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# New compounds with 4-azatricyclo[4.3.1.1$^{3,8}$]undecane framework

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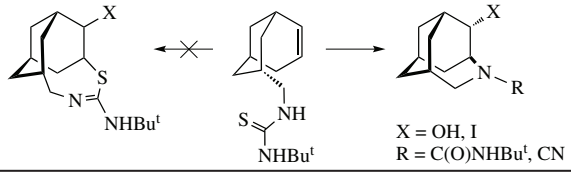
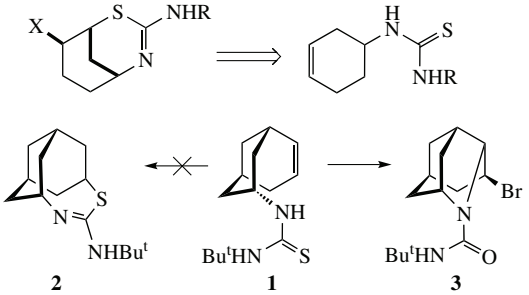
**Reactions of 1-[(*endo*-bicyclo[3.3.1]non-6-en-3-yl)methyl]-3-*tert*-butylthiourea with $I_2$/Bu$^t$OOH and $I_2$/$K_2CO_3$ afforded 4-azatricyclo[4.3.1.1$^{3,8}$]undecane based products *via* intramolecular cyclization, as determined by X-ray analysis and NMR spectroscopy.**



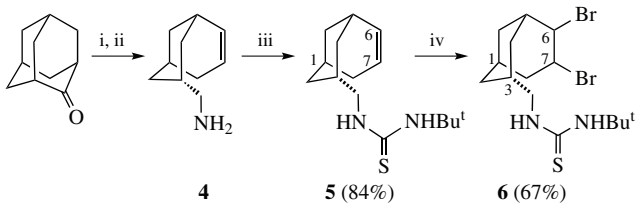

*Keywords*: *N*-[(*endo*-bicyclo[3.3.1]non-6-en-3-yl)methyl]thiourea, intramolecular cyclization, bridged tricyclic compounds, ureas, thioureas, azahomoadamantanes, electrophilic addition.

To achieve prolongation of drug action in organism through in increase in lipophilicity of active ingredient, we recently obtained bicyclic isothiourea inhibitors of nitric oxide synthase with extended vasoconstrictive action *in vivo*.[1,2] The key step of this synthesis was the cyclization of unsaturated cyclic thioureas after treatment with hydrogen halides or halogens (Scheme 1, top). However, application of this approach to 1-(*endo*-bicyclo[3.3.1]non-6-en-3-yl)-3-*tert*-butylthiourea **1** (see Scheme 1, bottom) to synthesize lipophilic tricyclic isothioureas of type **2** led in fact to tricyclic ureas **3** due to simultaneous oxidation of thiourea moiety to the urea one by bromine.[3] We suggested that the mobility and flexibility of the thiourea fragment could facilitate the intramolecular cyclization assisted by sulfur atom. In this work, we carried out the analogous reaction using the homologue of compound **1** to check the possibility of its cyclization into isothiourea derivative.

The homologous thiourea **5** was obtained from adamantanone (Scheme 2) through the Schmidt rearrangement into *endo*-bicyclo[3.3.1]non-6-ene-3-carbonitrile,[4] reduction to *endo*-bicyclo[3.3.1]non-6-en-3-ylmethylamine **4**[5] (for spectral characteristics of compounds, see Online Supplementary Materials) and its reaction with *tert*-butyl isothiocyanate. In the $^1$H NMR spectrum of compound **5**, signals of methylene protons neighbouring to the thiourea moiety are shifted downfield (3.47, 3.63 ppm) in comparison with amine **4** (2.54–2.64 ppm). In $^{13}$C NMR spectrum, the




**Scheme 1**

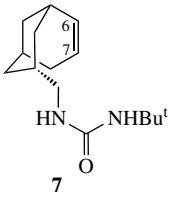



**Scheme 2** *Reagents and conditions*: i, $NaN_3$, $MeSO_3H$, AcOH, room temperature, 30 min; ii, $LiAlH_4$, $AlCl_3$, room temperature, 2 h, then aq. NaOH; iii, Bu$^t$NCS, $Pr^i_2NEt$, $CH_2Cl_2$, room temperature, 12 h; iv, $Br_2$, $CH_2Cl_2$, room temperature, 24 h.

