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Synthesis and Properties of 3-Substituted 3-Azabicyclo-[3.3.1]nonan-9-amines

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Abstract—Catalytic hydrogenation of 3-benzyl- and 3-*tert*-butoxycarbonyl-3-azabicyclo[3.3.1]nonan-9-one oximes over Raney nickel gave the corresponding 3-substituted 3-azabicyclo[3.3.1]nonan-9-amines which were converted into amides via reactions with acetyl and chloroacetyl chlorides and maleic and succinic anhydrides, into Schiff bases by condensation with benzaldehyde and 4-chlorobenzaldehyde, and into isothiocyanates by treatment with thiophosgene in the presence of K_2CO_3. 3-Benzyl- and 3-*tert*-butoxycarbonyl-3-azabicyclo-[3.3.1]nonan-9-yl isothiocyanates readily reacted with methanol, aniline, and sodium azide to produce methyl thiocarbamate, thiourea, and dihydrotetrazole-5-thione derivatives having a 3-azabicyclo[3.3.1]nonane fragment.

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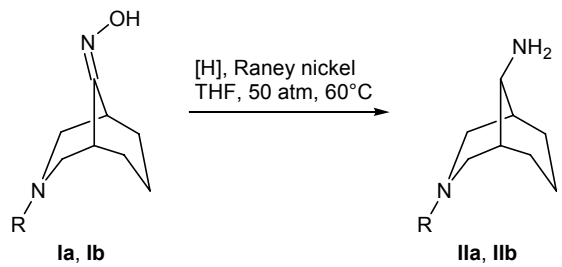
In continuation of our studies on 3-azabicyclo-[3.3.1]nonane derivatives [1, 2] as potential biologically active compounds [3], in the present work we synthesized for the first time some 3-substituted 3-azabicyclo[3.3.1]nonan-9-amines having a primary amino group and obtained a number of their derivatives at the amino group. The optimal procedure for the synthesis of 3-azabicyclo[3.3.1]nonan-9-amines **IIa** and **IIb** is catalytic reduction of the corresponding accessible 3-azabicyclo[3.3.1]nonan-9-one oximes **Ia** and **Ib** [2] with hydrogen over Raney nickel. This procedure ensured smooth formation of target amines **IIa** and **IIb** in 73–76% yield (Scheme 1).

Scheme 1.



Ia, **Ib** **IIa**, **IIb**

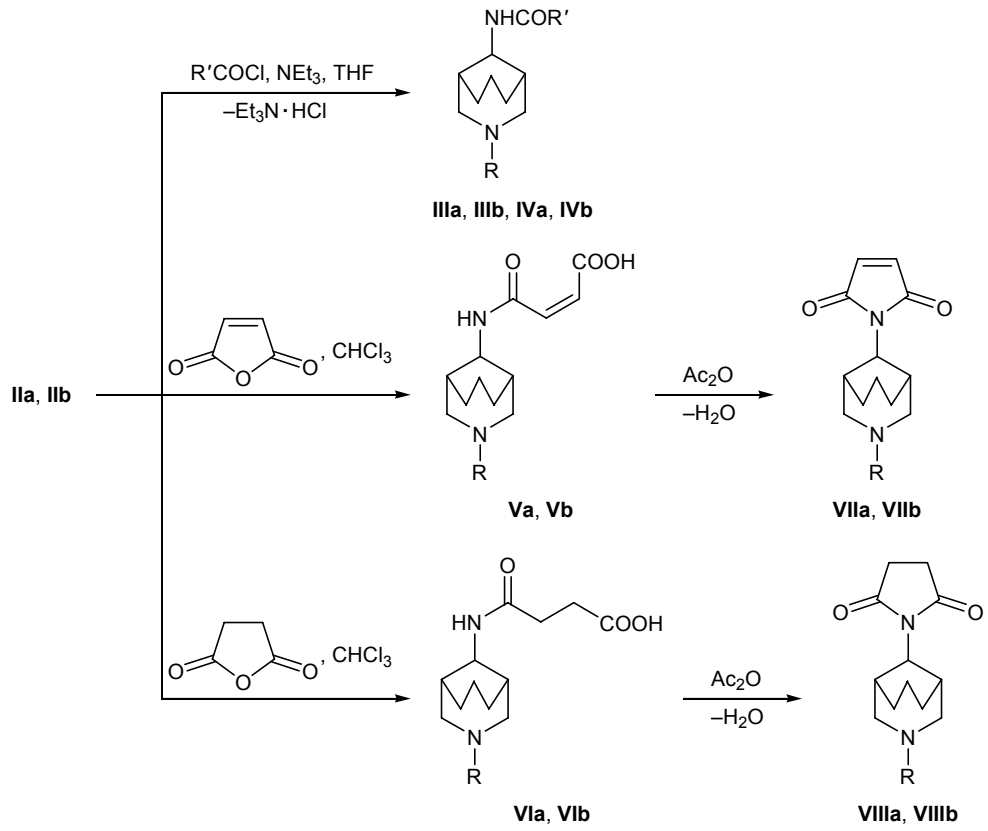
R = $PhCH_2$ (**a**), *t*-BuOC(O) (**b**).

The purity and structure of compounds **IIa** and **IIb** were confirmed by their elemental analyses and IR, ^{1}H NMR, and mass spectra (GC–MS). The IR spectra of **IIa** and **IIb** contained absorption bands in the region 3370–3360 cm^{-1} due to stretching vibrations of N–H bonds. In the ^{1}H NMR spectra of **IIa** and **IIb**, the NH_2 protons resonated as a broadened singlet at δ 4.23 ppm, and a new signal appeared in the region δ 3.62–3.80 ppm due to 9-H (no such signal was observed in the spectra of the initial compounds).

Diverse chemical transformations of amines **IIa** and **IIb** provided additional proofs for their structure and demonstrated wide potential of their application in organic synthesis for the preparation of new compounds having an azabicyclic fragment. Amines **IIa** and **IIb** readily reacted with acetyl and chloroacetyl chlorides in the presence of triethylamine, as well as with maleic and succinic anhydrides on heating in anhydrous chloroform. As a result, N-substituted amides **III**–**VI** were obtained. Maleamic and succinamic acid derivatives **Va**, **Vb**, **VIa**, and **VIb** were subjected to intramolecular cyclization on heating in acetic anhydride. We thus isolated the corresponding *N*-substituted maleimides **VIIa** and **VIIb** and succinamides **VIIIa** and **VIIIb** (Scheme 2).

