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Synthesis, molecular structure, conformation and biological activity of Ad-substituted *N*-aryl-tetraoxaspiroalkanes

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ABSTRACT

An efficient method has been developed for the synthesis of 7′-arylspiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-tetraoxazocanes)} by the ring transformation reaction of spiro{adamantane-[2,3']-(1′,2′,4′,5′,7′-pentaoxacane)} with arylamines in the presence of $Sm(NO_3)_3 \cdot 6H_2O$ as the catalyst. NMR signals of the synthesized compounds were assigned considering the conformation dynamics of the tetraoxazocane ring with two rigid peroxide bonds. The structures of some of the compounds were studied by X-ray diffraction. The thermal stability of single crystal was determined by DSC method. Compounds 7′-(2-methylphenyl)spiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-tetraoxazocane)} and 7′-(4-fluorophenyl)spiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-tetraoxazocane)} exhibited cytotoxicity towards cancer cells.

1. Introduction

Studies of peroxides represent a topical task owing to the important role they play in oxidation processes and light generation mechanisms in chemical and biochemical systems and to their wide use in organic synthesis and medicine.[1] The past decades can be rightfully termed the renaissance of the organic peroxide chemistry, which is related to the development of pharmaceutical drugs based on the natural trioxane, artemisinin, which has an antimalarial [2a,d] and anticancer activity [2b-d], and to the discovery of important pharmacological properties in synthetic 1,2,4-trioxolanes and 1,2,4,5-tetraoxanes.[2] In 2012, a synthetic trioxolane, Arterolane (OZ277),[3,4] became a part of the Synriam antimalarial drug (Ranbaxy company), and the tetraoxane RKA182 was recently selected for clinical trials.[5] It is noteworthy that apart the antimalarial properties, tetraoxanes were found to exhibit antitumor and anthelmintic activities. Although the mechanism of antimalarial activity still remains open, it was found that the key role in this process belongs to the interaction of iron(II) with the peroxide bond.[6]

Currently, a lot of attention is paid to studies of stability, reactivity, pharmacokinetics, and the mechanism of action of biologically active peroxides and to the synthesis of new derivatives. The antimalarial activity is considerably enhanced by the presence of an adamantane substituent and nitrogen-containing (amino or amido) basic groups in the molecule.[7-9] Indeed, the molecules of known antimalarial agents of both synthetic[10] and natural (verruculogen[11a] or dioxetanone[11b]) origin incorporate the nitrogen-containing peroxide $-N-CH_2-O-O-$ moiety. In this connection, of considerable interest from the biological activity standpoint are *N*-containing cyclic peroxides,[12] which remain poorly studied, since they are difficult to synthesize and only few methods for their

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synthesis are available.[10,12,13] Thermal stability is also an important issue for amino peroxides.

In view of the above, we suggested that Ad-substituted *N*-aryl-tetraoxaspiroalkanes combining the necessary pharmacologically active groups in the molecule could be of considerable interest as potential antimalarial agents. The target compounds were synthesized using the approach proposed in our earlier works, which is based on ring transformation of pentaoxaspiroalkanes with arylamines.[14] The first synthesis of *N*-aryl-substituted tetraoxazaspiroalkanes was accomplished by this method.[14]

Thus, our goal was to develop a catalytic method for the selective synthesis of Ad-substituted *N*-aryl-tetraoxazaspiroalkanes and to study the structure and conformations of the resulting heterocyclic compounds. Despite the fact that the conformational behavior of compounds considerably affects their biological activity, there are only few publications devoted to the conformational analysis of heteroatom-containing peroxides.[15,16] Furthermore, the spectral parameters of cyclic compounds depend not only on isomerism, but also on the conformational state of the ring; therefore, conformational analysis is exceptionally important for reliable identification of new Ad-substituted *N*-aryl-tetraoxaspiroalkanes, which present interest for their biological activity. All synthesized compounds were tested in vitro for anticancer activity.

2. Results and discussion

The ring transformation reaction between the Ad-substituted pentaoxacanes and primary amines catalyzed by $Sm(NO_3)_3 \cdot 6H_2O$ made it possible to solve the problem of selective synthesis of adamantyl-substituted cycloamino diperoxides. The choice of the catalyst was due to its high activity in the synthesis of *N*-aryl-tetraoxazaspiroalkanes that we described previously.[14]

In relation to the reaction of spiro{adamantane-[2,3']-(1′,2′,4′,5′,7′- pentaoxacane)}[17] **1** with *o*-fluoroaniline **2a**, it was found that the reaction carried out in the presence of $Sm(NO_3)_3 \cdot 6H_2O$ (0.5 mol. %) as the catalyst for 6 h at ~20°C in THF gives 7′-(*o*-fluorophenyl)spiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-tetraoxazocane)} **3a** in 95% yield. Under the chosen conditions (5 mol. % $Sm(NO_3)_3 6H_2O$, 20°C, 6 h, THF), aryl (*m*,*p*-fluorophenyl, *o*,*m*,*p*-chlorophenyl, *o*,*m*,*p*-methoxymethyl, *o*,*m*,*p*-methylphenyl) amines **3b-i** undergo ring transformation reaction with spiro{adamantane-[2,3']-(1′,2′,4′,5′,7′-pentaoxacane)} **1** to give 7′-arylspiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-tetraoxazocanes)} **3a-i** in 80–99% yields.

