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New Stereoselective Intramolecular Redox Reaction in the System of 3,7-Diazabicyclo[3.3.1]nonan-9-one

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Abstract—The ring opening in the 1-benzyl-5,7-dimethyl-6-oxo-1-azonia-3-azaadamantane chloride under the treatment with excess aqueous alkali led to a stereoselective formation of *anti*-1,5-dimethyl-7-benzyl-3-formyl-3,7-diazabicyclo[3.3.1]nonan-9-ol whose structure was established by means of X-ray diffraction analysis and NMR spectroscopy. A reaction mechanism was suggested involving an intramolecular redox hydride transfer.

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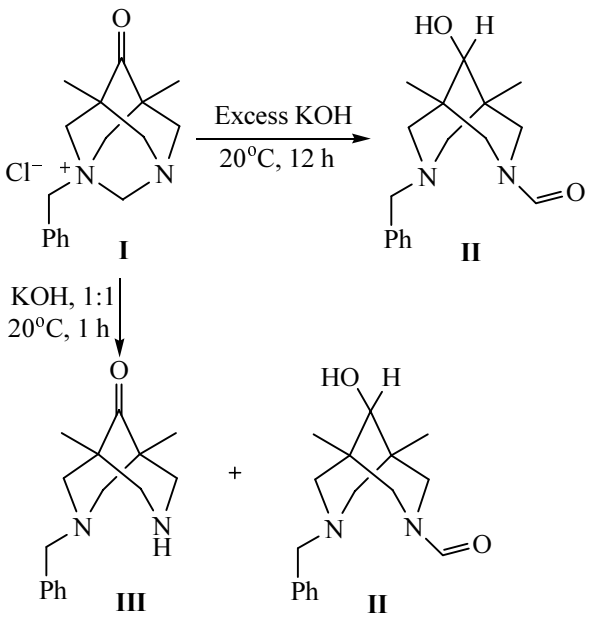
The compounds of the series of 3,7-diazabicyclo-[3.3.1]nonane (bispidine) within the last three decades attracht high attention, and a constant growth of interest to these substances is observed [1]. The research activity concerning this class compounds is due to the large potential in their application to the medicine [2] and as enantioselective catalysts [3]. Diazabicyclononanes with a keto group in the position *9* and also 1,3-diazaadamantan-6-ones exhibit an analgesic activity [4]. The established antiarrhythmic activity of bispidines should be especially mentioned for it can be tuned by varying the substituents at the nitrogen [5]. These compounds function as blockaders of K^+ channels and are promising pharmaceuticals for treating fatally dangerous arrhythmia and for preventing sudden cardiac arrest [6, 7]. Therefore the stereoselective synthesis of various diazabicyclo-nonane derivatives is especially urgent. We report here on the results of a study of one among new syntheses of unsymmetrical bispidines involving the opening with a base of a diazaadamantanone quaternary salt **I** [8, 9].