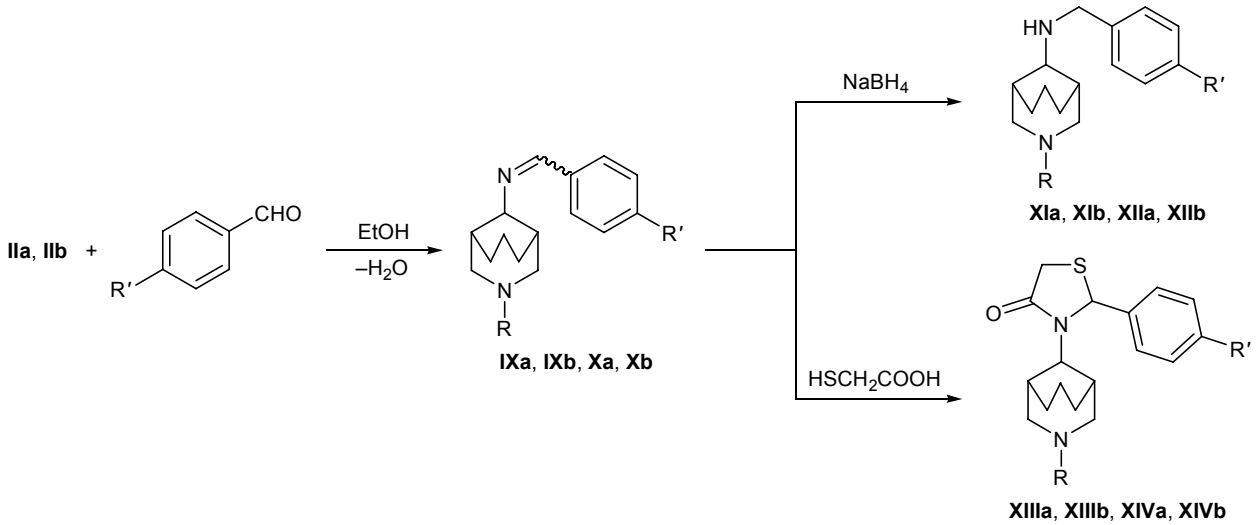
Schiff bases **IXa**, **IXb**, **Xa**, and **Xb** were synthesized by condensation of amines **IIa** and **IIb** with benzaldehyde and 4-chlorobenzaldehyde on heating in boiling anhydrous ethanol. Compounds **IXa**, **IXb**, **Xa**, and **Xb** are promising as intermediate products in organic synthesis. Their reduction with sodium tetrahydridoborate afforded secondary aromatic amines

Scheme 2.



R = $PhCH_2$ (**a**), *t*-BuOC(O) (**b**); **III**, Me; **IV**, R′ = $ClCH_2$.

Scheme 3.

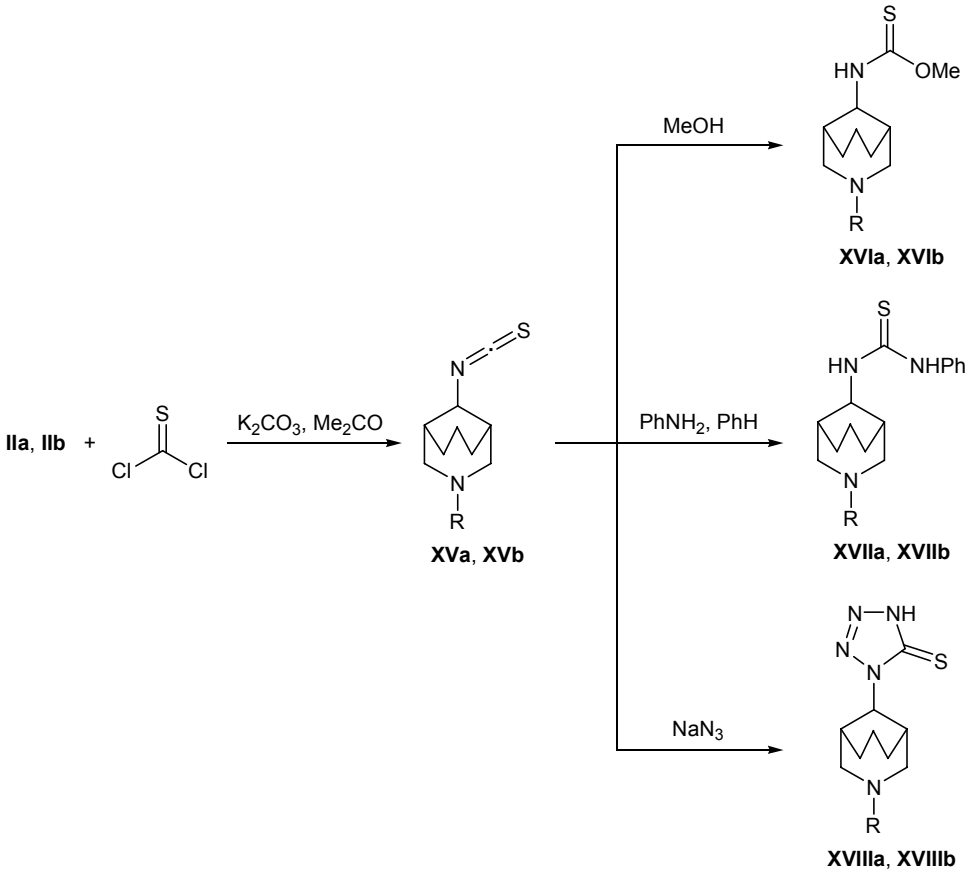


R = $PhCH_2$ (**a**), *t*-BuOC(O) (**b**); **IX**, **XI**, **XIII**, R′ = H; **X**, **XII**, **XIV**, R′ = Cl.

XIa, **XIb**, **XIIa**, **XIIb**, and the reaction with 2-sulfanylacetic acid in boiling anhydrous benzene led to the formation of bicyclic thiazolidin-4-one derivatives **XIIIa**, **XIIIb**, **XIVa**, and **XIVb** (Scheme 3).

An important synthetic transformation of primary amino group is achieved via reaction with thiophosgene. In such a way we obtained bicyclic isothiocyanates **XVa** and **XVb**. As might be expected, com-

Scheme 4.



