Russian Journal of Organic Chemistry, Vol. 39, No. 11, 2003, pp. 1593–1602. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 11, 2003, pp. 1663–1672.

Aminomethylation by Formaldehyde and Primary Amines of Anionic σ-Adduct Obtained from 2,4-Dinitrophenol and Acetophenone Carbanion

I. V. Shakhkel'dyan[1], O. V. Leonova[1], Yu. M. Atroshchenko[1], O. I. Boikova[1], O. Ya. Borbulevych[2], G. V. Grintselev-Knyazev[2], I. E. Yakunina[1], A. N. Shchukin[1], E. N. Alifanova[1], and V. A. Subbotin[1]

[1]*L. N. Tolstoi Tula State Pedagogical University, Tula, 300026 Russia*
[2]*Nesmeyanov Institute of Organoelemental Compounds, Russian Academy of Sciences, Moscow, 119991 Russia*

Received March 6, 2003

Abstract—By condensation of 2,4-bis(aci-nitro)-3-(2-phenyl-2-oxoethyl)cyclohex-5-en-1-one with formaldehyde and primary amines a series of N-substituted 9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo-[3.3.1]non-7-en-6-ones was synthesized. With the use of X-ray analysis the cyclohexenone fragment in the 3-(2-bromoethyl)-1,5-dinitro-9-(2-phenyl-2-oxoethyl)-3-azabicyclo[3.3.1]non-7-en-6-ones was established to exist in *sofa* conformation, and the nitrogen-containing ring to have the *chair* conformation with equatorial orientation of substituents in *3* and *9* positions. The regio- and stereoselectivity of the reaction under study was interpreted relying on the quantum-chemical calculations by AM1 and PM3 procedures.

Nitroarenes attract recently progressively growing attention as initial compounds for preparation of heterocyclic systems, e.g., indoles, quinolines, benzimidazoles, benzofuroxanes etc. which are widely applied as pharmaceuticals, plant protecting agents, growth stimulant etc. [1, 2]. This field of development is due to the progress in the new methods of nitroarenes functionalization with the use of vicarious nucleophilic hydrogen substitution VNS [3], oxidative nucleophilic hydrogen substitution ONS [4], kine- and telesubstitution [5], radical nucleophilic substitution $S_{RN}1$, $S_{RN}2$ [6], photosubstitution [7], substitution with ring opening and ring closure S_N*(ANRORC)* [8] etc. Therewith the choice of nitro compounds for heterocyclization was significantly extended. The key stage of the above functionalization procedures is the primary addition of a nucleophile to an electron-deficient aromatic ring providing anionic adducts of quinoid type which further undergo aromatization by elimination of a leaving group.

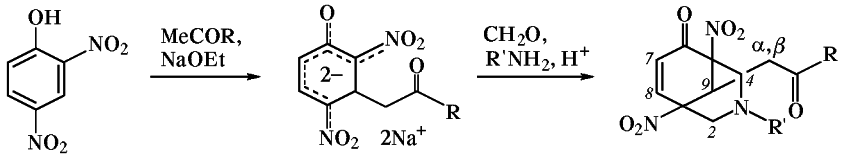
In this connection our attention was drawn to the report [9] on a two-stage synthesis of 3-methyl-9-(2-oxopropyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-7-en-6-one (**II**) by Mannich reaction with formaldehyde and methylamine of an anionic adduct of 2,4-dinitrophenol (I) obtained previously [10] at treatment with a base of the nitro compound in acetone solution (Scheme 1). Note that the 3-azabicyclo[3.3.1]nonane fragment is contained in the structure of many naturally occurring alkaloids [11], and also among synthetic compounds of this class are present biologically active substances promising for treatment of cardiovascular, gastroenteric, and mental diseases [12, 13].

Unlike the above cited procedures this method of nitroarene functionalization does not require performing aromatization of the anionic adduct but on the contrary provides a possibility of aromatic system transformation into saturated azabicyclic one under mild conditions. The number of nitro derivatives of 3-azabicyclo[3.3.1]nonane prepared from 2,4-dinitrophenol and acetone was considerably increased by involving into the Mannich condensation various primary amines [14]. In continuation of this research we report here on the study of 3-azabicyclo[3.3.1]-nonanes synthesis proceeding from an adduct of 2,4-dinitrophenol and a carbanion generated from acetophenone by a base (Scheme 1).

As seen from the above Scheme, the synthesis of bicyclononanes involves two stages. The first stage consist in treating a solution of 2,4-dinitrophenol in acetophenone with sodium ethoxide to obtain a

1070-4280/03/3911-1593$25.00 © 2003 MAIK "Nauka/Interperiodica"

Scheme 1.



I, III **II, IVa–h**

R = Me (**I, II**), Ph (**III, IV**); R' = Me (**II, IVa**), Et (**IVb**), *n*-Bu (**IVc**), Bn (**IVd**), $(CH_2)2Br$ (**IVe**), $(CH_2)_2OH$ (**IVf**), CH_2CO_2H (**IVg**), $(CH_2)_2CO_2H$ (**IVh**).

sodium salt of Yanovskii adduct **III**. This intermediate compound is sufficiently stable to be isolated as adduct **I** from the reaction mixture by adding ethyl ether where it is insoluble.

It was previously reported [10] on formation of a colored product at treating the acetone solution of 2,4-dinitrophenol with sodium ethoxide, but no proofs of its structure was given. Adduct **I** was shown in [14] to have a structure of a product resulting from C^3-addition of 2-oxopropanide ion to 2,4-dinitrophenol. In the same manner the reaction between 2,4-dinitrophenol and acetophenone in the presence of a base yields analogous adduct **III** as evidenced by its ^{1}H NMR spectrum registered in DMSO. The signals of aromatic protons of the phenyl group appear in the weak field as a doublet of protons 2H-*o* at δ 8.00 ppm and triplets of protons 2H-*m* and H-*p* at δ 7.60 and 7.75 ppm respectively. Olefin protons H^5 and H^6 constitute an *AB*-system of two doublets at 5.70 and 7.30 ppm that can be in agreement only with a structure of C^3-isomer. The multiplets corresponding to H^3 protons and the CH_2CO group of the ketone rest are observed at δ 5.10 and 3.50 ppm respectively.