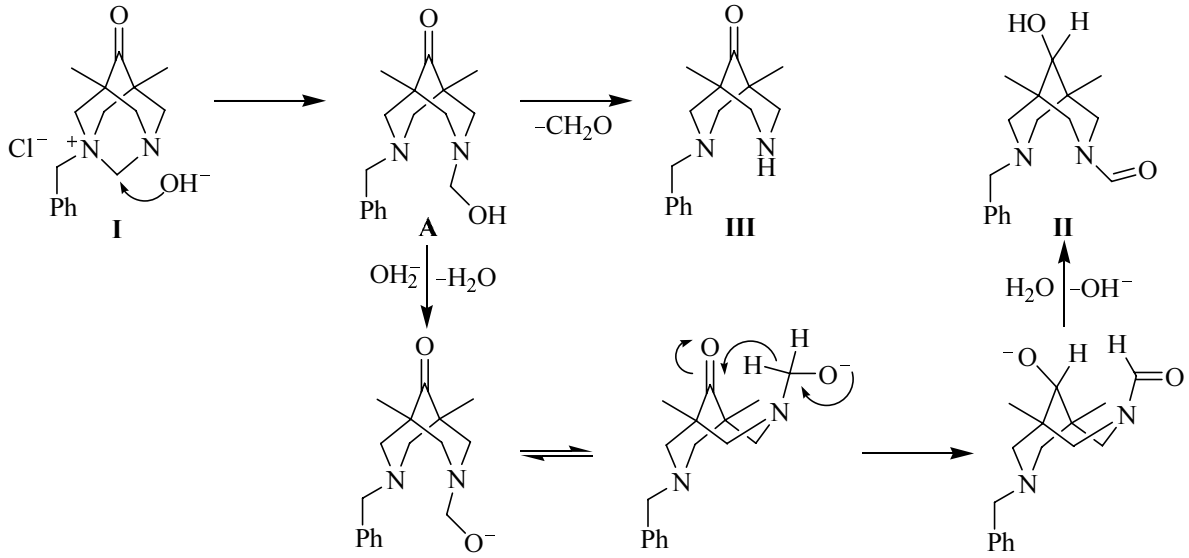
Investigating the alkaline ring opening in diaza-adamantanone we observed the keto group reduction in the 1-benzyl-5,7-dimethyl-6-oxo-1-azonia-3-aza-adamantane chloride (**I**) resulting in the stereoselective formation of *anti*-1,5-dimethyl-7-benzyl-3-formyl-3,7-diazabicyclo[3.3.1]nonan-9-ola (**II**) (Scheme 1). The reduction of the keto group in the position *9* of unsymmetrical diazabicyclononanones led usually to the formation of a stereoisomers mixture. A highly stereoselective reduction is observed in the presence of pyridine or phenyl substituents in the positions *2* and *4* [10, 11]. In our case the total stereoselectivity is ensured by the assumed intramolecular hydride transfer mechanism resembling the Cannizzaro reaction.

The reaction of adamantanonium salt **I** with a 5-fold excess of potassium hydroxide water solution at room temperature within 12 h gave rise to a single reaction product **II** in a 64% yield. The treatment with an

Scheme 1.



Scheme 2.



equivalent quantity of alkali for 1 h led to the formation of a mixture of compounds **II** and **III** in a 9:1 ratio, with 3-benzyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**III**) prevailing.

When the obtained mixture of compounds **II** and **III** was treated with 5 equiv of aqueous KOH and 2 equiv. of formaldehyde solution the only reaction product was compound **II**. This means that amine **III** can be converted into formamide **II** under the reaction conditions. The reaction carried out in D_2O provided the corresponding mixture of compounds **II** and **III** where only the labile hydrogen atoms of the OH and NH groups were replaced by deuterium.

This result is rationalized by Scheme 2. One equiv of alkali is sufficiently fast consumed in the opening of the ring resulting in intermediate **A**, that further eliminated a formaldehyde molecule transforming into compound **III**. The excess alkali favors another reaction path where aminoalcohol **A** is deprotonated, and a hydride anion from the electron-excessive oxymethyl group is transferred to the carbonyl. This hydride transfer is facilitated by the spatial proximity of the interacting hydrogen atom and carbonyl group in the *chair-boat* conformation of the bicyclononane skeleton. A similar redox process occurs with tropine and benzoyl chloride in an alkaline medium [12]. The carbonyl group of the N-benzoylated tropine is favorably oriented with respect to the hydrogen atom of the CHO^- group whose negative charge facilitates the hydride anion transfer.

The assumed mechanism is confirmed by the complete *anti*-stereoselectivity of the reaction.

The reduction of the keto group at heating the 1,5,7-trimethyl-6-oxo-1-azonia-3-azaadamantane iodide in ethanol in the presence of KOH was mentioned in [12], but the sterical structure of the product was not established. Minasyan et al. [9] also published the study on salt **I** transformation into ketone **III** in 1 h at room temperature in the presence of the 5-fold excess of aqueous alkali, but they did not isolate the reduction product **II**.

The structure of compound **II** was studied by means of NMR spectroscopy and X-ray diffraction analysis. The experiments employing NOE and double resonance technique made it possible to assign nearly all signals in the ^1H and ^{13}C NMR spectra, and also to suggest that the bicyclic skeleton of the molecule existed in the *double-chair* conformation (Scheme 3).