R = $PhCH_2$ (**a**), *t*-BuOC(O) (**b**).

pounds **XVa** and **XVb** turned out to be highly reactive toward various nucleophiles. By heating isothiocyanates **XVa** and **XVb** in anhydrous methanol we synthesized methyl thiocarbamates **XVIa** and **XVIb** in quantitative yield; the reaction of **XVa** and **XVb** with aniline in boiling anhydrous benzene gave thiourea derivatives **XVIIa** and **XVIIb**, and treatment of the same substrates with sodium azide in water afforded 1-substituted dihydrotetrazole-5-thiones **XVIIIa** and **XVIIIb** (Scheme 4).

Compounds **IIb**–**XVIIIb** having a *tert*-butoxycarbonyl group (Boc) on the nitrogen atom were readily deprotected by treatment with a saturated solution of hydrogen chloride in anhydrous dioxane to produce the corresponding 3-azabicyclo[3.3.1]nonane derivatives having no substituent on N^3 as hydrochlorides. Analogous water-soluble hydrochlorides were obtained from compounds **IIa**–**XVIIIa** with conservation of the initial structure.

The structure of the newly synthesized compounds was confirmed by analytical and spectral data. Due to the presence of highly reactive functional groups the products may be used to create combinatorial libraries with a view to perform broader biological screening.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The ^1H NMR spectra were measured on a Varian Mercury Plus-400 spectrometer (400 MHz) from solutions in $CDCl_3$ using hexamethyldisiloxane as internal reference. The mass spectra (atmospheric pressure chemical ionization) were obtained on a Thermo Finnigan Surveyor MSQ GC–MS instrument (USA). The purity of the isolated compounds was checked by thin-layer chromatography on Silufol UV-254 plates using hexane–ethyl acetate (1 : 1) as eluent; spots were visualized under UV light or by treatment with iodine vapor.

3-Benzyl-3-azabicyclo[3.3.1]nonan-9-amine (IIa). A high-pressure reactor was charged with 24.4 g (0.1 mol) of oxime **Ia** [2] and 10 g of Raney nickel in 250 ml of anhydrous THF, and hydrogen was supplied

at a pressure of 50 atm at 60°C over a period of 10 h until the initial oxime disappeared (according to the TLC data) and hydrogen was no longer absorbed. The catalyst was filtered off and washed with 100 ml of THF, the filtrate was evaporated under reduced pressure, and the oily residue was dissolved in ethyl acetate and purified by chromatography on silica gel using ethyl acetate–hexane (1:1) as eluent. Yield 16.82 g (73%), mp 66–68°C. IR spectrum, ν, cm^{-1}: 3369, 3358 (NH_2). ^1H NMR spectrum, δ, ppm: 1.36–2.05 m (6H, CH_2), 2.12–2.21 m (2H, CH), 2.78 d (2H, NCH_2), 2.85 d (2H, NCH_2), 3.35 s (2H, PhC**H**$_2$), 3.74 m (1H, 9-H), 4.24 br.s (2H, NH_2), 7.04–7.18 m (5H, C_6H_5). Mass spectrum: *m/z* 231 $[M + H]^+$. Found, %: C 78.13; H 9.45; N 12.08. $C_{15}H_{22}N_2$. Calculated, %: C 78.26; H 9.57; N 12.17. *M* 230.

***tert*-Butyl 9-amino-3-azabicyclo[3.3.1]nonane-3-carboxylate (IIb)** was synthesized in a similar way. Yield 71%, mp 87–90°C. IR spectrum, ν, cm^{-1}: 3365, 3351 (NH_2); 1684 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.46–2.12 m (6H, CH_2), 2.36–2.42 m (2H, CH), 3.42 d (2H, NCH_2), 3.60 d (2H, NCH_2), 3.81 m (1H, 9-H), 4.25 br.s (2H, NH_2). Mass spectrum, *m/z*: 241 $[M + H]^+$, 140 $[M - 101 + H]^+$. Found, %: C 64.83; H 10.14; N 11.52. $C_{13}H_{24}N_2O_2$. Calculated, %: C 65.00; H 10.00; N 11.67. *M* 240.

***N*-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)acetamide (IIIa).** A solution of 0.47 g (6 mmol) of acetyl chloride in 5 ml of methylene chloride was added under stirring at 0–5°C to a solution of 1.15 g (5 mmol) of amine **IIa** and 0.6 g (6 mmol) of triethylamine in 20 ml of anhydrous methylene chloride. The mixture was then allowed to warm up to room temperature, stirred for 1 h until the initial amine disappeared completely (TLC), and poured into 100 ml of water. The organic phase was separated, the aqueous phase was extracted with methylene chloride (2×30 ml), the extracts were combined with the organic phase and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The oily residue crystallized on storage and was recrystallized from hexane–ethyl acetate (4:1). Yield 1.27 g (93%), mp 101–103°C. IR spectrum, ν, cm^{-1}: 3396 (NH), 1697 (C=O). ^1H NMR spectrum, δ, ppm: 1.38–2.06 m (6H, CH_2), 1.98 s (3H, CH_3), 2.14–2.24 m (2H, CH), 2.81 d (2H, NCH_2), 2.87 d (2H, NCH_2), 3.39 s (2H, PhC**H**$_2$), 3.87 m (1H, 9-H), 6.94 br.s (2H, NH_2), 7.10–7.23 m (5H, C_6H_5). Mass spectrum: *m/z* 273 $[M + H]^+$. Found, %: C 75.18; H 8.67; N 10.42. $C_{17}H_{24}N_2O$. Calculated, %: C 75.00; H 8.82; N 10.29. *M* 272.

Compounds **IIIb**, **IVa**, and **IVb** were synthesized in a similar way.

***tert*-Butyl 9-acetylamino-3-azabicyclo[3.3.1]-nonane-3-carboxylate (IIIb).** Yield 92%, mp 135–137°C. IR spectrum, ν, cm^{-1}: 3401 (NH); 1698, 1683 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.46–2.14 m (6H, CH_2), 2.03 s (3H, CH_3), 2.35–2.42 m (2H, CH), 3.41 d (2H, NCH_2), 3.61 d (2H, NCH_2), 3.98 m (1H, 9-H), 7.01 br.s (1H, NH). Mass spectrum, *m/z*: 283 $[M + H]^+$, 182 $[M - 101 + H]^+$. Found, %: C 63.71; H 9.36; N 9.81. $C_{15}H_{26}N_2O_3$. Calculated, %: C 63.83; H 9.22; N 9.93. *M* 282.