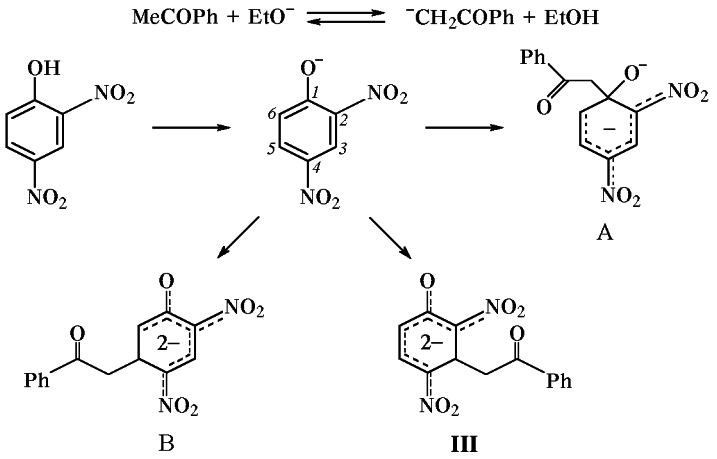
It is known [15] that carbanion addition to unsymmetrically substituted dinitroarenes yields isomeric C-adducts. It may be a limitation for application the reaction to a synthesis for a mixture of products might arise. It was presumable that addition of a bulky acetophenone carbanion also would furnish a mixture of C^3 and C^5 adducts. However as followed from the ^{1}H NMR spectrum of intermediate **III** which was isolated in almost quantitative yield the addition of 2-phenyl-2-oxopropanide ion occurred exclusively in *3*-position of the substrate. To reach an understanding of the high regioselectivity in reaction of 2,4-dinitrophenol with C-nucleophiles we carried out a quantum-chemical study of the reaction in the gas phase using semiempirical procedures AM1 and PM3. These methods were previously successfully applied to calculation of nitroarene anion adducts [16–20].

The addition of 2-oxopropanide ion to the aromatic ring of the sodium 2,4-dinitrophenoxide formed in the presence of excess EtONa may occur at three electrophilic reaction centers: carbon atoms C^1, C^3 and C^5 giving rise to isomeric Yanovskii adducts [A, **III**, and B respectively (Scheme 2)].

The kinetic preference in the nucleophilic attack on the substrate by the ketone carbanion is governed by charge and (or) orbital factors. As show the AM1 calculations the carbon atoms of 2,4-dinitrophenoxide form the following series according to the value of the positive charge (q): qC^1 (0.31) > qC^3 (0.08) > qC^5 (–0.02). Consequently, in keeping with the charge distribution the formation of *ipso*-C^1 adduct A would be the most favored. It is known from the published data on the aromatic nucleophilic substitution [15], that carbanions add to nitroarenes prevailingly at the unsubstituted position of the substrate, apparently due to steric reasons. In the case of 2,4-dinitrophenoxide a shielding effect of oxygen also should be taken into consideration, for a significant negative charge is localized thereon (–0.37). The charge factor favors formation of adduct C^3 (**III**) as compared to adduct C^5 (B). The contribution of carbon atoms p_z orbitals of 2,4-dinitrophenoxide into the LUMO of the substrate that characterizes the orbital control of the reaction decreases in the series: p_zC^3 (0.58) > p_zC^1 (0.11) > p_zC^5 (0.01). Thus the orbital factor favors the formation of C^3 adduct. The caclculation of atomic charges by PM3 methol gave similar results.

The enthalpy of formation for the adducts in question calculated by PM3 procedure [ΔH_f = –366 (**III**), –223 (A), –336 kJ mol^{-1} (B)] shows that the 3-substituted adduct **III** is more stable than adducts A and B. This result may be rationalized as follows. The extent to which the electron-withdrawing groups take part in the delocalization of the negative charge in the nitroarene adducts that governs their stability essentially depends on coplanarity of the nitro groups. The calculated values of torsion angles EC^{1}C^{2}N^{1}O^2 in adduct B and C^{3}C^{2}N^{1}O^2 in adduct A are 40.8° and –63.24° respectively. Thus the nitro group in position *2* of adducts A and B is strongly turned with respect

Scheme 2.



to the ring plane and consequently is less efficient in the anion charge delocalization. This is also proved by the overall charge on the 2-NO_2 group equal 0.012 and –0.026 a.u. for adducts A and B respectively. In contrast the torsion angle $C^1C^2N^1O^2$ in adduct **III** is 7.57°, and the overall charge on the nitro group in position *2* is larger by an order of magnitude and equals to –0.164 a.u. Thus both orbital kinetic and thermodynamic factors favor formation of intermediate C^3-adduct **III** ensuring high regioselectivity of the nucleophilic stage of the process. This conclusion is consistent with experimental data for exclusively this isomer was isolated from the reaction mixture and identified by spectral methods.

The isolated salt **III** was further immediately subjected to aminomethylation. To this end it was added by portions to ice-cooled mixture of amine or its hydrochloride water solution with 30% formaldehyde solution. After acidifying the mixture with 20% phosphoric acid a precipitate separated which was subjected to column chromatography. Thus was isolated a number of 3-R-9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-7-en-6-ones (**IVa–h**). The yield and characteristics of compounds obtained are complied in Table 1.