Inasmuch as compound **II** contains an amide moiety it was presumable that due to the hindered rotation around the N–C(O) bond at room temperature the observed spectra would correspond to a molecule lacking any symmetry elements. Actually, both methyls give rise to separate signals, and the diastereotopic methylene protons of the benzyl group appear as an *AB* system. The aliphatic part of the compound **II** proton spectrum (Fig. 1) contains a set of doublets, and some of them are additionally split by long-distance couplings with small constants: five pairs of geminal protons doublets from CH_2 groups and a doublet from the vicinal pair CHOH are observed. In the signals of the skeleton protons the geminal coupling constants are clearly seen, and also some *W*-couplings characteristic of the diazabicyclononane framework

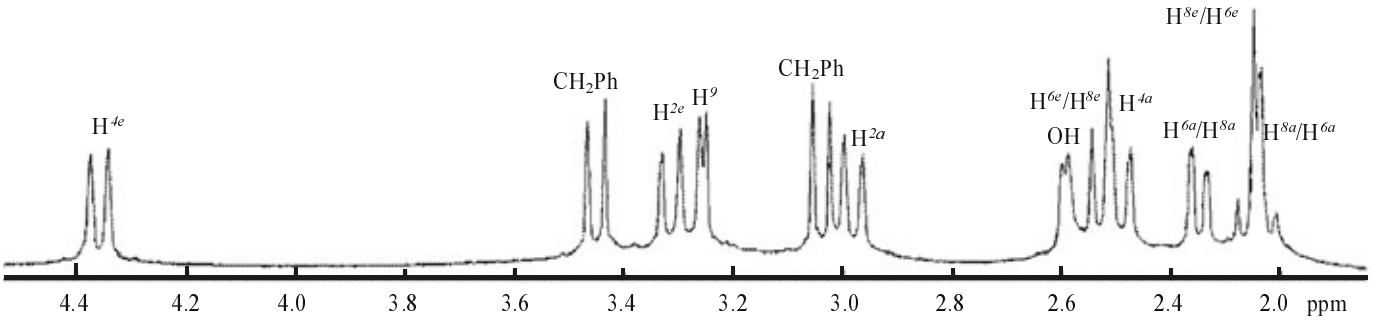
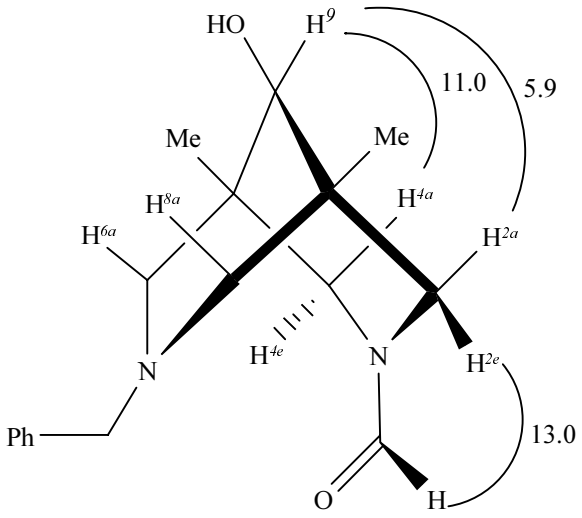


Fig. 1. Upfield region of the ^{1}H NMR spectrum of compound **II**.

(*e–e* in one ring and *a–a* in the adjacent ones), for instance, H^{2e}–H^{4e}, H^{4a}–H^{6a}, H^{2a}–H^{8a} (Scheme 3). The existence of these couplings is characteristic of bispidines with unsymmetrically substituted rings, and also at the lack of equivalence of the protons in one ring.

The analysis of signals belonging to CH_2 groups is logically started from the easily understandable *AB*-system of benzyl protons at 3.48 and 3.09 ppm. Then the proton of formyl group at 7.91 ppm is also easily assigned. In the NOE experiment a considerable response is observed on this proton from the skeleton proton at 3.35 ppm that corresponds to the equatorial H^{2e}. A double resonance experiment with decoupling from the signal at 4.38 ppm showed that the signal at 3.35 ppm lost the *W*-coupling constant 1.6 Hz characteristic of a pair of the equatorial protons belonging to the same six-membered ring. The shielding of the proton at 4.38 ppm (compared with its partner at 3.35 ppm) permits its assignment to the proton H^{4e} located in the *syn*-position to the carbonyl group known for its anisotropy of the magnetic susceptibility.

Scheme 3.