***N*-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)-2-chloroacetamide (IVa).** Yield 90%, mp 114–116°C. IR spectrum, ν, cm^{-1}: 3398 (NH), 1698 (C=O). ^1H NMR spectrum, δ, ppm: 1.38–2.05 m (6H, CH_2), 2.15–2.24 m (2H, CH), 2.83 d (2H, NCH_2), 2.89 d (2H, NCH_2), 3.41 s (2H, PhC**H**$_2$), 3.85 m (1H, 9-H), 4.45 s (2H, CH_2Cl), 6.97 br.s (1H, NH), 7.11–7.24 m (5H, C_6H_5). Mass spectrum: *m/z* 307 $[M + H]^+$. Found, %: C 66.38; H 7.42; N 9.26. $C_{17}H_{23}ClN_2O$. Calculated, %: C 66.56; H 7.50; N 9.14. *M* 306.

***tert*-Butyl 9-(chloroacetylamino)-3-azabicyclo-[3.3.1]nonane-3-carboxylate (IVb).** Yield 87%, mp 128–130°C. IR spectrum, ν, cm^{-1}: 3402 (NH); 1701, 1684 (C=O). ^1H NMR spectrum, δ, ppm: 1.32 s (9H, *t*-Bu), 1.47–2.15 m (6H, CH_2), 2.36–2.44 m (2H, CH), 3.42 d (2H, NCH_2), 3.60 d (2H, NCH_2), 4.01 m (1H, 9-H), 4.48 s (2H, CH_2Cl), 7.03 br.s (1H, NH). Mass spectrum, *m/z*: 317 $[M + H]^+$, 216 $[M - 101 + H]^+$. Found, %: C 56.71; H 7.69; N 8.74. $C_{15}H_{25}ClN_2O_3$. Calculated, %: C 56.87; H 7.90; N 8.85. *M* 316.

4-(3-Benzyl-3-azabicyclo[3.3.1]non-9-ylamino)-4-oxobut-2-enoic acid (Va). Maleic anhydride, 0.216 g (2.2 mmol), was added to a solution of 0.5 g (2.2 mmol) of amine **IIa** in 5 ml of anhydrous chloroform, and the mixture was heated for 1 h under reflux until the initial amine disappeared completely (TLC). The solvent was removed under reduced pressure, and the residue was recrystallized from hexane–ethyl acetate (1:1). Yield 0.46 g (64%), mp 116–117°C. IR spectrum, ν, cm^{-1}: 3482 (OH); 3404 (NH); 1728, 1719 (C=O); 1622 (C=C). ^1H NMR spectrum, δ, ppm: 1.38–2.07 m (6H, CH_2), 2.09–2.24 m (2H, CH), 2.93 d (2H, NCH_2), 3.05 d (2H, NCH_2), 3.41 s (2H, PhC**H**$_2$), 3.89 m (1H, 9′-H), 6.05 d (1H, 3-H, J = 15.1 Hz), 6.74 d (1H, 2-H, J = 15.1 Hz), 6.98 br.s (1H, NH), 7.12–7.26 m (5H, C_6H_5), 11.78 br.s (1H, COOH). Mass spectrum: *m/z* 329 $[M + H]^+$. Found, %: C 69.38; H 7.36; N 8.31. $C_{19}H_{24}N_2O_3$. Calculated, %: C 69.51; H 7.32; N 8.54. *M* 328.

Compounds **Vb**, **VIa**, and **VIb** were synthesized in a similar way.

4-(3-*tert*-Butoxycarbonyl-3-azabicyclo[3.3.1]non-9-ylamino)-4-oxobut-2-enoic acid (Vb). Yield 69%, mp 131–132°C. IR spectrum, ν, cm^{-1}: 3483 (OH); 3402 (NH); 1726, 1708, 1685 (C=O); 1622 (C=C). ^1H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 1.47–2.16 m (6H, CH_2), 2.36–2.44 m (2H, CH), 3.43 d (2H, NCH_2), 3.62 d (2H, NCH_2), 3.97 m (1H, 9′-H), 6.05 d (1H, 3-H, J = 14.9 Hz), 6.75 d (1H, 2-H, J = 14.9 Hz), 6.98 br.s (1H, NH), 11.83 br.s (1H, COOH). Mass spectrum, m/z: 339 $[M + H]^+$, 238 $[M - 101 + H]^+$. Found, %: C 60.43; H 7.74; N 8.16. $C_{17}H_{26}N_2O_5$. Calculated, %: C 60.36; H 7.69; N 8.28. M 338.

4-(3-Benzyl-3-azabicyclo[3.3.1]non-9-ylamino)-4-oxobutanoic acid (VIa). Yield 74%, mp 121–122°C. IR spectrum, ν, cm^{-1}: 3486 (OH); 3401 (NH); 1726, 1713 (C=O). ^1H NMR spectrum, δ, ppm: 1.36–2.08 m (6H, CH_2), 2.10–2.23 m (2H, CH), 2.42–2.73 m (4H, CH_2CH_2), 2.95 d (2H, NCH_2), 3.06 d (2H, NCH_2), 3.42 s (2H, PhC**H**$_2$), 3.89 m (1H, 9′-H), 6.97 br.s (1H, NH), 7.10–7.24 m (5H, C_6H_5), 12.02 br.s (1H, COOH). Mass spectrum: m/z 331 $[M + H]^+$. Found, %: C 68.82; H 7.64; N 8.53. $C_{19}H_{26}N_2O_3$. Calculated, %: C 69.09; H 7.88; N 8.48. M 330.

4-(3-*tert*-Butoxycarbonyl-3-azabicyclo[3.3.1]non-9-ylamino)-4-oxobutanoic acid (VIb). Yield 76%, mp 141–142°C. IR spectrum, ν, cm^{-1}: 3485 (OH); 3398 (NH); 1727, 1712, 1686 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.46–2.15 m (6H, CH_2), 2.37–2.45 m (2H, CH), 2.48–2.75 m (4H, CH_2CH_2), 3.42 d (2H, NCH_2), 3.62 d (2H, NCH_2), 3.97 m (1H, 9′-H), 7.01 br.s (1H, NH), 12.04 br.s (1H, COOH). Mass spectrum, m/z: 341 $[M + H]^+$, 240 $[M - 101 + H]^+$. Found, %: C 59.91; H 8.33; N 8.17. $C_{17}H_{28}N_2O_5$. Calculated, %: C 60.00; H 8.24; N 8.24. M 340.