The structure of compounds synthesized was studied by molecular spectroscopy. In the IR spectra of the substances appeared a number of absorption bands supporting the assumed structures. The strong absorption bands in the region 1324–1395 and 1541–1571 cm^{-1} correspond to symmetric and asymmetric stretching vibrations of the aliphatic nitro groups. The doublet band of carbonyl group vibrations is observed at 1687–1715 cm^{-1}, and the vibrations of the C=C bond appear at 1611–1637 cm^{-1}. The stretching and bending vibrations of $C–H_{aliph}$ bonds give rise to absorption bands in the regions 2824–2979 and 1411–1495 cm^{-1} respectively.

The analysis of ^1H NMR spectra of compounds synthesized **IV–h** (Table 2) provided more conclusive proofs on the structure of the substances under study. While interpreting the ^1H NMR spectra we took into account the published experimental data [21] which suggested that the majority of heteroderivatives of bicyclo[3.3.1]nonanes existed in a *chair–chair* conformation. However the presence of *7,8*-double bond in compounds **IV** and of the trigonal carbon atom of the carbonyl group results in reduced *3,7*-repulsion due to the flattening of the cyclohexenone ring. Since the rings are rigidly fused and the fragment $C^1C^8C^7C^6C^5$ is obliged to be planar the cyclohexenone ring becomes rigid and incapable of inversion. The saturated piperidine ring retains the *chair* conformation which is stabilized due to introduction of a nitrogen into *3*-position of the bicyclononane system because of reduction of *3,7*-repulsion.

Let us consider for example the ^1H NMR spectrum of 3-methyl-9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-7-en-6-one (**IVa**). The signals of phenyl group protons are observed downfield as a doublet and two triplets with a vicinal coupling constant ^3J 7.94 Hz at δ 7.92 (2H-*o*), 7.63 (H-*p*) and 7.50 ppm (2H-*m*). The protons at the double bond appear as an *AB*-system containing a doublet of doublets corresponding to proton H^8 (^2J 10.38, ^3J 2.44 Hz) at δ 7.62 and of a doublet belonging to proton H^7 (^2J 10.38 Hz) at δ 6.56 ppm. The signal of bridging proton H^9 is a doublet at δ 4.13 ppm with a coupling constant ^3J 7.94 Hz.The methylene group protons of the ketone rest H^α and H^β are magnetically

Table 1. Yields, melting points, retention indices, IR spectra, and elemental analyses of 3-R-9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]-non-7-en-6-ones **IVa–h**

Compd. no.	Yield, %	mp (decomp.), °C	R_f	IR spectra, ν, cm^{-1}					Found, %			Formula	Calculated, %		
				CH_{arom}	CH_{aliph} [a]	C=O	C=C	NO_2	C	H	N		C	H	N
IVa	48	136–137	0.45	3086	2824, 2865, 2960	1707, 1689	1625	1560, 1379, 1345	55.19, 55.10	4.59, 4.60	11.78, 11.71	$C_{17}H_{17}N_3O_6$	56.80	4.76	11.69
IVb	37	134–135	0.54	3067	2835, 2883, 2979	1710, 1692	1615	1561, 1368, 1332	57.73, 57.44	4.98, 4.82	10.11, 11.34	$C_{18}H_{19}N_3O_6$	57.90	5.12	11.25
IVc	34	148–149	0.64	3095	2880, 2953, 2980	1708, 1694	1625	1553, 1377, 1336	59.76, 59.67	5.97, 5.86	10.10, 10.12	$C_{20}H_{23}N_3O_6$	59.84	5.77	10.46
IVd	20	161–162	0.60	3053	2839, 2872, 2927	1700, 1680	1617	1541, 1368, 1329	62.61, 62.35	4.81, 4.85	9.38, 9.41	$C_{23}H_{21}N_3O_6$	63.44	4.86	9.65
IVe [b]	26	137–138	0.48	3087	2840, 2916, 2978	1711, 1692	1613	1547, 1340, 1373	48.57, 47.95	4.03, 4.29	9.48, 9.54	$C_{18}H_{18}N_3O_6Br$	47.80	4.01	9.29
IVf	23	140–141	0.57	3069	2844, 2891, 2952	1715, 1691	1651	1571, 1395, 1360	55.67, 54.61	4.98, 4.93	10.47, 10.52	$C_{18}H_{19}N_3O_7$	55.50	4.90	10.79
IVg	37	162–163	0.58	3067	2904, 2928, 2991	1712, 1687	1611	1549, 1360, 1342	54.86, 54.60	5.48, 5.19	10.57, 10.36	$C_{18}H_{17}N_3O_8$	53.60	4.24	10.41
IVh	20	158–160	0.66	3073	2851, 2940, 2980	1705, 1696	1637	1543, 1368, 1332	55.20, 55.16	4.68, 4.77	9.78, 9.74	$C_{19}H_{19}N_3O_8$	54.67	4.58	10.06
IVi	38	134–138	0.46	3054	2890, 2915, 2979	1700, 1688	1610	1545, 1336, 1310	50.78, 50.87	5.64, 5.66	12.93, 12.98	$C_{13}H_{17}N_3O_6$	50.15	5.50	13.49
IVj	36	175–180	0.50	3072	2824, 2901, 2987	1700, 1684	1625	1556, 1352, 1345	52.70, 52.91	5.52, 5.33	13.76, 13.94	$C_{15}H_{19}N_3O_6$	53.40	5.67	12.46

[a] $\delta(CH_{aliph})$ 1410–1480 cm^{-1}. [b] Found Br, %: 17.86, 1794. Calculated Br, %: 17.66.