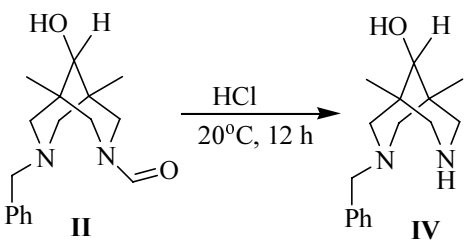


In the NOE experiment at the irradiation of the proton H^9, δ 3.25 ppm, the response was observed of the signal located at 3.01 ppm with an integral intensity of 5.9% , and of the proton at 2.52 ppm with an integral intensity of 11.0%. These resonances have geminal couplings with a presumable pair of equatorial protons (H^{2e} and H^{4e}), consequently, the latter correspond to the axial protons (H^{2a} and H^{4a}) evidencing the *anti*-position of the OH group with respect to the formamide group.

The rest of the signals was assigned employing the double resonance technique, and also using the known data on the features of the chemical shifts and coupling in the bicyclononane systems. In particular, we used the data on relation between the chemical shifts of the axial and equatorial protons, namely $\delta_{eq} > \delta_{ax}$ [13, 14].

The existence of the *double-chair* conformation follows from the appearance of the *W*-coupling (H^{4a}–H^{6a}, H^{2a}–H^{8a}) and is consistent with the NOE data. The reason for the existence of this conformation may be the interaction nucleophile–electrophile between the unshared electron pair of nitrogen bearing a benzyl substituent and the carbonyl group of the formamide fragment. Similar conformational control was formerly reported for the diazabicyclononane systems [15, 16]. This intramolecular interaction is also reflected in the reactivity of the carbonyl group: the hydrolysis of the formamide group in compound **II** occurs exclusively readily. The proximity of the reacting atoms in the initial molecule (Scheme 4) enhances

Scheme 4.



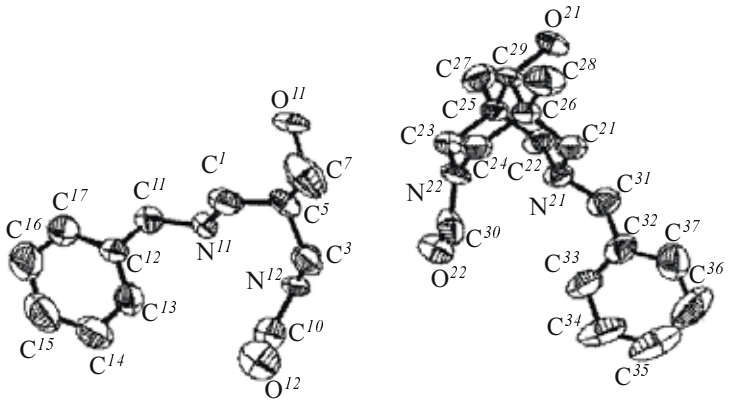


Fig. 2. Structure of compound **II**: two crystallographically independent molecules in the unit cell. Hydrogen atoms are not shown.

their interaction and promotes the reaction as has been elegantly demonstrated in the case of amide proton sponge where the strong hydrogen bond with the amide nitrogen facilitates the nucleophile attack on the carbonyl group and accelerates the amide hydrolysis [17].

The X-ray diffraction analysis unambiguously proved the structure of crystalline compound **II** deduced from the NMR spectra. The unit cell contains two crystallographically independent molecules **II** (Fig. 2). The crystallographic data on the structure are given in Table1, and selected bond lengths and bond angles, in Table 2. The aliphatic nitrogen atoms are in the tetrahedral configuration (bond angles sum at N^{11} and N^{21} is 331.3 and 332.0°, respectively). Amide nitrogen atoms are planar (bond angles sum at N^{12} and N^{22} is 359.4 and 359.6° respectively). The distance between the aliphatic nitrogens and carbonyl carbons amounts to 3.27 and 3.25 Å. These values are at the upper border of those published for such bonding interaction governing the presence in the solution of the double-chair conformation *a* [15, 16].

