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Stereoisomerism in the representative tetracyclic dispiro ozonide derived from (methylene)dicyclohexanone with the 1,5-diketo arrangement

Taisia I. Akimova,* Olga A. Soldatkina, Vyacheslav G. Savchenko, Anna V. Pilipenko and Alevtina A. Kapustina

School of Natural Sciences, Far Eastern Federal University, 690922 Vladivostok, Russian Federation.
E-mail: akimova.ti@dvfu.ru

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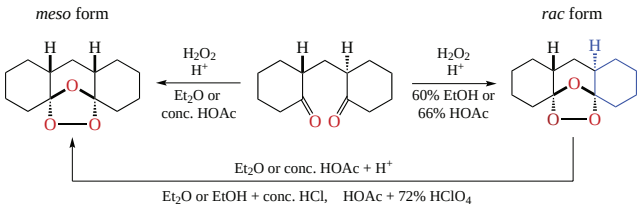
The conditions and reasons for the stereoselective transformation of the *rac* form of 2,2′-(methylene)-dicyclohexanone into the *meso*- or *rac*-diastereomer of tetracyclic dispiro ozonide (1,2,4-trioxolane) in the reaction with 30% aqueous H_2O_2 in the presence of acid have been determined. A mechanism for the stereoisomerization of ozonides was proposed, and the stereochemistry of diastereomeric ozonides was established by NMR data.



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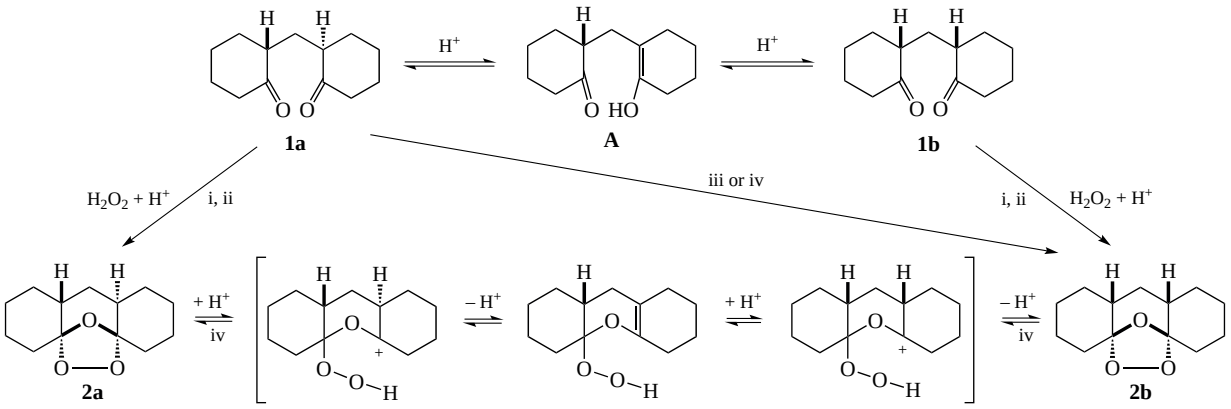
In recent decades, ozonides (1,2,4-trioxolanes) like peroxides have attracted increased attention, since among them compounds with high antimalarial activity have been identified.[1,2] Ozonides are considered as synthetic analogues of the natural peroxide artemisinin, the main drug for malaria. The importance of studying these compounds is confirmed by the award of the 2015 Nobel Prize for the development and use of artemisinin. In addition, ozonides possess anticancer,[3,4] high anthelmintic,[3,5] antituberculosis,[6] and fungicidal[7] activity.

The classical approach for the synthesis of ozonides consists in the treatment of unsaturated compounds with ozone. At the end of the last century, the Griesbaum method[8,9] was developed, in which ozonides are obtained by ozonolyses of *O*-alkylated ketoximes in the presence of monoketones. A recent new method for the synthesis of ozonides is based on the reaction of 1,5-diketones with hydrogen peroxide. Its originality lies in the fact that the ozonides are accessed without the use of ozone. This method was used to synthesize a series of bicyclic ozonides based on aliphatic 1,5-diketones.[10] A little earlier, we obtained a series of tetracyclic dispiro 1,2,4-trioxolanes (ozonides) by the reaction of alicyclic 1,5-diketones containing 5-, 6-, 7-membered rings with hydrogen peroxide in the presence of HCl, H_2SO_4 or $BF_3{\cdot}OEt_2$.[11,12] Ozonides with 6-membered rings were obtained earlier by another method.[13]