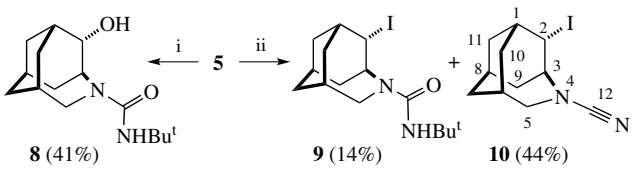
signals of carbon atoms corresponding to the Bu$^t$NHC(S)NH group of compound **5** are observed at 29.57 (C*Me*$_3$), 52.61 (*C*Me$_3$) and 180.77 (C=S) ppm.

Treatment of thiourea **5** with bromine resulted in the addition of halogen molecule to the double bond and led to dibromide **6** (*m/z*: 412 [M + 4]$^+$, 410 [M + 2]$^+$, 408 [M]$^+$), the anticipated tricyclic product was not formed (see Scheme 2).

In an attempt to promote the intramolecular cyclization, we treated olefinic thiourea **5** with iodine, however, the double bond of the substrate remained untouched ($^1$H NMR control). HPLC–MS data for the resulting reaction mixture revealed the major resolved chromatographic peak with >70% area and *m/z* 251, which corresponded to the monoprotonated molecular ion for compound **7** as an urea analogue of thiourea **5**.




In the reaction of compound **5** with iodine in the presence of *tert*-butyl hydroperoxide (Scheme 3), a complex mixture of products was formed, from which only one individual compound **8** could be isolated by column chromatography. Its tricyclic azahomoadamantane structure was determined by




**Scheme 3** *Reagents and conditions*: i, $I_2$, Bu$^t$OOH, $CH_2Cl_2$, room temperature, 24 h; ii, $I_2$, $K_2CO_3$, $CH_2Cl_2$, room temperature, 24 h.

X-ray analysis of the cystal grown from *n*-butyl acetate† [(Figure 1(*a*)].

In the crystals of compound **8**, the O(19) atom of the hydroxyl group is involved in the formation of hydrogen bonds N(14)–H(14)···O(19) ($x$,–y+3/2,$z$+1/2) and O(19)–H(19)···O(13) (–$x$ + 1, –y + 1, –$z$ + 1) and thus the layers are formed in the plane *ac* [Figure 1(*b*)]. Interestingly, the rings of initial bicyclo[3.3.1] nonane system in the tricyclic framework in **8** adopt conformation close to the *chair–chair* one, while for compound **3**, their conformation is close to the *chair–boat* one resulting from the conformational constrain exerted by pyrrolidine cycle. For the quantitative estimation of the rings distortion from *chair* conformation using Ricon program,[6] see Online Supplementary Materials.

Finally, reaction of olefinic thiourea **5** with iodine and $K_2CO_3$ as a base gave no product of the structural type **2**, however, two iodo amides **9** and **10** were isolated (see Scheme 3). Their structures were assigned based on mass spectrometry ($[M + 1]^+$ 377 and 303, respectively), IR spectroscopy (an intensive absorption band from carbonitrile group at 2203 cm$^{-1}$ for **10**) as well as NMR spectroscopy data. In the $^{13}C$ NMR spectra, the signals for carbonyl group in compound **9** and carbonitrile group in tricycle **10** are observed at 156 and 118 ppm, respectively. $^1H$–$^{13}C$ and $^1H$–$^1H$ 2D NMR data for compound **10** (see Online Supplementary Materials) are in complete agreement with its azahomoadamantane structure. Configuration of iodine substituent in product **10** was confirmed by $^1H$–$^1H$ COSY, where C$^2$*H*I proton at 4.54 ppm had long-range 'W-coupling' with the *cis*-protons at C(9) (1.62 ppm) and C(11) (1.48 ppm) atoms and had no coupling with C$^{10}$*H*.