In the crystal the nearest translationally corresponding molecules of compound **II** are bound by the hydrogen

Table 1. Crystallographic data, experimental details, and refining of structure **II**

Empirical formula	$C_{17}H_{24}N_2O_2$
Molecular weight	288.38
Crystal system	Monoclinic
Space group	$P2_1/n$
a, A	18.367(10)
b, A	8.366(6)
c, A	22.056(9)
β, deg	109.84(4)
V, A^3	3188(3)
Z	8
C_{calc}, g/cm^3	1.202
F(000)	1248
μ(MoK_α), mm^{-1}	0.079
Crystal size, mm	0.4×0.1×0.1
Scanning region by θ, deg	ω 2.36–24.97
Spherical segment	$-21 \le h \le 21$
	$-9 \le k \le 2$
	$-3 \le l \le 26$
Measured reflections	8609
Independent reflections	5576 (R_{int} 0.0652)
Number of refined parameters	381
R-factors at $I > 2\sigma(I)$	R_1 0.0817, wR_2 0.2227
Quality factor for F^2	1.067
Extinction factor	0.0021(10)
Residual electron density, min/max, e/A^3	–0.362/1.091

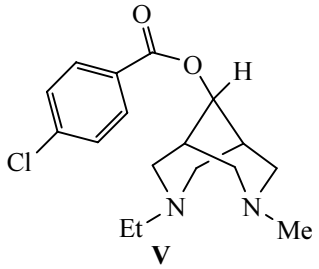
Table 2. Selected bond lengths (Å) and bond angles (deg) in the structure **II**

Bond lengths			
O^{11}–C^9	1.428(7)	O^{21}–C^{29}	1.436(7)
O^{12}–C^{10}	1.169(8)	O^{22}–C^{30}	1.183(7)
N^{11}–C^{11}	1.437(7)	N^{21}–C^{21}	1.452(7)
N^{11}–C^2	1.448(7)	N^{21}–C^{22}	1.464(8)
N^{11}–C^1	1.478(7)	N^{21}–C^{31}	1.470(7)
N^{12}–C^{10}	1.406(8)	N^{22}–C^{30}	1.364(9)
N^{12}–C^4	1.448(8)	N^{22}–C^{24}	1.428(8)
N^{12}–C^3	1.457(7)	N^{22}–C^{23}	1.467(8)
Bond angles			
$C^{11}N^{11}C^2$	111.4(5)	$C^{21}N^{21}C^{22}$	111.7(5)
$C^{11}N^{11}C^1$	109.3(5)	$C^{21}N^{21}C^{31}$	110.2(5)
$C^2N^{11}C^1$	110.6(5)	$C^{22}N^{21}C^{31}$	110.2(5)
$C^{10}N^{12}C^4$	127.4(6)	$C^{30}N^{22}C^{24}$	119.0(6)
$C^{10}N^{12}C^3$	116.1(6)	$C^{30}N^{22}C^{23}$	124.5(6)
$C^4N^{12}C^3$	115.9(5)	$C^{24}N^{22}C^{23}$	116.1(5)
$O^{12}C^{10}N^{12}$	116.8(7)	$O^{22}C^{30}N^{11}$	121.4(9)

bond CHO···H–O (2.02–2.03 Å) leading to the presence of infinite chains located along the crystallographic axis *b* (Fig. 3).

The hydrolysis of amide **II** yields compound **IV** where a free amino group is present and a tertiary amino group attached to a benzyl. This combination of functions provides a possibility to carry out a selective successive functionalization of both amine sites opening a new way to unsymmetrically substituted bispidines. Using the known reactivity difference of the secondary amines and secondary alcohols it is possible to effect the selective functionalization of the latter.

Thus we developed a new method of synthesis for diazabicyclononanols with various substituents at the nitrogen atoms and with a fixed hydroxy group configuration in the position *9*. The synthesis of such compounds was before difficult because the selective methods of carbonyl reduction in the unsymmetrically substituted diazabicyclononanes were lacking. This type compounds obviously are promising as possible pharmaceuticals [18]; in particular, compound **V** is used as antiarrhythmic drug Bisaramyl [19].



V

The application of the method we developed to the synthesis of medicinals will be published later.