We have previously[11,12] discovered that an individual racemic diastereomer of a diketone depending on the reaction conditions could give the product either with the retention or reversal of the configuration of the stereogenic centers. This work is devoted to elucidating the reasons for such behavior. Working with mixtures does not make it possible to trace the stereochemical transformation of the individual diastereoisomer.[10] Having in hands the pure racemic form of diketone, we were able to fulfill this task and to develop conditions for the selective preparation of diastereomeric ozonides. It is known that diastereomers differ in both chemical[14] and biological[15] properties.

1,5-Diketone **1** (Scheme 1) is a mixture of solid and liquid fractions.[16] The liquid part is the mixture of diastereomers **1a** and **1b** with the ratio of 1:1 (according to GC/MS). The recrystallization of the solid part from ethanol yielded racemic form **1a** with a purity of 98%. In an ethereal solution, under the



Scheme 1 *Reagents and conditions*: 30% aq. H_2O_2, 20 °C: i, 60% EtOH, conc. HCl, 30 min; ii, 66% HOAc, 72% $HClO_4$, 1 h; iii, Et_2O, conc. HCl, 24 h; iv, conc. HOAc, 72% $HClO_4$, 48 h.

action of 30% aqueous H_2O_2 in the presence of HCl (ratio diketone/H_2O_2/HCl = 1 : 2 : 3 mmol) pure diastereomer *rac*-**1a** at 20 °C within 24 h is converted into a mixture of ozonides (91% yield) containing 70% *meso*-**2b** (mp 119–120 °C), instead of the expected predominance of racemic form *rac*-**2a** (see Scheme 1). The solution remains homogeneous in this case. When the reaction is carried out in a 60% aqueous-alcoholic solution under the same conditions, after 2–3 min an abundant precipitation begins and in 30 min the reaction ends with an 88% yield of ozonides contaning 94% of *rac*-**2a** (mp 69–71 °C). These results suggest that, upon 'ozonation' in an ethereal solution, the configuration of the stereogenic centres of the initial diketone is changed while in an alcoholic solution the configuration is retained.

The observed transformation of diketone **1a** into ozonide **2b** in an ethereal solution, in our opinion, can occur in two ways (see Scheme 1). First, in a homogeneous solution the initial diketone *rac*-**1a** is converted through enol **A** into *meso*-**1b**, which then gives *meso*-ozonide **2b**. Second, the racemic form of ozonide *rac*-**2a**, originating from *rac*-**1a**, is then isomerized into *meso*-**2b**.

Control experiments on the isomerization of pure diketone *rac*-**1a** in a homogeneous ether solution in the presence of hydrochloric acid showed that after 20 min the content of *meso*-**1b** was 38%, and after 20 h it was 41%. At the same time, a control experiment with pure racemic ozonide *rac*-**2a** in an ethereal solution in the presence of hydrochloric acid showed that conversion *rac*-**1a** → *meso*-**2b** approached 30% in 24 h and 70% in 72 h. These results indicate that high yield of *meso*-ozonide **2b** from racemic diketone *rac*-**1a** is a consequence of both isomerization of the starting diketone and isomerization of the initially formed ozonide *rac*-**2a** into a more stable *meso*-form **2b** (thermodynamic factor). In a water–alcohol solution, the reaction proceeds quickly, moreover, the possibility to isolate pure *rac*-**2a** is facilitated by its precipitation, this shifts the equilibrium to the right (kinetic factor). The isomerization of both the starting diketone and the ozonide are insignificant under these conditions. A control experiment showed that after 30 min the content of *meso*-form **1b** was 16%.

