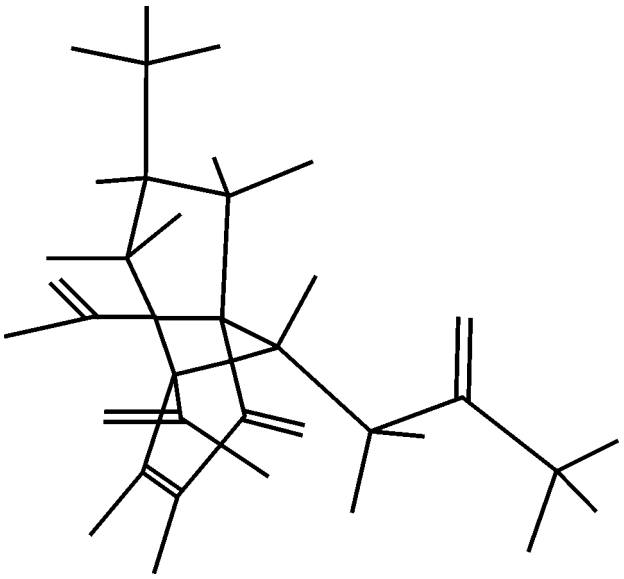


Fig. 2. Structure of 9-acetonyl-3-methyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-one (**IIa**) according to the MM2 calculations.

1,4-Bis(9-acetonyl-1,5-dinitro-8-oxo-3-azabicyclo[3.3.1]non-6-en-3-yl)butane (IIi) was obtained in a similar way from 5 mmol of 1,4-diaminobutane and 5 ml of 30% aqueous formaldehyde (52 mmol). After chromatographic treatment, the residue was dissolved in toluene on heating, and the solution was treated with charcoal, filtered, and evaporated under reduced pressure.

The elemental analyses, melting points, and R_f values of compounds **IIa**–**IIi** are given in Table 1, and their IR and ^{1}H NMR data are presented in Tables 2 and 3.

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