EXPERIMENTAL

Solvents used in the synthesis were purified by standard procedures [20]. NMR spectra were registered on a spectrometer Varian VXR-400 at operating frequencies 400 (^{1}H) and 100 MHz (^{13}C). The chemical shifts are reported in the δ scale with respect to TMS used as internal reference. Mass spectra were measured on a GC-MS instrument VG-70/70. Single crystals of compound **II** were obtained by crystallization from ethanol. The X-ray diffraction was measured on a diffractometer Enraf-Nonius CAD4 (graphite monochromator, ω-scanning). Crystallographic data, the parameters of the X-ray experiment and of the refining are given in Table 1. The structure was solved by the direct method (SHELXS-86 [21]) and refined by a full-matrix anisotropic least-squares procedure by F^2 (SHELXL-93 [22]). The hydrogen atoms were placed geometrically in the structure and involved into the refinement by the *rider* model.

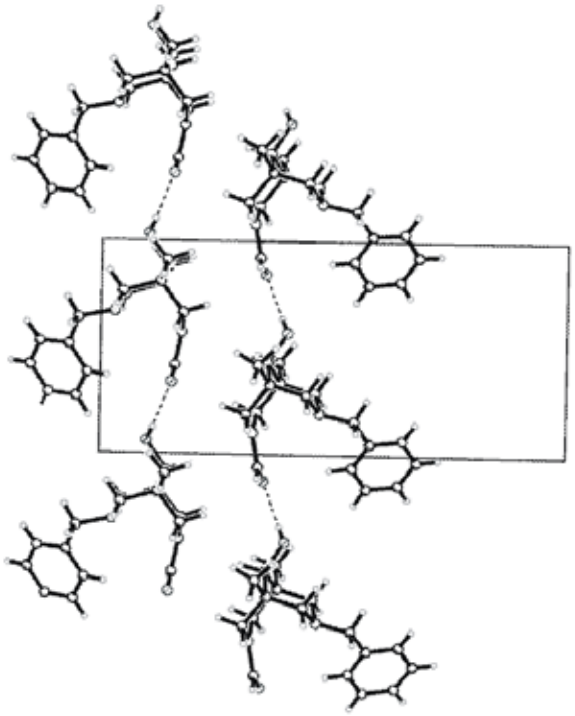


Fig. 3. Arrangement of molecules in the crystal of compound **II**.

1-Benzyl-5,7-dimethyl-6-oxo-1-azonia-3-aza-adamantane chloride (I). In 25 ml of benzene was dissolved 3 g (16.6 mmol) of 5,7-dimethyl-1,3-diaza-adamantan-6-one, 2.11 g(16.6 mmol) of benzyl chloride was added, and the mixture was boiled for 4 h. On cooling the precipitate was filtered off and washed with benzene, then recrystallized from chloroform. Yield 3.55 g (70%), mp 239–242°C (lit.: mp 242–247°C [9]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.97 s (6H, CH_3), 2.91 d (2H, CH_2, ^2J 12.9 Hz), 3.32 d (2H, CH_2, ^2J 11.8 Hz), 3.72 d (1H, CH_2, ^2J 12.9 Hz), 4.71 d (1H, CH_2, ^2J 11.8 Hz), 5.2 s (2H, $PhCH_2$), 5.6 s (2H, NCH_2N), 7.3–7.6 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.3 (CH_3), 45.6 (CH_2Ph), 62.4 (CH_2), 63.7 (C^5, C^7), 64.6 (CH_2), 78.7 (NCH_2N), 125.5, 129.1, 130.6, 133.3 (Ph), 206.4 (C=O).

***anti*-1,5-Dimethyl-7-benzyl-3-formyl-3,7-diaza-bicyclo[3.3.1]nonan-9-ol (II).** Into a solution of 1 g (20 mmol) of KOH in 20 ml of H_2O was placed 1.2 g (3.9 mmol) of compound I, and the mixture was stirred for 12 h. Then it was diluted with water (100 ml) and left standing overnight at 4°C. The separated precipitate was