1-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)-1*H*-pyrrole-2,5-dione (VIIa). A mixture of 0.5 g (1.5 mmol) of compound **Va**, 0.2 g of anhydrous sodium acetate, and 3 ml of acetic anhydride was heated for 1 h at 100°C (until the initial compound disappeared completely according to the TLC data). The mixture was treated with 10 ml of water and left to stand for 12 h at room temperature, and the precipitate was filtered off, washed with water, and recrystallized from aqueous ethanol. Yield 0.36 g (77%), mp 102–103°C. IR spectrum, ν, cm^{-1}: 1722, 1718 (C=O); 1620 (C=C). ^1H NMR spectrum, δ, ppm: 1.35–2.06 m (6H, CH_2), 2.07–2.25 m (2H, CH), 2.94 d (2H, NCH_2), 3.04 d (2H, NCH_2), 3.42 s (2H, PhC**H**$_2$), 3.87 m (1H, 9′-H), 5.98 d (2H, CH=CH, J = 12.3 Hz), 7.08–7.18 m (5H, C_6H_5). Mass spectrum: m/z 311 $[M + H]^+$. Found, %: C 73.46; H 7.16; N 8.85. $C_{19}H_{22}N_2O_2$. Calculated, %: C 73.55; H 7.10; N 9.03. M 310.

Compounds **VIIb**, **VIIIa**, and **VIIIb** were synthesized in a similar way.

***tert*-Butyl 9-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-3-azabicyclo[3.3.1]nonane-3-carboxylate (VIIb).** Yield 79%, mp 121–122°C. IR spectrum, ν, cm^{-1}: 1724, 1720, 1688 (C=O); 1621 (C=C). ^1H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 1.48–2.17 m (6H, CH_2), 2.35–2.46 m (2H, CH), 3.42 d (2H, NCH_2), 3.64 d (2H, NCH_2), 3.98 m (1H, 9′-H), 6.04 d (2H, CH=CH, J = 12.5 Hz). Mass spectrum, m/z: 321 $[M + H]^+$, 220 $[M - 101 + H]^+$. Found, %: C 63.57; H 7.58; N 8.61. $C_{17}H_{24}N_2O_4$. Calculated, %: C 63.75; H 7.50; N 8.75. M 320.

1-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)pyrrolidine-2,5-dione (VIIIa). Yield 69%, mp 98–100°C. IR spectrum, ν, cm^{-1}: 1725, 1710 (C=O). ^1H NMR spectrum, δ, ppm: 1.35–2.05 m (6H, CH_2), 2.11–2.34 m (6H, CH, CH_2CH_2), 2.97 d (2H, NCH_2), 3.08 d (2H, NCH_2), 3.43 s (2H, PhC**H**$_2$), 3.88 m (1H, 9-H), 7.12–7.25 m (5H, C_6H_5). Mass spectrum: m/z 313 $[M + H]^+$. Found, %: C 73.18; H 7.56; N 8.74. $C_{19}H_{24}N_2O_2$. Calculated, %: C 73.08; H 7.69; N 8.97. M 312.

***tert*-Butyl 9-(2,5-dioxopyrrolidin-1-yl)-3-azabicyclo[3.3.1]nonane-3-carboxylate (VIIIb).** Yield 74%, mp 110–112°C. IR spectrum, ν, cm^{-1}: 1726, 1711, 1687 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.47–2.15 m (6H, CH_2), 2.17–2.28 m (4H, CH_2CH_2), 2.38–2.46 m (2H, CH), 3.43 d (2H, NCH_2), 3.64 d (2H, NCH_2), 4.01 m (1H, 9-H). Mass spectrum, m/z: 323 $[M + H]^+$, 222 $[M - 101 + H]^+$. Found, %: C 63.52; H 7.94; N 8.73. $C_{17}H_{26}N_2O_4$. Calculated, %: C 63.35; H 8.07; N 8.70. M 322.

3-Benzyl-*N*-benzylidene-3-azabicyclo[3.3.1]-nonan-9-amine (IXa). A solution of 0.24 g (2.2 mmol) of freshly distilled benzaldehyde in 3 ml of anhydrous ethanol was added under stirring to a solution of 0.5 g (2.2 mmol) of amine **IIa** in 5 ml of anhydrous ethanol. The mixture was heated for 12 h under reflux with stirring, the solvent was distilled off under reduced pressure, and the residue was dissolved in hexane–ethyl acetate (3:1) and purified by column chromatography on silica gel. Yield 0.48 g (69%), oily substance. IR spectrum: ν 1608 cm^{-1} (C=N). ^1H NMR spectrum, δ, ppm: 1.39–2.08 m (6H, CH_2), 2.17–2.26 m (2H, CH), 2.82 d (2H, NCH_2), 2.93 d (2H, NCH_2), 3.41 s

(2H, PhC**H**$_2$), 3.95 m (1H, 9-H), 6.78 s (1H, N=CH), 7.00–7.43 m (10H, C_6H_5). Mass spectrum: *m*/*z* 319 [*M* + H]$^+$. Found, %: C 82.91; H 8.03; N 8.74. $C_{22}H_{26}N_2$. Calculated, %: C 83.02; H 8.18; N 8.81. *M* 318.

Compounds **IXb**, **Xa**, and **Xb** were synthesized in a similar way.

***tert*-Butyl 9-benzylideneamino-3-azabicyclo-[3.3.1]nonane-3-carboxylate (IXb).** Yield 70%, mp 74–76°C. IR spectrum, ν, cm^{-1}: 1684 (C=O), 1608 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 1.46–2.10 m (6H, CH_2), 2.37–2.45 m (2H, CH), 3.42 d (2H, NCH_2), 3.62 d (2H, NCH_2), 3.98 m (1H, 9-H), 6.81 s (1H, N=CH), 7.02–7.21 m (5H, C_6H_5). Mass spectrum, *m*/*z*: 329 [*M* + H]$^+$, 228 [*M* – 101 + H]$^+$. Found, %: C 73.26; H 8.48; N 8.39. $C_{20}H_{28}N_2O_2$. Calculated, %: C 73.17; H 8.54; N 8.54. *M* 328.