The formation of products **8** and **9** seems to be a result of simultaneous *exo*-electrophilic attack at the double bond of compound **5** with epoxidation step in the case of compound **8** or iodonium ion formation in the case of compound **9** and oxidation of the thiourea moiety into the urea one followed by intramolecular nucleophilic substitution at C(7) atom, affording azahomoadamantane framework. This process differs from the cyclization of homologous thiourea **1** (see Scheme 1)[3] assisted by C(6) carbon atom of its bicyclic system resulting in the formation of isoadamantane structure. *N*-Carbonitrile derivative **10** is most probably formed *via* base-assisted dehydration of urea **9**.[7]

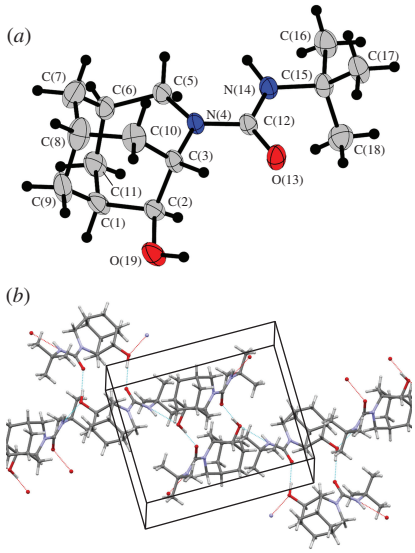



**Figure 1** X-ray data for (1*RS*,2*RS*,3*RS*,6*SR*,8*RS*)-*N*-*tert*-butyl-2-hydroxy-4-azatricyclo[4.3.1.1$^{3,8}$]undecane-4-carboxamide **8**: (*a*) general view with representation of atoms by thermal ellipsoids ($p$ = 50%) and (*b*) layer of molecules **8** in the plane *ac*.

In summary, upon the treatment with bromine or iodine, 1-[(*endo*-bicyclo[3.3.1]non-6-en-3-yl)methyl]-3-*tert*-butylthiourea **5** did not undergo intramolecular cyclization, while its reaction with $I_2$/Bu$^t$OOH or $I_2$/$K_2CO_3$ led to the products of intramolecular cyclization with the formation of azahomoadamantane core. These products represent a new structural type of tricyclic bridged ureas and *N*-carbonitriles.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.004.

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† *Crystal data for* **8**. $C_{15}H_{26}N_2O_2$ ($M$ = 266), monoclinic, space group $P2_1/c$; at 295(2) K: $a$ = 10.1380(6), $b$ = 11.2516(8) and $c$ = 13.5392(8) Å, $\beta$ = 93.186(5)°, $V$ = 1542.01(17) Å$^3$, $Z$ = 4, $d_{calc}$ = 1.147 g cm$^{-3}$. Intensities of 15110 reflections were measured using a STOE diffractometer with Pilatus100K detector and focusing mirror collimation CuKα 1.54086 Å radiation in rotation method mode. STOE X-Area software was used for cells refinement and data editing. Data collection and image processing was performed using X-Area 1.67 (STOE & Cie GmbH, Darmstadt, Germany, 2013). Intensity data were scaled with LANA (part of X-Area) to minimize differences of intensities for the symmetry-equivalent reflections (multi-scan method). The structure was solved and refined using SHELX program. The non-hydrogen atoms were refined by the anisotropic full matrix least square procedure. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared using DIAMOND software.

CCDC 1910104 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.