

Effect of Temperature on the Reaction of 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic Acid with Oxygen in an Alkaline Condition

A. A. Volodkin¹, G. E. Zaikov¹, L. N. Kurkovskaja¹, S. M. Lomakin¹, I. M. Levina¹,
E. V. Koverzanova²

¹Federal State Budgetary Establishment of a Science of Institute of Biochemical Physics of N. M. Emanuelja of Russian Academy of Sciences, Moscow, Russia

²Federal State Budgetary Establishment of a Science of Institute of Chemical Physics of N. N. Semenov of Russian Academy of Sciences, Moscow, Russia

Email: chembio@sky.chph.ras.ru

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Abstract

Results of oxidation 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid oxygen depend on temperature. At 55°C - 60°C, 2,4-di-*tert*-butylbicyclo(4,3,1)deca-4,6-dien-8-(N-acetylamino)-3,9-dion-1-oxa is formed. The constitution is based on dates of spectrums ¹H and ¹³C NMR. At 95°C - 97°C, mixtures of 2,4-di-*tert*-butylbicyclo(4,3,1)deca-4,6-dien-8-(N-acetylamino)-3,9-dion-1-oxa and of 6,8-di-*tert*-butyl-3-(N-acetylamino)spiro(4,5)deca-1-oxa-5,8-dien-2,7-dione are produced. Structures are calculated by the method of Hartrii-Foka. Values of enthalpies and of entropies allow to assume dynamic isomerism.

Keywords

2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic Acid, 6,8-di-*tert*-butyl-3-(N-acetylamino)spiro(4,5)deca-1-oxa-5,8-dien-2,7-dione Oxidation by Oxygen, 2,4-Di-*tert*-butylbicyclo(4,3,1)deca-4,6-dien-8-(N-acetylamino)-3,9-dion-1-oxa, NMR-Spectroscopy

1. Introduction

The oxidation by oxygen 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid (analogue ty-
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rosine) is of interest in research of products oxidations in a presence of an antioxidant. Results of early works [1]-[3] have shown possibility to use of a synthesis of analogues tyrosine in research of biology and a investigation of specificity properties in the conditions of a reactions with acid agents. For example, in classical reaction with thionyl chloride instead of acid chloride 2-(N-acetylamino)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid, a oxidative dimerization is produced [4]. There is an eliminate of *tert*-butyl groups in reaction 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid with hydrogen chloride [5].

The direction of oxidation by oxygen 4-replaced 2,6-di-*tert*-butylphenols depends on conditions and a constitution of substituent and in each specific case results, as a rule, are ambiguous [6].

In the present work, we studied the oxidation of 2-(N-acetylamino)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid by oxygen. Results of a oxidation of 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid may be impotents in process research of products inhibitors of oxidation, especially in the conditions of a biological. We have positioned that in process interaction of 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid with oxygen in the presence of alkali are formed 2,4-di-*tert*-butylbicyclo(4,3,1)-deca-4,6-dien-8-(N-acetylamino)-3,9-dion-1-oxa and 6,8-di-*tert*-butyl-3-(N-acetylamino)-spiro(4,5)deca-1-oxa-5,8-dien-2,7-dione. The interrelation of results of oxidation by oxygen depends on temperature.

2. Experimental Part

NMR spectrums registered on the device "Avance-500 Bruker" rather TMS.

2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid it is synthesis on a method [7], m.p. 204°C - 206°C according to [8]: m.p. 204°C - 206°C.

Example 1. Oxidation 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid at 55°C - 60°C. In solution of 3.35 g (0.01 mol) 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid 1.2 g (0.04 mol) NaOH in 60 ml of ethanol at 55° - 60° passed oxygen within 6 h. In a day to solution added HCl prior to the beginning of breaking (pH ≈ 6). Organic part have separated and after crystallization in the course of solvent evaporation received 0.6 g (≈18%) 2,4-di-*tert*-butylbicyclo(4,3,1)deca-4,6-dien-8-(N-acetylamino)-3,9-dion-1-oxa (**2**); m.p. 101°C - 105°C. Found %: C 68.32 H 8.34. C₁₉H₂₇NO₄. Calculated %: C 68.44 H 8.16.