Table 2. ^{1}H NMR spectra of 3-R-9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]-non-7-en-6-ones **IVa–h** in DMSO-d_6, δ, ppm (J, Hz)

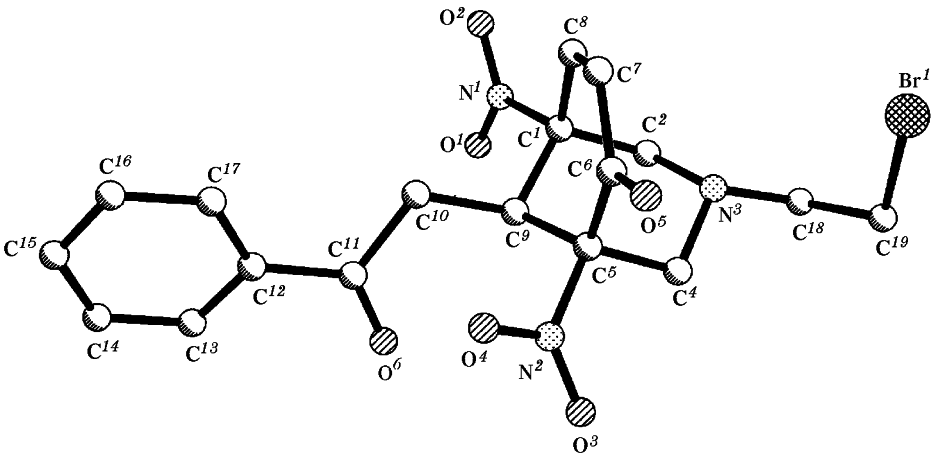
	H^7	H^8	H^9	H_e^4	H_a^4	H_a^2	H_e^2	H^α	H^β	2H-*o*	2H-*m*	2H-*p*	R
IVa	6.56 d (10.38)	7.62 d.d (10.38, 2.44)	4.13 d (7.94)	3.35 d (10.37)	3.18 d (10.37)	3.03 d (11.60)	3.15 d (11.60)	3.75 d.d (19.08, 8.24)	2.30 d (19.08)	7.92 d (7.94)	7.50 t (7.94)	7.63 d (7.94)	2.39 s (3H, CH_3)
IVb	6.56 d (10.38)	7.61 d.d (10.38, 2.44)	4.15 d (7.93)	3.40 d (10.99)	3.22 d (10.99)	3.10 d (11.23)	3.20 d (11.23)	3.75 d.d (19.08, 7.93)	2.99 d (19.08)	7.91 t (7.64)	7.49 t (7.64)	7.63 t (7.64)	0.97 t (3H, $CH_2\underline{C}\underline{H}_3$, 7.07), 2.64 q (2H, $\underline{C}\underline{H}_2CH_3$, 7.07)
IVc	6.55 d (10.38)	7.61 d.d (10.38, 2.44)	4.15 d (8.54)	3.38 d (10.68)	3.21 d (10.68)	3.08 d (10.99)	3.18 d (10.99)	3.75 d.d (19.38, 8.24)	2.98 d (19.38)	7.92 d (7.79)	7.49 t (7.79)	7.62 t (7.79)	0.84 t [3H, $(CH_2)_3\underline{C}\underline{H}_3$, 7.33], 2.55 t [2H, $\underline{C}\underline{H}_2(CH_2)_2CH_3$, 7.33], 1.35 m (2H, $CH_2\underline{C}\underline{H}_2CH_2CH_3$, 7.33), 1.19 m [2H, $(CH_2)_2\underline{C}\underline{H}_2CH_3$, 7.33]
IVd	6.65 d (10.37)	7.63 d.d (10.37, 2.44)	4.16 d (7.94)	3.36 d (10.69)	3.23 d (10.69)	3.15 d (10.99)	3.19 d (10.99)	3.76 d.d (19.24, 7.32)	2.95 d (19.24)	7.91 d (7.79)	7.49 t (7.79)	7.62 t (7.79)	3.80 d (2H, $\underline{C}\underline{H}_2$COPh, 13.42), 3.76 d (2H, $\underline{C}\underline{H}_2$COPh, 13.42)
IVe	6.56 d (10.38)	7.59 d.d (10.38, 2.44)	4.16 d (7.94)	3.50 d (11.30)	3.45 d (11.30)	3.28 d (10.98)	3.32 d (10.98)	3.75 d.d (19.08, 8.24)	2.98 d.d (19.08, 1.22)	7.92 d (7.63)	7.49 t (7.63)	7.62 t (7.63)	3.47 t (2H, $CH_2\underline{C}\underline{H}_2$Br, 6.72), 3.01 t (2H, $\underline{C}\underline{H}_2CH_2$Br, 6.72)
IVf	6.59 d (10.38)	7.61 d.d (10.38, 2.44)	4.12 d (7.94)	3.50 d (10.99)	3.40 d (10.99)	3.25 d (10.98)	3.28 d (10.98)	3.75 d.d (19.08, 8.24)	3.03 d (19.08)	7.92 d (7.73)	7.50 t (7.73)	7.64 t (7.73)	3.46 d.t (2H, $CH_2\underline{C}\underline{H}_2$OH, 5.49, 4.89), 2.68 t (2H, $\underline{C}\underline{H}_2CH_2$OH, 5.49), 4.54 t (1H, OH, 4.89)
IVg	6.56 d (10.38)	7.62 d.d (10.38, 2.44)	4.10 d (7.94)	3.61 d (10.99)	3.54 d (10.99)	3.27 d (10.68)	3.50 d (10.68)	3.76 d.d (19.53, 7.94)	2.98 d (19.53)	7.92 d (7.63)	7.49 t (7.63)	7.63 t (7.63)	12.52 br.s (1H, CO_2H) 3.49 d, 3.41 d (2H, CH_2CO_2H, 18.01)
IVh	6.52 d (10.38)	7.57 d.d (10.38, 2.44)	4.15 d (7.53)	3.41 d (10.69)	3.33 d (10.69)	3.18 d (10.99)	3.21 d (10.99)	3.73 d.d (19.23, 8.25)	2.98 d.d (19.23, 1.53)	7.91 d (7.69)	7.49 t (7.69)	7.63 t (7.69)	11.99 br.s (1H, CO_2H) 2.85 t (2H, $CH_2\underline{C}\underline{H}_2$OH, 7.02), 2.33 t (2H, $\underline{C}\underline{H}_2CH_2$OH, 7.02)