filtered off, washed with water, and recrystallized from ethanol. Yield 0.46 g (64%). IR spectrum (mull in mineral oil), ν, cm^{-1}: 1660 (C=O), 2870, 2930 (CH), 3320 sh (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 s (3H, CH_3), 0.94 s (3H, CH_3), 2.23 d.d (1H, H^{8a}/H^{6a}, ^2J 11.9, ^4J 2.0 Hz), 2.28 d (1H, H^{8e}/H^{6e}, ^2J 11.9 Hz), 2.35 d.d (1H, H^{6a}/H^{8a}, ^2J 11.2, ^4J 2.0 Hz), 2.52 d.d (1H, H^{4a}, ^2J 13.2, ^4J 2.1 Hz), 2.57 d (1H, H^{6e}/H^{8e}, ^2J 11.3 Hz), 2.59 d (1H, OH, ^3J 4 Hz), 3.01 d.d (1H, H^{2a}, ^2J 13.2, ^4J 1.9 Hz), 3.09 d (1H, $PhCH_2$, ^2J 12.7 Hz), 3.25 d (1H, CHOH, ^3J 4 Hz), 3.35 d.d (1H, H^{2e}, ^2J 12.8, ^4J 1.6 Hz), 3.48 d (1H, $PhCH_2$, ^2J 12.7 Hz), 4.38 d.d (1H, H^{4e}, ^2J 12.8, ^4J 1.6 Hz), 7.24–7.33 m (5H, Ph), 7.91 s (1H, HCON). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0, 21.2 (CH_3), 35.7, 36.0 (CMe), 50.2, 56.7, 56.8, 58.1, 63.2 (CH_2), 78.5 (CHOH), 127.0, 128.2, 129.1, 138.5 (Ph), 162.1 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 288 (73) $[M]^+$, 197 (86), 157 (65), 108 (82), 91 (100) (tropylium cation). Found, %: C 70.42; H 8.34; N 9.66. $C_{17}H_{24}N_2O_2$. Calculated, %: C 70.33; H 8.36; N 9.55.

7-Benzyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]-nonan-9-one (III). In 30 ml of $CHCl_3$ was dissolved 3.3 g (10.8 mmol) of compound **I**, 20 ml of water was added, and at vigorous stirring was added within 40 min a solution of 0.6 g (10.7 mmol) of KOH in 10 ml of H_2O. On completing the KOH addition the reaction mixture was stirred for 20 min. Then the organic layer was separated, the reaction product was extracted from the water layer with 20 ml of $CHCl_3$, the extract was washed with water (20 ml), dried with Na_2SO_4, evaporated, and the residue was recrystallized from ethanol. Yield 1.35 g (48%). IR spectrum (mull in mineral oil), ν, cm^{-1}: 1715 (C=O), 2860–2980 (CH), 3325 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 s (6H, CH_3), 2.38 d (2H, CH_2, ^2J 11.2 Hz), 2.82 d (2H, CH_2, ^2J 13.5 Hz), 3.11 d (2H, CH_2, ^2J 11.2 Hz), 3.30 d (2H, CH_2, ^2J 13.5 Hz), 3.39 s (2H, $PhCH_2$), 3.7 br.s (1H, OH/NH), 7.2–7.4 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.1 (CH_3), 48.9 (CH_2Ph), 62.2 (CMe), 63.2, 66.5 (CH_2), 127.4, 128.6, 128.7, 137.7 (Ph), 215.1 (C=O).

***syn*-7-Benzyl-1,5-dimethyl-3,7-diazabicyclo-[3.3.1]nonan-9-ol (IV).** In 10 ml of concn. HCl was dissolved 0.29 g (1 mmol) of compound **II**, and the mixture was left overnight. Then the solution was neutralized with KOH and cooled to 0°C, the separated precipitate was filtered off and dried in a vacuum. Yield 0.26 g (99%). IR spectrum (mull in mineral oil), ν, cm^{-1}: 2860–2980 (CH), 3315 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.75 s (6H, CH_3), 1.83 br.s (1H, OH/NH), 2.36 d.d (2H, CH_2, ^2J 11.4, ^4J 3.0 Hz), 2.47 d (2H, CH_2, ^2J 11.2 Hz), 2.54 d (2H, CH_2, ^2J 13.8 Hz), 2.87 d (2H, CH_2, ^2J 13.8 Hz), 3.21 s (1H, CH), 3.33 s (2H, $PhCH_2$), 3.7 br.s (1H, OH/NH), 7.2–7.4 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.9 (CH_3), 36.3 (C^5, C^7), 58.2 (CH_2), 59.6 (CH_2), 63.5 (CH_2Ph), 78.8 (CH), 127.0, 128.4, 128.7, 138.7 (Ph) (C=O).

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