3-Benzyl-*N*-(4-chlorobenzylidene)-3-azabicyclo-[3.3.1]nonan-9-amine (Xa). Yield 73%, mp 51–53°C. IR spectrum: ν 1610 cm^{-1} (C=N). ^{1}H NMR spectrum, δ, ppm: 1.38–2.09 m (6H, CH_2), 2.18–2.27 m (2H, CH), 2.85 d (2H, NCH_2), 2.97 d (2H, NCH_2), 3.45 s (2H, PhC**H**$_2$), 3.98 m (1H, 9-H), 6.84 s (1H, N=CH), 7.18–7.82 m (9H, H_{arom}). Mass spectrum: *m*/*z* 353 [*M* + H]$^+$. Found, %: C 74.67; H 7.01; N 7.82. $C_{22}H_{25}ClN_2$. Calculated, %: C 74.89; H 7.09; N 7.94. *M* 352.5.

***tert*-Butyl 9-(4-chlorobenzylideneamino)-3-azabicyclo[3.3.1]nonane-3-carboxylate (Xb).** Yield 78%, mp 88–90°C. IR spectrum, ν, cm^{-1}: 1685 (C=O), 1610 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.32 s (9H, *t*-Bu), 1.48–2.12 m (6H, CH_2), 2.41–2.48 m (2H, CH), 3.45 d (2H, NCH_2), 3.71 d (2H, NCH_2), 4.03 m (1H, 9-H), 6.95 s (1H, N=CH), 7.42–7.84 m (4H, C_6H_4). Mass spectrum, *m*/*z*: 363 [*M* + H]$^+$, 262 [*M* – 101 + H]$^+$. Found, %: C 66.13; H 7.52; N 7.64. $C_{20}H_{27}ClN_2O_2$. Calculated, %: C 66.21; H 7.45; N 7.72. *M* 362.5.

***N*,3-Dibenzyl-3-azabicyclo[3.3.1]nonan-9-amine (XIa).** Sodium tetrahydridoborate, 0.1 g (2.7 mmol), was added to a solution of 0.64 g (2 mmol) of Schiff base **IXa** in 20 ml of a 1:1 mixture of anhydrous methanol and tetrahydrofuran, and the mixture was stirred for 5 h, poured into 50 ml of water, and extracted with ethyl acetate (2×30 ml). The combined extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the oily residue was dissolved in hexane–ethyl acetate (3:1) and purified by column chromatography on silica gel. Yield 0.52 g (81%), oily substance. IR spectrum: ν 3352 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 1.32–2.04 m (6H, CH_2), 2.15–2.23 m (2H, CH), 2.80 d (2H, NCH_2), 2.90 d (2H, NCH_2), 3.38 s (2H, PhC**H**$_2$), 3.93 m (1H, 9-H), 4.98 s (2H, NHC**H**$_2$), 5.24 br.s (1H, NH), 7.02–7.34 m (10H, C_6H_5). Mass spectrum: *m*/*z* 321 [*M* + H]$^+$. Found, %: C 82.35; H 8.64; N 8.57. $C_{22}H_{28}N_2$. Calculated, %: C 82.50; H 8.75; N 8.75. *M* 320.

Compounds **XIb**, **XIIa**, and **XIIb** were synthesized in a similar way.

***tert*-Butyl 9-benzylamino-3-azabicyclo[3.3.1]-nonane-3-carboxylate (XIb).** Yield 80%, mp 56–57°C. IR spectrum, ν, cm^{-1}: 3354 (NH), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.46–2.12 m (6H, CH_2), 2.34–2.42 m (2H, CH), 3.40 d (2H, NCH_2), 3.60 d (2H, NCH_2), 3.94 m (1H, 9-H), 5.08 s (2H, PhC**H**$_2$), 5.36 br.s (1H, NH), 7.05–7.21 m (5H, C_6H_5). Mass spectrum, *m*/*z*: 331 [*M* + H]$^+$, 230 [*M* – 101 + H]$^+$. Found, %: C 72.78; H 8.93; N 8.39. $C_{20}H_{30}N_2O_2$. Calculated, %: C 72.73; H 9.09; N 8.48. *M* 330.

3-Benzyl-*N*-(4-chlorobenzyl)-3-azabicyclo[3.3.1]-nonan-9-amine (XIIa). Yield 80%, oily substance. IR spectrum: ν 3358 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 1.35–2.08 m (6H, CH_2), 2.13–2.25 m (2H, CH), 2.84 d (2H, NCH_2), 2.95 d (2H, NCH_2), 3.42 s (2H, PhC**H**$_2$), 3.95 m (1H, 9-H), 5.08 s (2H, C_6H_4C**H**$_2$), 5.25 br.s (1H, NH), 7.16–7.80 m (9H, H_{arom}). Mass spectrum: *m*/*z* 355 [*M* + H]$^+$. Found, %: C 74.32; H 7.55; N 7.78. $C_{22}H_{27}ClN_2$. Calculated, %: C 74.47; H 7.62; N 7.90. *M* 354.5.

***tert*-Butyl 9-(4-chlorobenzylamino)-3-azabicyclo-[3.3.1]nonane-3-carboxylate (XIIb).** Yield 77%, mp 73–74°C. IR spectrum, ν, cm^{-1}: 3356 (NH), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.42–2.09 m (6H, CH_2), 2.32–2.41 m (2H, CH), 3.44 d (2H, NCH_2), 3.65 d (2H, NCH_2), 3.95 m (1H, 9-H), 5.12 s (2H, C_6H_4C**H**$_2$), 5.38 br.s (1H, NH), 7.38–7.79 m (4H, C_6H_4). Mass spectrum, *m*/*z*: 365 [*M* + H]$^+$, 264 [*M* – 101 + H]$^+$. Found, %: C 65.71; H 7.98; N 7.43. $C_{20}H_{29}ClN_2O_2$. Calculated, %: C 65.84; H 7.96; N 7.68. *M* 364.5.