Spectrum ¹H NMR (DMSO-d₆, δ, ppm, J/Hz): 1.20 (s, 18H, ^tBu); 1.89 (s, 3H, CH₃CO); 2.40 (dd, 2H, CH₂CH, J = 12.9); 4.85 (m, 1H, CH₂CH); 6.69 (d, 1H, Ar, J = 2.9); 6.95 (d, 1H, Ar, J = 2.9); 8.56 (d, 1H, NH, J = 7.8). Spectrum ¹³C NMR (DMSO-d₆, δ, ppm): 22.18 (CH₃CO); 29.09 (C-CH₃); 36.84 (CH₂); 48.56 (CH); 76.28 (C); 138.9 (C-H) 139.6 (C-H); 145.3 (C=C) 4 146.0 (C=C) 169.3 (CONH); 174.0 (COO); 185.4 (C=O).

2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionate sodium (**3**)

Mixture of 3.35 g (0.01 mol) **1**, 0.5 g (0.01 mol) NaOH in 20 ml of ethanol maintain ≈15 min time, solvent evaporate, the residue crystallization from EtOH-H₂O (1:1). A yield ≈3 g, m.p. > 250°. Spectrum ¹H NMR (DMSO-d₆, δ, ppm, J/Hz): 1.35 (s, 18 H, ^tBu); 1.77 (s, 3H, COCH₃); 2.73 (dd, 1H, CH-CHH, J = 6.8); 2.95 (dd, 1H, CH-CHH, J = 4.6); 3.97 (m, 1H, CH-CH₂); 6.6 (s, 1H, OH); 6.89 (s, 2H, Ar); 7.23 (d, 1 H, J = 7.4). Spectrum ¹³C NMR (DMSO-d₆, δ, ppm): 22.93 (CH₃CO); 30.48 (C-CH₃); 34.27 (C); 37.45 (CH₂); 55.73 (CH); 125.5 (C=C-H); 130.46 (C-C=C); 138.09 (C-C=C); 151.58 (C-C=O); 167.63 (CONHCH₃); 173.93 (COO).

Example 2. Oxidation 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid at 95°C - 97°C. In solution of 3.35 g (0.01 mol) 2-(N-acetylamino)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid, 1.2 g (0.04 mol) NaOH in 60 ml of ethanol at 55°C - 60°C passed oxygen within 6 h. Processing and allocation of resultants of reaction made similarly to an example 1. 6,8-Di-*tert*-butyl-3-(N-acetylamino)spiro(4,5) deca-1-oxa-5,8-dien-2,7-dione from a reaction mixture divide on Al₂O₃; m.p. 102°C - 105°C.

Spectrum ¹H NMR (**1**) (DMSO-d₆, δ, ppm, J/Hz): 1.36 (s, 18 H, ^tBu); 1.82 (s, 3H, CH₃CO); 2.74 (dd, 1H, CH-CHH, J = 9.2; J = 9.2; J = 13.9); 2.91 (dd, 1H, CH-CHH, J = 4.85; J = 6.94; J = 13.9); 4.32 (m, 1H, CH-CH₂); 6.94 (s, 2H, Ar); 8.16 (d, 1H, NH, J = 7.8); Spectrum ¹H NMR (**2**) (DMSO-d₆, δ, ppm, J/Hz): 1.36 (s, 18 H, ^tBu); 1.80 (s, 3H, CH₃CO); 2.74 (d, 2H, CH₂, J = 3.2); 4.01 (m, 1H, CH-CH₂); 6.90 (s, 2H, Ar); 8.30 (d, 1H, NH, J = 7.3);

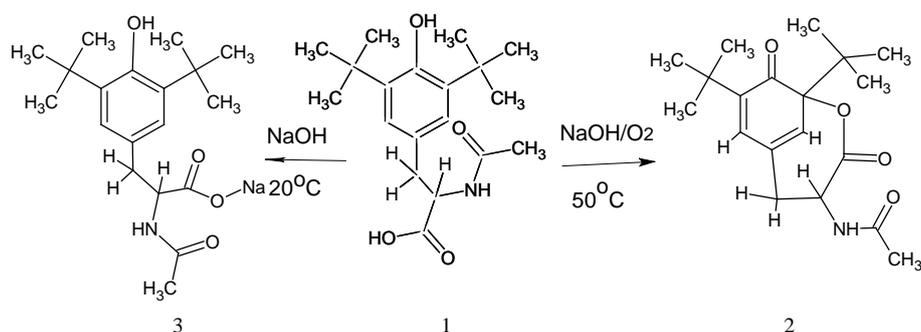
Spectrum ¹³C NMR (DMSO-d₆, δ, ppm): 22.4 (CH₃CO); 26.9 (C); 30.32 (C-CH₃); 36.57 (CH₂); 53.58 (C¹H); 53.84 (C²H); 60.18 (C-spiro); 125.07 (C=C¹-H); 125.15 (C=C¹-H); 127.8 (C=C²-H); 128.4 (C=C²-H); 145.90 (C¹=C); 145.95 (C¹=C); 152.24 (C²=C); 152.37 (C²=C); 168.97 (C¹ONH); 169.09 (C²ONH); 171.83 (C¹OO); 173.22 (C²OO); 185.37 (C=O).