nonequivalent and thus give rise to separate signals: a doublet of doublets (^2J 19.08, ^3J 8.24 Hz) at δ 3.76 ppm and a doublet (^2J 19.08 Hz) at δ 2.30 ppm. The equatorial and axial protons of CH_2 groups of the piperidine ring H^2 and H^4 are observed as four doublets at δ 3.35, 3.18, 3.15, and 3.03 ppm with a geminal coupling constant ^2J 10.37–11.60 Hz. The substituent attached to the nitrogen gives rise to an expected singlet at δ 2.39 ppm. In the ^{13}C NMR spectrum of compound **IVa** signals from carbons of both carbonyl groups are observed at δ_C 187.0 and 193.98 ppm. The carbon atoms of phenyl group and of the double bond (C^7, C^8) appear as signals in the region δ_C 128–142 ppm. Resonances of the quaternary carbons C^1, C^5 linked to the nitro groups are observed at δ_C 89.16 and 90.89 ppm. The signals at δ_C 59.37, 58.67, and 44.61 ppm belong respectively to methylene (C^2, C^4) and N-methyl carbons of the piperidine ring. The bridging carbon signal is located most upfield (δ_C 36.05 ppm). To the methylene group carbon from the 2-phenyl-2-oxoethyl moiety corresponds the peak at δ_C 43.57 ppm.

To confirm the structure of the synthesized N-substituted 9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-7-en-6-ones we performed X-ray diffraction study of compound **IVe** (see figure, Tables 3 and 4). The piperidine ring in compound **IVe** is in the *chair* conformation. The deviations of atoms N^3 and C^9 from the plane going through the other atoms of the ring amounts to –0.691 and 0.783 Å respectively. The cyclohexene ring $C^1{\cdot}C^8{\cdot}C^7{\cdot}C^6{\cdot}C^5{\cdot}C^9$ is in the *sofa* conformation with the C^9 deviating from the plane containing all the other atoms of the ring by –0.784 Å. The conformation of the eight-membered ring $C^1 \ldots C^8$ is close to *boat-boat* conformation and is characterized by the following Zefirov–Palyulin folding parameters [22]: S_2 = 1.216, S_3 = 0.548, S_4 = 0.496, φ_2 = 178.19, φ_3 = 182.71. Nitro groups in compound **IVe** are located in equatorial positions [torsion angles $N^1C^1C^9C^5$ and $N^2C^5C^9C^1$ equal to 175.9(2) and 178.8(2)° respectively]. The nitro group attached to C^5 is considerably turned with respect to the flattened fragment of the cyclohexene ring [torsion angle $O^2N^1C^1C^8$ equals 47.6(2)°], whereas the second nitro group is essentially coplanar with this fragment [torsion angle $O^4N^2C^5C^6$ equals 9.2(2)°].

The nitrogen N^3 deviation from the plane drawn through three atoms linked thereto is 0.429 Å evidencing the trigonal-pyramidal configuration of this fragment. The bromine atom has a synclinal orientation, since the torsion angle $Br^1C^{19}C^{18}N^3$ is –57.6(2)°. The acetophenyl group is situated in an axial position to the cyclohexene ring [torsion angle $C^6C^5C^9C^{10}$ equals –64.9(2)°], and with respect to the piperidine ring this group is in equatorial position with torsion angle $C^4C^5C^9C^{10}$ of 173.1(2)°. The data obtained are similar to the results of X-ray studies of the other nitro derivatives of azabicyclo[3.3.1]-nonanes [23–28].

The second, electrophilic stage of the process under study (Scheme 1) consists in condensation of adduct **III** with formaldehyde and primary amines. The probable mechanism of formation of nitro derivatives from the 3-azabicyclo[3.3.1]nonane series **IV** is presented on Scheme 3. The addition of electrophilic species which in the Mannich reaction is represented by dimethyliminium cation [29] occurs at two nucleo-



Molecular structure of 3-(2-bromoethyl)-9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-7-en-6-one (**IVe**) with hydrogen atoms omitted.

Table 3. Some bond lengths in compound **IVe**

Bond	*d*, Å	Bond	*d*, Å
$Br^{1}-C^{19}$	1.930(4)	$C^{1}-C^{2}$	1.530(4)
$O^{1}-N^{1}$	1.169(3)	$C^{1}-C^{8}$	1.509(3)
$O^{2}-N^{1}$	1.169(3)	$C^{1}-C^{9}$	1.539(3)
$O^{4}-N^{2}$	1.223(2)	$C^{5}-C^{9}$	1.530(3)
$O^{3}-N^{2}$	1.211(2)	$C^{5}-C^{4}$	1.522(3)
$O^{5}-C^{6}$	1.208(3)	$C^{5}-C^{6}$	1.549(3)
$O^{6}-C^{11}$	1.210(3)	$C^{6}-C^{7}$	1.469(3)
$N^{1}-C^{1}$	1.535(3)	$C^{7}-C^{8}$	1.304(4)
$N^{2}-C^{5}$	1.523(3)	$C^{9}-C^{10}$	1.525(4)
$N^{3}-C^{2}$	1.454(3)	$C^{10}-C^{11}$	1.528(3)
$N^{3}-C^{4}$	1.464(3)	$C^{11}-C^{12}$	1.474(3)
$N^{3}-C^{18}$	1.457(3)	$C^{18}-C^{19}$	1.492(4)

Table 4. Coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($Å^2 \times 10^3$) of nonhydrogen atoms in structure **IVe**