3-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)-2-phenyl-1,3-thiazolidin-4-one (XIIIa). A mixture of 0.64 g (2 mmol) of Schiff base **IXa** and 0.2 g (2.2 mmol) of sulfanylacetic acid in 20 ml of anhydrous benzene was heated for 10 h under reflux with stirring. The solvent was removed under reduced pressure, the residue was treated with hot hexane, and the precipitate was filtered off and recrystallized from aqueous ethanol (1:2). Yield 0.38 g (49%), mp 164–166°C. IR spectrum: ν 1705 cm^{-1} (C=O). ^{1}H NMR

spectrum, δ, ppm: 1.38–2.09 m (6H, CH_2), 2.18–2.25 m (2H, CH), 2.84 d (2H, NCH_2), 2.95 d (2H, NCH_2), 3.41 s (2H, PhC**H**$_2$), 3.96 m (1H, 9-H), 4.10 s (2H, CH_2S), 6.24 s (1H, SCHN), 7.04–7.46 m (10H, C_6H_5). Mass spectrum: *m*/*z* 393 $[M + H]^+$. Found, %: C 73.22; H 6.85; N 7.04. $C_{24}H_{28}N_2OS$. Calculated, %: C 73.47; H 7.14; N 7.14. *M* 392.

Compounds **XIIIb**, **XIVa**, and **XIVb** were synthesized in a similar way.

***tert*-Butyl 9-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-3-azabicyclo[3.3.1]nonane-3-carboxylate (XIIIb).** Yield 52%, mp 183–185°C. IR spectrum, ν, cm^{-1}: 1705, 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 1.45–2.12 m (6H, CH_2), 2.36–2.47 m (2H, CH), 3.44 d (2H, NCH_2), 3.65 d (2H, NCH_2), 3.96 m (1H, 9-H), 4.12 s (2H, CH_2S), 6.28 s (1H, SCHN), 7.14–7.39 m (5H, C_6H_5). Mass spectrum, *m*/*z*: 403 $[M + H]^+$, 302 $[M - 101 + H]^+$. Found, %: C 65.71; H 7.35; N 6.92. $C_{22}H_{30}N_2O_3S$. Calculated, %: C 65.67; H 7.46; N 6.97. *M* 402.

3-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (XIVa). Yield 46%, mp 178–180°C. IR spectrum, ν, cm^{-1}: 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.37–2.09 m (6H, CH_2), 2.19–2.27 m (2H, CH), 2.86 d (2H, NCH_2), 2.96 d (2H, NCH_2), 3.41 s (2H, PhC**H**$_2$), 3.97 m (1H, 9-H), 4.10 s (2H, CH_2S), 6.26 s (1H, SCHN), 7.03–7.48 m (9H, H_{arom}). Mass spectrum: *m*/*z* 427 $[M + H]^+$. Found, %: C 67.28; H 6.29; N 6.34. $C_{24}H_{27}ClN_2OS$. Calculated, %: C 67.53; H 6.33; N 6.57. *M* 426.5.

***tert*-Butyl 9-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-3-azabicyclo[3.3.1]nonane-3-carboxylate (XIVb).** Yield 47%, mp 185–186°C. IR spectrum, ν, cm^{-1}: 1705, 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 1.46–2.14 m (6H, CH_2), 2.35–2.46 m (2H, CH), 3.46 d (2H, NCH_2), 3.68 d (2H, NCH_2), 3.97 m (1H, 9-H), 4.12 s (2H, CH_2S), 6.28 s (1H, SCHN), 7.43–7.84 m (4H, C_6H_4). Mass spectrum, *m*/*z*: 437 $[M + H]^+$, 336 $[M - 101 + H]^+$. Found, %: C 60.56; H 6.77; N 6.23. $C_{22}H_{29}ClN_2O_3S$. Calculated, %: C 60.48; H 6.64; N 6.41. *M* 436.5.

3-Benzyl-9-isothiocyanato-3-azabicyclo[3.3.1]-nonane (XVa). A solution of 2.9 g (25.2 mmol) of thiophosgene in 30 ml of anhydrous acetone was cooled to 0–5°C, a solution of 5.75 g (25 mmol) of amine **IIa** in 30 ml of acetone was added under stirring, and 3.6 g (26 mmol) of anhydrous potassium carbonate was then added in small portions. The mixture was stirred for 3 h at room temperature, poured into 200 ml of water, and extracted with methylene chloride (3×50 ml). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Yield 6.12 g (90%), oily substance. IR spectrum: ν 2092 cm^{-1} (NCS). ^{1}H NMR spectrum, δ, ppm: 1.38–2.07 m (6H, CH_2), 2.15–2.26 m (2H, CH), 2.83 d (2H, NCH_2), 2.87 d (2H, NCH_2), 3.38 s (2H, PhC**H**$_2$), 3.78 m (1H, 9-H), 7.08–7.24 m (5H, C_6H_5). Mass spectrum: *m*/*z* 273 $[M + H]^+$. Found, %: C 70.42; H 7.18; N 10.13. $C_{16}H_{20}N_2S$. Calculated, %: C 70.59; H 7.35; N 10.29. *M* 272.

***tert*-Butyl 9-isothiocyanato-3-azabicyclo[3.3.1]-nonane-3-carboxylate (XVb).** Yield 96%, mp 58–60°C. IR spectrum, ν, cm^{-1}: 2095 (NCS), 1686 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.30 s (9H, *t*-Bu), 1.47–2.15 m (6H, CH_2), 2.35–2.48 m (2H, CH), 3.45 d (2H, NCH_2), 3.64 d (2H, NCH_2), 3.86 m (1H, 9-H). Mass spectrum, *m*/*z*: 283 $[M + H]^+$, 182 $[M - 101 + H]^+$. Found, %: C 59.67; H 7.61; N 10.04. $C_{14}H_{22}N_2O_2S$. Calculated, %: C 59.57; H 7.80; N 9.93. *M* 282.

***O*-Methyl (3-benzyl-3-azabicyclo[3.3.1]non-9-yl)-carbamothioate (XVIa).** A mixture of 0.272 g (1 mmol) of isothiocyanate **XVa** and 10 ml of anhydrous methanol was heated for 10 h under reflux, and the solvent was distilled off under reduced pressure. Yield 0.3 g (98%), mp 118–120°C. IR spectrum: ν 3358 cm^{-1} (NH). ^{1}H NMR spectrum, δ, ppm: 1.36–2.08 m (6H, CH_2), 2.13–2.25 m (2H, CH), 2.81 d (2H, NCH_2), 2.88 d (2H, NCH_2), 3.40 s (2H, PhC**H**$_2$), 3.74 m (1H, 9-H), 3.96 s (3H, OCH_3), 7.02–7.21 m (5H, C_6H_5), 9.05 s (1H, NH). Mass spectrum: *m*/*z* 305 $[M + H]^+$. Found, %: C 66.93; H 7.76; N 9.17. $C_{17}H_{24}N_2OS$. Calculated, %: C 67.11; H 7.89; N 9.21. *M* 304.