3. Results and Discussions

In conditions of interaction 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid (**1**) with NaOH in air atmosphere at ambient temperature 2-(N-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionate sodium is formed, solvable in aqueous-alcoholic solutions. However at temperature of 55°C - 60°C oxidation process proceeds, which speed above in oxygen atmosphere. For 6 h reactions $\approx 18\%$ 2,4-di-*tert*-butyl-bicyclo(4,3,1)deca-4,6-dien-8-(N-acetylamino)-3,9-dion-1-oxa (**2**) is formed (**Scheme 1**) At ambient temperature on air salt **3** does not react with oxygen. The composition analysis of reactionary masses and a yield of compound **2** are resulted from the data of the spectrum ^1H NMR (**Figure 1**).

From the data of the spectrum ^1H NMR follows that signals of 6.69 and 6.95 ppm ($J = 2.9$ Hz) to belong to two various protons in a hexatomic cycle of structure **2**. In the spectrum ^{13}C NMR signals of 138.92 and 139.59 ppm from atoms of carbeneum correspond to the data, which analysis in a format *debt* (**Figure 2**) specifies in communication of these atoms with hydrogen.

Signal of 185.4 ppm in spectrum ^{13}C NMR (**Figure 3**) confirms presence of a carbonyl group at a hexatomic cycle of structure **2**.



Scheme 1. Structures of compounds **2** and **3**.