The use of acetic acid as a solvent made it possible to selectively convert diketone *rac*-**1a** to any diastereomer **2a** or **2b**. Carrying out the reaction in 66% acetic acid with the addition of 72% $HClO_4$ leads to a mixture of isomers which precipitate immediately after the addition of a 30% solution of H_2O_2, with a total yield of 94% and the ratio of isomers **2a**/**2b** = 7 : 3. If homogeneous conditions are created for the reaction, using conc. HOAc, then after 48 h a mixture of isomers (yield 70%) with the ratio **2a**/**2b** = 3 : 7 is formed. We also showed that the isolated mixture of isomers from the experiment with 66% HOAc (**2a**/**2b** = 7 : 3), after dissolution in conc. HOAc in the presence of 72% $HClO_4$, is converted into a mixture of isomers **2a**/**2b** = 2 : 8. This means that in a homogeneous solution the isomerization of isomer *rac*-**2a** to more stable isomer *meso*-**2b** occurs. The proposed mechanism for stereoisomerization of ozonide **2a** to **2b** is outlined in Scheme 1.

A specific feature of the stereochemistry of ozonides obtained on the basis of 1,5-diketones is that the resulting 6-membered hydropyran ring is rigidly bonded by a peroxide bridge, which can be located only at the 1,3-diaxial position of the ring. In this case, the methine protons relative to it can be in the *cis*- or *trans*-position. The equatorial bond of the hydropyran ring is involved in junction with other hydroxantene rings. As a result, the racemic ozonide can have only one form **2a**, while the *meso* ozonide has two diastereomeric forms **2b** and **2′b** (Figure 1).

The structure and stereochemistry of the synthesized ozonides were established on the basis of 1D and 2D NMR. The

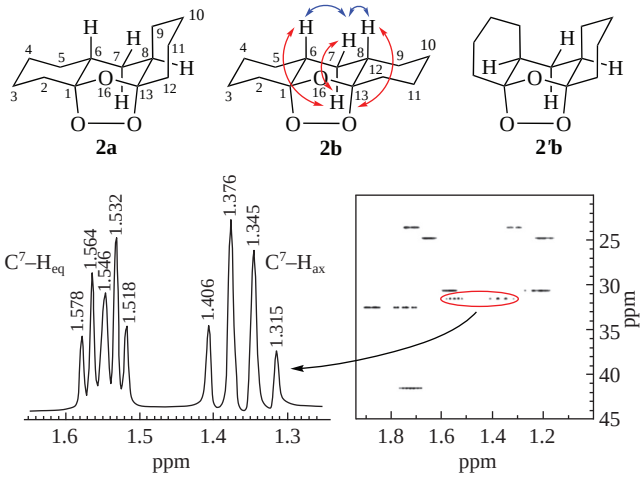


Figure 1 Diastereomeric forms of ozonides **2**. Signals of C^7–H_{ax} and C^7–H_{eq} protons were derived from HSQC spectrum of symmetric isomer **2b**.

^{13}C spectrum of the unsymmetrical isomer **2a** contains all thirteen peaks, while the spectrum of the symmetric product contains seven peaks, six of which are of double intensity. The type of ring junction in symmetric product was established based on the analysis of the spin–spin coupling of the C^7–H_{ax} and C^7–H_{eq} proton signals (see Figure 1). In ^1H spectrum the signals of interest overlap with other proton signals, so we used the 1D HSQC projection instead. In the spectrum of the symmetric isomer, the axial proton multiplet C^7–H_{ax} at δ 1.37 ppm has the form of a *pseudo*-quartet with $J \approx 13$ Hz and $\Sigma = 37$ Hz. The shape and width of the multiplet indicate that the spin–spin coupling constant of C^7–H_{ax} with the methine protons C^6–H and C^8–H has a value close to the constant of the geminal interaction, which can only be in the case of the *trans*-position of the protons C^6–H and C^8–H relative to C^7–H_{ax}. Therefore, the symmetric isomer should have a *trans*-*syn*-*trans*-type of ring junction, as shown in structure **2b**, that rejects structure **2′b**.

In conclusion, the change in the configuration of stereogenic centers during the synthesis of ozonides in the reaction of 1,5-diketone with 30% aqueous H_2O_2 in homogeneous solutions of ether or HOAc is the result of isomerization of both the diketone itself and the initially formed ozonide. The conditions for the selective preparation of diastereomeric forms of ozonides from the racemic form of the starting 1,5-diketone were found. The possibility of isomerization of the pure racemic form of ozonide into a more stable *meso*-form was demonstrated, and a conversion mechanism was proposed.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.040.

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