***tert*-Butyl 9-(methoxycarbonothioylamino)-3-azabicyclo[3.3.1]nonane-3-carboxylate (XVIb)** was synthesized in a similar way. Yield 99%, mp 136–138°C. IR spectrum, ν, cm^{-1}: 3359 (NH), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.48–2.16 m (6H, CH_2), 2.36–2.49 m (2H, CH), 3.45 d (2H, NCH_2), 3.65 d (2H, NCH_2), 3.85 m (1H, 9-H), 4.01 s (3H, OCH_3), 9.12 s (1H, NH). Mass spectrum, *m*/*z*: 315 $[M + H]^+$, 214 $[M - 101 + H]^+$. Found, %: C 57.19; H 8.38; N 8.76. $C_{15}H_{26}N_2O_3S$. Calculated, %: C 57.32; H 8.28; N 8.92. *M* 314.

1-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)-3-phenylthiourea (XVIIa). A mixture of 0.272 g (1 mmol) of isothiocyanate **XVa** and 0.093 g (1 mmol) of aniline in 5 ml of anhydrous benzene was heated for 7 h under reflux. The solvent was distilled off under reduced pressure, and the residue was treated with hot

hexane. The precipitate was filtered off and recrystallized from ethyl acetate. Yield 0.21 g (58%), mp 156–158°C. IR spectrum, ν, cm^{-1}: 3356, 3268 (NH). ^1H NMR spectrum, δ, ppm: 1.37–2.09 m (6H, CH_2), 2.11–2.24 m (2H, CH), 2.83 d (2H, NCH_2), 2.89 d (2H, NCH_2), 3.38 s (2H, PhC**H**$_2$), 3.74 m (1H, 9-H), 7.03–7.43 m (10H, C_6H_5), 8.04 s (1H, NH), 9.18 s (1H, NH). Mass spectrum: *m*/*z* 366 $[M + H]^+$. Found, %: C 72.24; H 7.52; N 11.33. $C_{22}H_{27}N_3S$. Calculated, %: C 72.33; H 7.40; N 11.51. *M* 365.

***tert*-Butyl 9-(phenylcarbamothioylamino)-3-azabicyclo[3.3.1]nonane-3-carboxylate (XVIIb)** was synthesized in a similar way. Yield 63%, mp 171–173°C. IR spectrum, ν, cm^{-1}: 3362, 3274 (NH), 1687 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.47–2.15 m (6H, CH_2), 2.34–2.50 m (2H, CH), 3.44 d (2H, NCH_2), 3.66 d (2H, NCH_2), 3.87 m (1H, 9-H), 7.02–7.28 m (5H, C_6H_5), 8.06 s (1H, NH), 9.21 s (1H, NH). Mass spectrum, *m*/*z*: 376 $[M + H]^+$, 275 $[M - 101 + H]^+$. Found, %: C 63.85; H 7.84; N 11.07. $C_{20}H_{29}N_3O_2S$. Calculated, %: C 64.00; H 7.73; N 11.20. *M* 375.

1-(3-Benzyl-3-azabicyclo[3.3.1]non-9-yl)-4,5-dihydro-1*H*-tetrazole-5-thione (XVIIIa). A mixture of 0.272 g (1 mmol) of isothiocyanate **XVa** and 0.098 g (1.5 mmol) of sodium azide in 5 ml of water was heated for 4 h under reflux. The mixture was cooled and washed with 20 ml of diethyl ether. The aqueous solution was acidified with 10% hydrochloric acid to pH 2–3 and left to stand for 10 h in a refrigerator, and the precipitate was filtered off, washed with cold water and diethyl ether, and dried. Yield 0.28 g (89%), mp 187–190°C. IR spectrum, ν, cm^{-1}: 3405 (NH), 1528 (N=N). ^1H NMR spectrum, δ, ppm: 1.38–2.10 m (6H, CH_2), 2.12–2.26 m (2H, CH), 2.85 d (2H, NCH_2), 2.92 d (2H, NCH_2), 3.39 s (2H, PhC**H**$_2$), 3.85 m (1H, 9-H), 7.04–7.26 m (5H, C_6H_5). Mass spectrum: *m*/*z* 316 $[M + H]^+$. Found, %: C 60.73; H 6.45; N 21.80. $C_{16}H_{21}N_5S$. Calculated, %: C 60.95; H 6.67; N 22.22. *M* 315.

***tert*-Butyl 9-(5-thioxo-4,5-dihydro-1*H*-tetrazol-1-yl)-3-azabicyclo[3.3.1]nonane-3-carboxylate (XVIIIb)** was synthesized in a similar way. Yield 86%, mp 196–198°C. IR spectrum, ν, cm^{-1}: 3406 (NH), 1687 (C=O), 1528 (N=N). ^1H NMR spectrum, δ, ppm: 1.32 s (9H, *t*-Bu), 1.48–2.15 m (6H, CH_2), 2.36–2.52 m (2H, CH), 3.46 d (2H, NCH_2), 3.68 d (2H, NCH_2), 3.89 m (1H, 9-H). Mass spectrum, *m*/*z*: 326 $[M + H]^+$, 225 $[M - 101 + H]^+$. Found, %: C 52.01; H 7.23; N 21.43. $C_{14}H_{23}N_5O_2S$. Calculated, %: C 51.69; H 7.08; N 21.54. *M* 325.

Reaction of compounds IIb–XVIIIb with HCl. Compound **IIb**–**XVIIIb**, 2 mmol, was dissolved in 5 ml of anhydrous ethanol, 10 ml of a saturated (~16%) solution of hydrogen chloride in anhydrous dioxane was added, and the mixture was stirred for 1 h and then heated for 1 h under reflux. The solvent was removed under reduced pressure, the residue was dissolved in 3 ml of hot propan-2-ol, the solution was cooled, 15 ml of anhydrous diethyl ether was added, and the mixture was left to stand for 20 h. The precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure over P_2O_5. The yields of the corresponding 3-unsubstituted 3-azabicyclo[3.3.1]-nonane derivatives ranged from 87 to 98%.

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