ALH2608 14

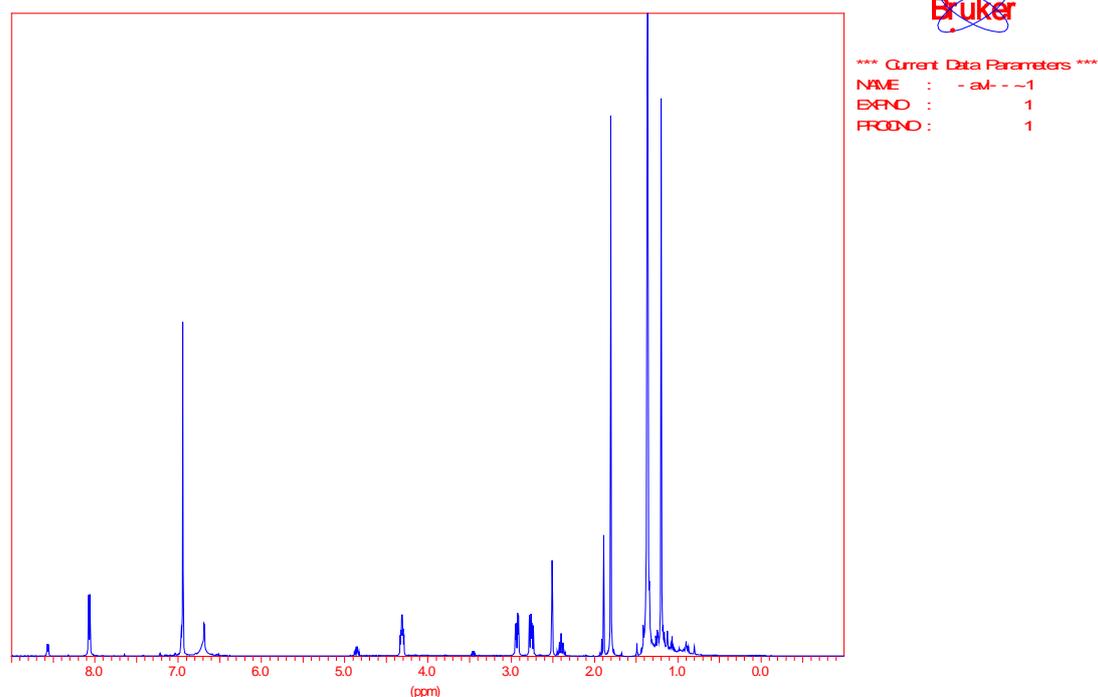
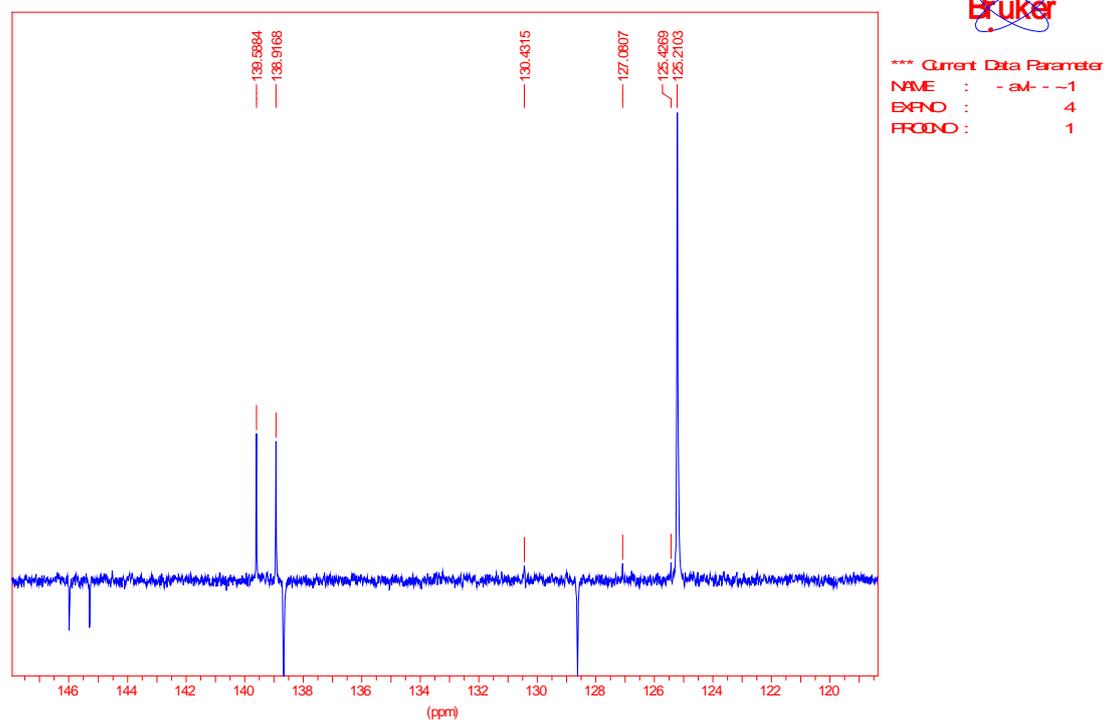
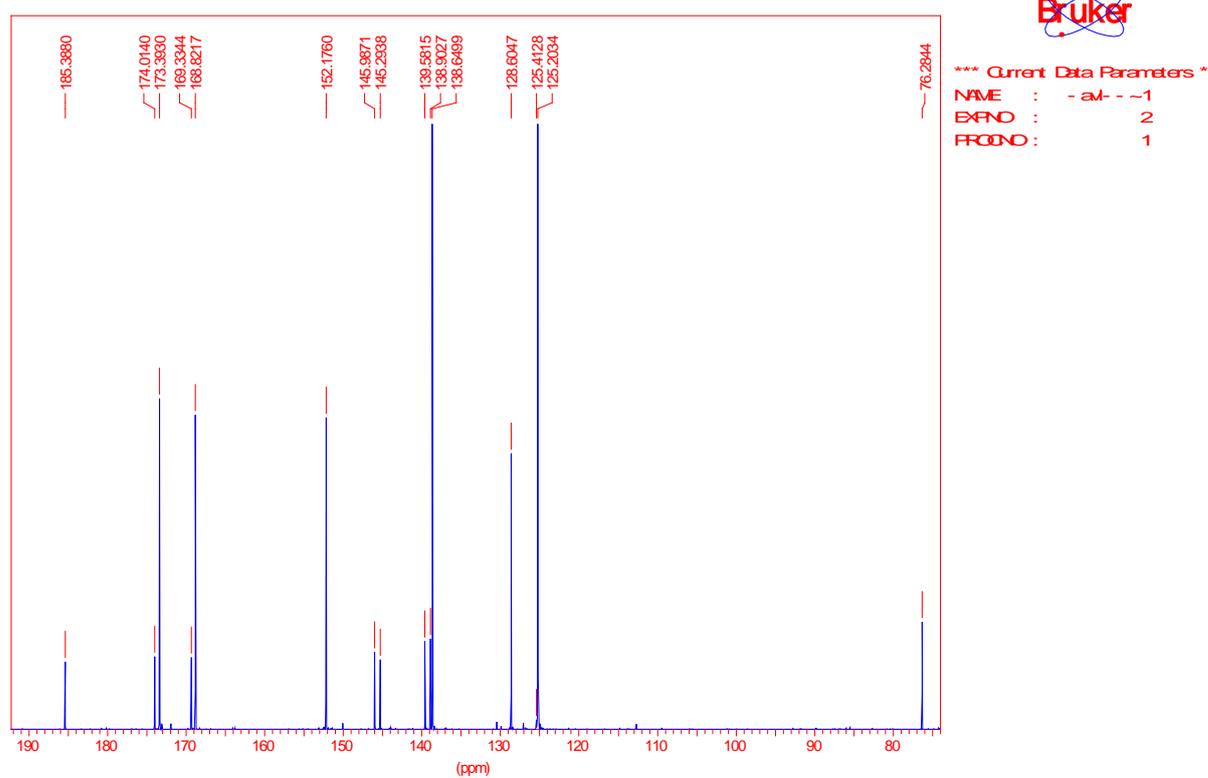