Apart from arylamines, the catalytic ring transformation with spiro{adamantane-[2,3']-(1′,2′,4′,5′,7′-pentaoxacane)} **1** was carried out for aromatic diamines (*o*,*m*,*p*-phenylenediamines). The ring transformation of compound **1** with *p*-phenylenediamine **4** under the developed conditions (5 mol.% $Sm(NO_3)_3 6H_2O$, 20°C, 6 h, THF) also gives rise to the target 4-spiro[adamantane-2,3'-[1,2,4,5,7]tetraoxazocane]-7′yl)aniline **5**, whereas the reaction with *m*–phenylenediamine affords a precipitate insoluble in organic solvents and difficult to identify. It was found that spiro{adamantane-[2,3']-(1′,2′,4′,5′,7′- pentaoxacane)} **1** reacts with *o*-phenylenediamine **6** to give adamantanone **8** and 2H,5H-1,6-(methanedioxymethano)benzo[e][1,2,4,7]-dioxazocine **7** (Scheme 2).

The structures of 7′-arylspiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-tetraoxazocanes)} **3b,d,h,i** (Fig. 1) and **7** (Fig. 7) were reliably established by NMR spectroscopy and X-ray diffraction.

According to the single crystal X-ray diffraction studies of compounds **3b**, **3d, 3h**, and **3g** have the molecular structure that is shown in Fig. 1. These compounds are characterized by the presence of a common moiety, spiro[adamantane-2,2'-[1,3,4,8,6]tetraoxazocane], in which the tetraoxazocane moiety has a distorted *twist-chair* conformation. The *N*-aryl substituents occupy the axial position relative to the tetraoxazocane ring plane. The O–O bond length in the tetraoxazocane moiety varies over a broad range from 1.446 to 1.475 Å. (Table 1).

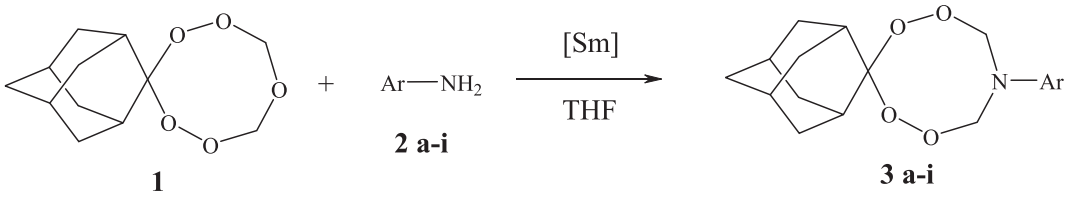
According to published data for tetraoxane rings, the O–O bond lengths are in the range of 1.471–1.477 Å (Table 1). In addition, the peroxide bonds in the tetraoxazocane ring are nonequivalent in structures **3h**, **3g** and **3d**. By considering the C–N and C–O bond lengths in structures **3h**, **3b, 3g**, and **3d**, one can follow the effect of substituent (Table 2). The presence of halogens in the *para*-position of the aryl moiety decreases the length of the exocyclic C–N bond and increases the endocyclic bond lengths in the structures **3b** and **3d**, and the inverse relationship is observed for compounds **3h** and **3g** (Fig. 2). The C–O bond lengths are minimized if the methyl group occurs in the *para*-position of the aromatic ring (Table 2, Fig. 2).

Thus, eight-membered amino peroxide ring derivatives crystallize in the *twist-chair* ring conformation.

However, we found that at room temperature in solution, a multicomponent equilibrium occurs between conformations with different spatial ring arrangements. For example, the ^1H and ^{13}C NMR spectra for the series of compounds contain a double set of hydrogen and carbon signals for the whole molecule. The signal intensities in each pair considerably differ, their ratio being about 1: 2.5 in the ^1H NMR spectra, for example, for the methylene protons of the characteristic N–$\underline{CH_2}$ groups (Fig. 3). As can be seen from Fig. 3, these diastereotopic protons in compound **3b** in chloroform and toluene solutions exhibit two pairs of doublets, particularly, the relatively low-field doublets at 5.09 ppm and 5.17 ppm with a geminal constant of 14.5 Hz, which are correlated with the minor ^{13}C signal at $\delta = 88.9$ ppm according to HSQC data, and doublets at 4.83 ppm and 4.96 ppm with $^2J = 10.0$ Hz, correlated with the major carbon signal at 86.2 ppm (Fig. 3a).

The above-mentioned signals of the latter pair of doublets are clearly broadened, which evidently attests to conformational exchange and averaging of NMR spectral parameters on the NMR time scale. Indeed, at the coalescence temperature T = 243 K, these doublets are split into two doublets of doublets, and at 208 K three conformers can be observed separately (Fig. 3e).

In order to determine the structures of the conformers and also in view of the lack of literature data about the conformational behavior of this class of compounds, the potential energy surface (PES) of 7′-phenyl-spiro{adamantane-[2,3′]-(1′,2′,4′,5′,7′-



1 2 a-i 3 a-i

Scheme 1.