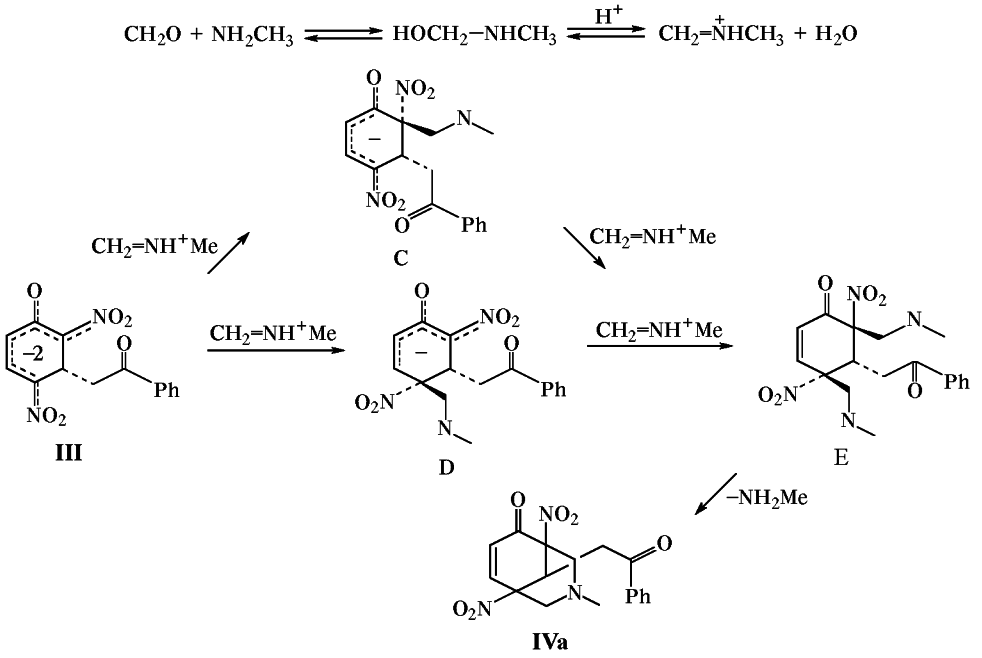
Atom	*x*	y	z	U(eq)
Br^{1}	3643(1)	–1352(1)	–3829(1)	107(1)
N^{1}	4374(3)	–7588(2)	–2142(3)	71(1)
N^{2}	–1029(2)	–4821(2)	–2073(2)	49(1)
N^{3}	3135(2)	–3961(2)	–2096(2)	47(1)
O^{1}	4182(4)	–8036(3)	–1146(3)	151(2)
O^{2}	5292(4)	–8123(3)	–2867(3)	148(1)
O^{3}	–1624(2)	–4295(2)	–1170(2)	59(1)
O^{4}	–1791(2)	–5325(2)	–2725(2)	72(1)
O^{5}	97(2)	–3662(2)	–4258(2)	61(1)
O^{6}	–652(2)	–7611(2)	–732(2)	74(1)
C^{1}	3398(3)	–6253(2)	–2502(2)	50(1)
C^{2}	4029(3)	–5258(3)	–1821(2)	55(1)
C^{4}	1410(3)	–3933(3)	–1711(2)	45(1)
C^{5}	786(2)	–4905(2)	–2412(2)	40(1)
C^{6}	1052(3)	–4497(2)	–3782(2)	47(1)
C^{7}	2558(3)	–5135(3)	–4413(2)	53(1)
C^{8}	3629(3)	–5955(3)	–3854(2)	56(1)
C^{9}	1601(3)	–6305(2)	–2091(2)	43(1)
C^{10}	948(3)	–7395(3)	–2617(2)	53(1)
C^{11}	–285(3)	–8005(2)	–1727(2)	50(1)
C^{12}	–949(3)	–9121(2)	–2096(2)	47(1)
C^{13}	–1648(3)	–9950(3)	–1211(2)	58(1)
C^{14}	–2269(3)	–10999(3)	–1512(3)	65(1)
C^{15}	–2220(3)	–11243(3)	–2689(3)	64(1)
C^{16}	–1568(4)	–10433(3)	–3599(3)	66(1)
C^{17}	–919(3)	–9383(3)	–3297(2)	61(1)
C^{18}	3820(4)	–2946(3)	–1602(3)	60(1)
C^{19}	3234(4)	–1585(3)	–2092(3)	76(1)

philic centers of anion **III**: at carbon atoms C^2 and C^4 linked to *aci*-nitro groups. As a result arise intermediate products of mono- (C, D) and bis-aminomethylation (E). The last part of the scheme in question involves the intramolecular condensation of the Mannich bis-base (E) under acid catalysis giving rise to the nitrogen-containing ring of compound **IVa** with liberation of a methylamine molecule.

The latter reaction can occur evidently only at axial orientation of the *N*-methylaminomethyl groups in 1,3-*cis*-isomer E. The calculations show that the six-membered ring in Yanovskii adducts **III** is not planar. The sp^3-hybridized carbon atom deviates from the plane going through the other atoms as indicates the value of the corresponding torsion angle (the angle $C^2C^3C^4C^5$ equals 21.9°). The attack of 2-phenyl-2-oxopropanide ion on the 2,4-dinitrophenoxide is equally probable to occur from both sides of the flat aromatic ring of the substrate. Therefore the adduct forms two *R*,*S*-conformers which are distinguished by the orientation with respect to the planar part of the ring of the sp^3-hybridized carbon atom attached to the ketone rest. It also follows from the calculated values of torsion angles (the angle $C^1C^2C^3C^7$ is 100.6°) that 2-phenyl-2-oxopropyl substituent in adduct **III** is located in pseudoaxial position. As a result the strain in the ring caused by adjacent nitro groups is reduced.