Figure 1. Spectrum ^1H NMR of reactionary mass of reaction compound **1** with oxygen in an alkaline condition at 55°C - 60°C for 6 h.

ALCdept135q 26.08 14

Figure 2. Fragment of the spectrum ^{13}C NMR compound 2 in a format *dept*.

ALC 26.08 14

Figure 3. Spectrum ^{13}C NMR from reactionary mass of compound 1 with oxygen in an alkaline condition at 55°C - 60°C for 6 h.

At last, a signal of 76.28 ppm belongs to tetrahedral atom of carbeneum, forming communications with cycle carbeneums atom, *tert*-butyl group and atom of oxygen (**Figure 4**).

According to [9], a position of a signal from tetrahedral atom of carbeneum in spiran to system with atom of nitrogen is in area of 75 ppm.

Data of spectrums NMR is sufficient for conclusions about structure of compound, producing by a interaction of 2-(*N*-acetylamino)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid with O₂ at temperature of 50°C - 60°C in solution of ethanol. This fact confirms bonding between atom of oxygen of a carboxyl group and of carbeneum atom from hexatomic cycle.

In reaction **1** at temperature 95°C - 97°C (thermostatic control) 6,8-di-*tert*-butyl-3-(*N*-acetylamino)spi-ro(4,5)deca-1-oxa-5,8-dien-2,7-dione (**4**) is formed, along with compound **2** (**Scheme 2**).

The interrelation of resultants of reaction (**2** and **4**) are found from comparison there of integrals signals in spectrum ¹H NMR reactionary mass (**Figure 5** and **Figure 6**).

The analysis of dates of a spectrum specifies in presence at reactionary mass of three compounds are identified: one of them is with structure **2** and two compounds are with structure **4** which, apparently, are structure of isomers (**Figure 6**).

Signals “doublet of doublets” belong to one of structure **4a**, the signal “triplet” belongs to **4b** (**Scheme 3**).