Such orientation of substituent at C^3 favors the attack of electrophilic species from the opposite side thus ensuring stereoselectivity at this stage of the process. The substituted cyclohexenes are known [30] to exist predominantly in the *semichair* conformation. Molecular simulation demonstrated that E intermediate formed 16 conformations distinguished by the spatial position of atoms C^5 and C^6 with respect to the plane through the atoms $C^1C^2C^3C^4$, and by substituents orientation. Therewith the *cis*-1,3-isomer with the diaxial position of *N*-methylaminomethyl groups was the most stable. As was stated above, according to the X-ray data the 2-phenyl-2-oxoethyl group in compound **IVe** retained the axial orientation with respect to the cyclohexenone fragment (the configuration of asymmetric atoms was 1*S*, 3*S*, 5*R*, 9*S*). Thus the calculation results do not contradict the assumed pattern of N-substituted 9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-7-en-6-ones (**IV**) formation, are in agreement with the experimental data and besides permit an understanding of the high regioselectivity of the nucleophilic stage of the process and the stereoselectivity of the electrophilic stage.

Scheme 3.



Thus we carried out a two-stage synthesis of polyfunctional derivatives of 3-azabicyclo[3.3.1]nonane from 2,4-dinitrophenol and acetophenone. The synthesis of compounds in this developed fashion is interesting because it provides a possibility to introduce into the bicyclononane system of two carbonyl functions and nitro groups which are promising in view of further transformations.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Specord 75IR from KBr pellets. ^{1}H NMR spectra were registered on spectrometer Bruker DRX-500 (500.13 MHz) from solutions in DMSO-d_6, internal reference HMDS. ^{13}C NMR spectrum was obtained on Bruker WM-250 at operating frequency 62.9 MHz. Retention indices (R_f) were measured on Silufol UV-254 plates, eluent acetone–toluene–hexane (1 : 4 : 1), development under UV irradiation. Melting points were determined on a Boetius heating block. Quantum-chemical calculations were carried out on PC (550 MHz) applying a software package Hyper Chem 6.0.

X-ray diffraction study of compound IVe. Crystals $C_{18}H_{18}BrN_3O_6$ (from toluene) at 293(2) K triclinic, *a* 8.417(2), *b* 10.379(2), *c* 11.158 (2) Å, α 84.61(3), β 83.67(3), γ 80.65(3)°, *V* 953.0(3) Å^3, crystal habit 0.5 × 0.4 × 0.3 mm, space group *P* $\bar{1}$, *Z* 2, d_{calc} 1.576 g cm^{-3}, *F*(000) 460, μ 2.198 mm^{-1}. The intensity of 6198 reflections (5546 independent, R_{int} 0.110) were measured on automatic four-circle diffractometer Siemens P3/PC (graphite monochromator, Mo-K_α radiation, ω scanning, $2\theta_{max}$ 60°). The absorption was accounted for by the method of φ-scanning [31]. The structure was solved by the direct method with the use of SHELXTL-97 software [32]. The positions of hydrogen atoms were revealed from the difference synthesis of electron density. The refinement by F^2 in anisotropic approximation for nonhydrogen atoms (isotropic for hydrogen atoms) was performed in full-matrix least-squares procedure (325 parameters) involving 5546 reflections till *R1* 0.049 [for reflections with $F >> 4\sigma(F)$], *wR2* 0.135, *S* 1.03. Coordinates of nonhydrogen atoms are listed in Table 3, and the lengths of some bonds in Table 4. The Zefirov–Palyulin folding parameters were calculated with the use of RICON routine [33].

3-(2-Oxoethyl-2-phenyl)-2,4-bis(aci-nitro)cyclohexen-5-one-1 disodium salt (III). To a solution of 2,4-dinitrophenol (0.92 g, 5 mmol) in acetophenone (7 ml) was slowly added at stirring a solution of sodium ethoxide prepared from sodium (0.5 g, 22 mol) and ethanol (15 ml). The reaction mixture was stirred for 30 min at 18–20°C, then the separated precipitate was isolated, washed with 5 ml of ethanol and 30 ml of ethyl ether, and dried in a vacuum-desiccator. We obtained 1.67 g (96%) of compound

III. The synthesis was carried out with the use of anhydrous solvents.

General procedure for preparation of 3-R-9-(2-phenyl-2-oxoethyl)-1,5-dinitro-3-azabicyclo[3.3.1]-non-7-en-6-ones IVa–h. To a mixture of 10 mmol of an appropriate amine hydrochloride, of 30% aqueous formaldehyde (5 ml, 52 mmol), and 10 ml of water was added by small portions at stirring adduct **III** (1.04 g, 3 mmol). In 2 h the reaction mixture was acidified with 20% orthophosphoric acid (2 ml) and extracted with toluene (3 × 10 ml). The extract was dried over $CaCl_2$ and passed through a column packed with silica gel (ASKG, eluent toluene for compounds **IVa–e**; toluene–acetone, 15 : 1 by volume, for compound **IVf**; toluene–acetone, 10 : 1, for compound **IVg**; toluene–acetone, 7 : 1, for compound **IVh**). The solutions obtained were evaporated in a vacuum till a volume of 20 ml, the products were precipitated by adding hexane and recrystallized from ethanol. Compounds **IVg, h** were additionally dissolved in THF and reprecipitated with 2-propanol.

Yields, melting points, retention indices (R_f), and elemental analyses of compounds **IVa–h** are compiled in Table 1, their spectral data in Tables 1 and 2.

The study was carried out under financial support of the Russian Foundation for Basic Research (grant no. 01-03-96002) and Russian Ministry of Education (grant no. E02-5.0-276).

REFERENCES

1. *The Nitro Group in Organic Synthesis*, Ono, N., Ed., New York: John Willey, 2001.
2. Makosza, M. and Wojciechowski, K., *Heterocycles*, 2001, vol. 54, p. 445.
3. Makosza, M., *Pure Appl. Chem.*, 1997, vol. 69, p. 559.
4. Chupakhin, O.N., Charushin, V.N., and van der Plas, H.C., *Nucleophilic Aromatic Substitution of Hydrogen*, San Diego: Academic Press, 1994.
5. Suwinski, J. and Swierczek, K., *Tetrahedron*, 2001, vol. 57, p. 1639.
6. Saveant, J.-M., *Tetrahedron*, 1994, vol. 50, p. 10117.
7. Kuz'min, N.G. and Ivanov, V.L., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, vol. 9/3, p. 40.
8. Wozniak, M. and van der Plas, H.C., *Acta Chem. Scand.*, 1993, vol. 47, p. 95.
9. Severin, T. and Temme, H.-L., *Chem. Ber.*, 1965, vol. 98, p. 1159.
10. Anslow, W.K. and King, H., *J. Chem. Soc.*, 1929, pt. 1, p. 1210.
11. Genri, T.A., *Khimiya rastitel'nykh alkaloidov* (Chemistry of Plant Alcaloids), Moscow: GNTIKhL, 1956.
12. Kogel, B., Christoph, T., Friderichs, E., Hennies, H.-H., Mathiesen, T., Schneider, J., and Holzgrabe, U., *CNS Drug Rev.*, 1998, vol. 4, p. 54.
13. Chen, C.L., Chandra, A.M., Kim, S., Sangiah, S., Chen, H., Roger, J.D., Qualls, C.W., Garrison, G.L., Cowell, R.L., Berlin, K.D., Scherlag, B.J., and Lazzara, R., *Food Chem. Toxicol.*, 2000, vol. 38, p. 817.
14. Leonova, O.V., Shakhkel'dyan, I.V., Grudtsyn, Yu.D., Atroshchenko, Yu.M., Alifanova, E.N., Gitis, C.C., Chudakov, P.V., Nikiforova, E.N., Alekhina, N.N., and Kaminskii, A.Ya., *Zh. Org. Khim.*, 2001, vol. 37, p. 421.
15. Buncel, E., Dust, J.M., and Terrier, F., *Chem. Rev.*, 1995, vol. 95, p. 2261.
16. Colkan, V.N. and Shevelev, C.A., *Izv. Akad. Nauk, Ser. Khim.*, 1993, p. 1892.
17. Colkan, V.N. and Shevelev, C.A., *Izv. Akad. Nauk, Ser. Khim.*, 1995, p. 624.
18. Alifanova, E.N., Chudakov, P.V., Kaminskii, A.Ya., Mamaev, V.M., Gloriozov, I.P., Akhmedov, N.G., Grudtsyn, Yu.D., Borbulevich, O.Ya., Shishkin, O.V., Antipin, M.Yu., Atroshchenko, Yu.M., and Gitis, S.S., *Izv. Akad. Nauk. Ser. Khim.*, 2001, p. 1012.
19. Alifanova, E.N., Kalnin'sh, K.K., Chudakov, P.V., Kaminskii, A.Ya., Kutsenko, A.D., and Gitis, C.C., *Zh. Obshch. Khim.*, 2001, vol. 71, p. 300.
20. Politanskaya, L., Malykhin, E., and Shteingarts, V., *Europ. J. Org. Chem.*, 2001, vol. 66, p. 405.
21. *Topics in Stereochemistry*, Eliel, E.L and Wilen, S.H., New York: John Willey, 1991, p. 171.
22. Zefirov, N.S., Palyulin, V.A., and Dashevskaya, E.E., *J. Phys. Org. Chem.*, 1990, vol. 3, p. 147.
23. Kaftory, M. and Dunitz, J.D., *Acta Cryst. (B)*, 1976, vol. 32, p. 1.
24. Zefirov, N.C., Palyulin, V.A., Efimov, G.A., Subbotin, O.A., Levina, O.I., Potekhin, K.A., and Struchkov, Yu.T., *Dokl. Akad. Nauk SSSR*, 1991, vol. 302, p. 1392.
25. Shishkin, O.V., Atroshchenko, Yu.M., Gitis, S.S., Alifanova, E.N., and Shakhkeldyan, I.V., *Acta Cryst. (C)*, 1998, vol. 54, p. 271.
26. Atroshchenko, Yu.M., Nikiforova, E.G., Gitis, S.S., Grudtsyn, Yu.D., Shishkin, O.V., Andrianov, V.F., and Shakhkel'dyan, I.V., *Zh. Org. Khim.*, 1999, vol. 35, p. 1339.
27. Atroshchenko, Yu.M., Nikiforova, E.G., Shakhkel'dyan, I.V., Grudtsyn, Yu.D., Akhmedov, N.D., Alifanova, E.N., Borbulevich, O.Ya., Shishkin, O.V., Gitis, S.S., and Kaminskii, A.Ya., *Zh. Org. Khim.*, 2000, vol. 36, p. 771.

28. Shakhkel'dyan, I.V., Nikiforova, E.G., Grudtsyn, Yu.D., Atroshchenko, Yu.M., Borbulevich, O.Ya., Efremov, Yu.A., Gitis, S.S., Alifanova, E.N., Chudakov, P.V., and Kovalevskii, A.Yu., *Zh. Org. Khim.*, 2001, vol. 37, p. 617.
29. Arend, M., Westerman, B., and Risch, N., *Angew. Chem. Int. Ed.*, 1998, vol. 37, p. 1044.
30. Johnson, F., *Chem Rev.*, 1968, vol. 68, p. 375.
31. North, A.C.T., Phillips, D.C., and Mathews, F.S., *Acta Cryst. (A)*, 1968, vol. 24, p. 351.
32. Sheldrick, G.M., *SHELXTL-97 V5.10*, 1997, Madison: Bruker AXS Inc.
33. Zotov, A.Yu., Palyulin, V.A., and Zefirov, N.S., *J. Chem. Inf. Comput. Sci.*, 1997, vol. 37, p. 766.