AVL H-C 26.08 14

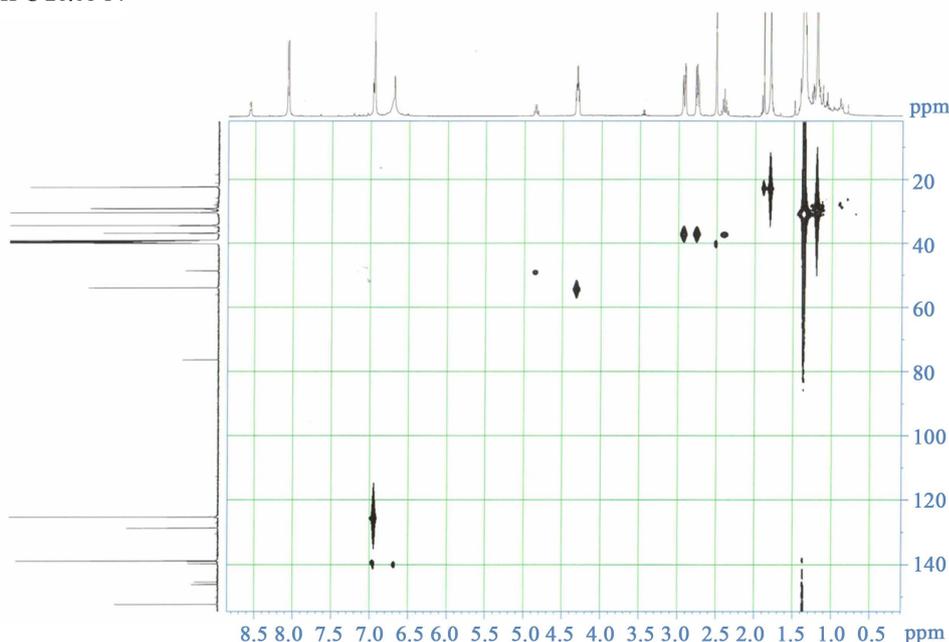
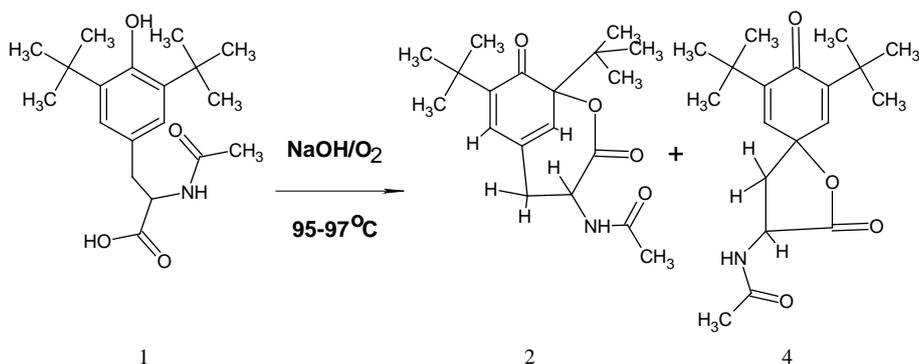


Figure 4. Correlation of data spectrums ¹H and ¹³C NMR in co-ordinates C-H.



Scheme 2. Structures of compounds isolating in reaction compound **1** with oxygen.

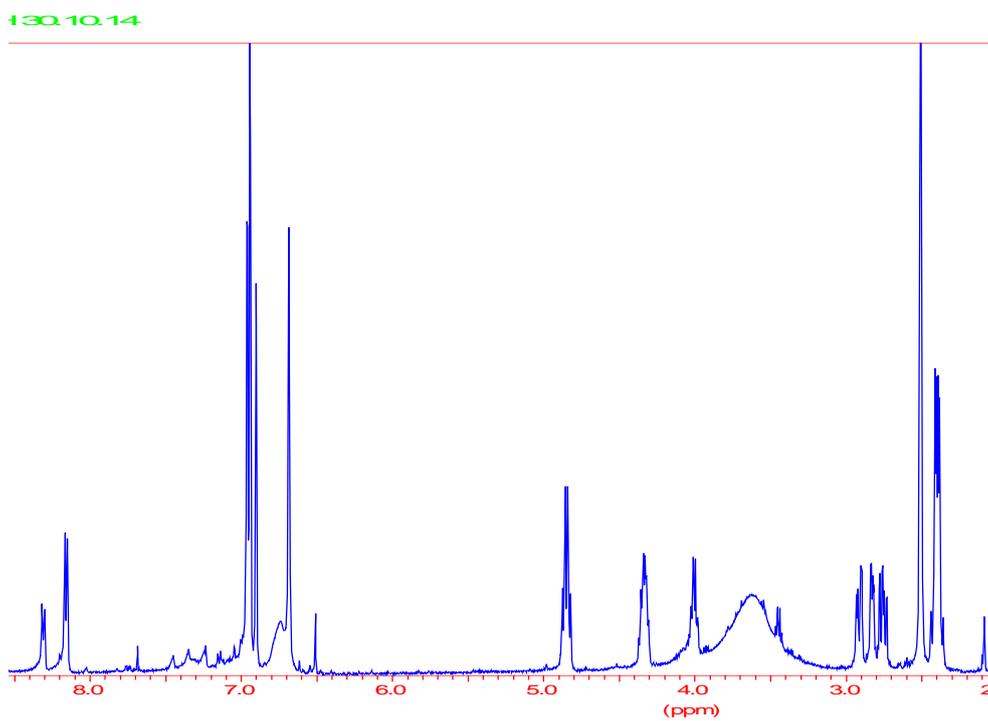


Figure 5. Spectrum ^1H NMR reactionary mass after oxidation of compound **1** by oxygen at 95°C - 97°C for 6 h.

ALVH30.10.14

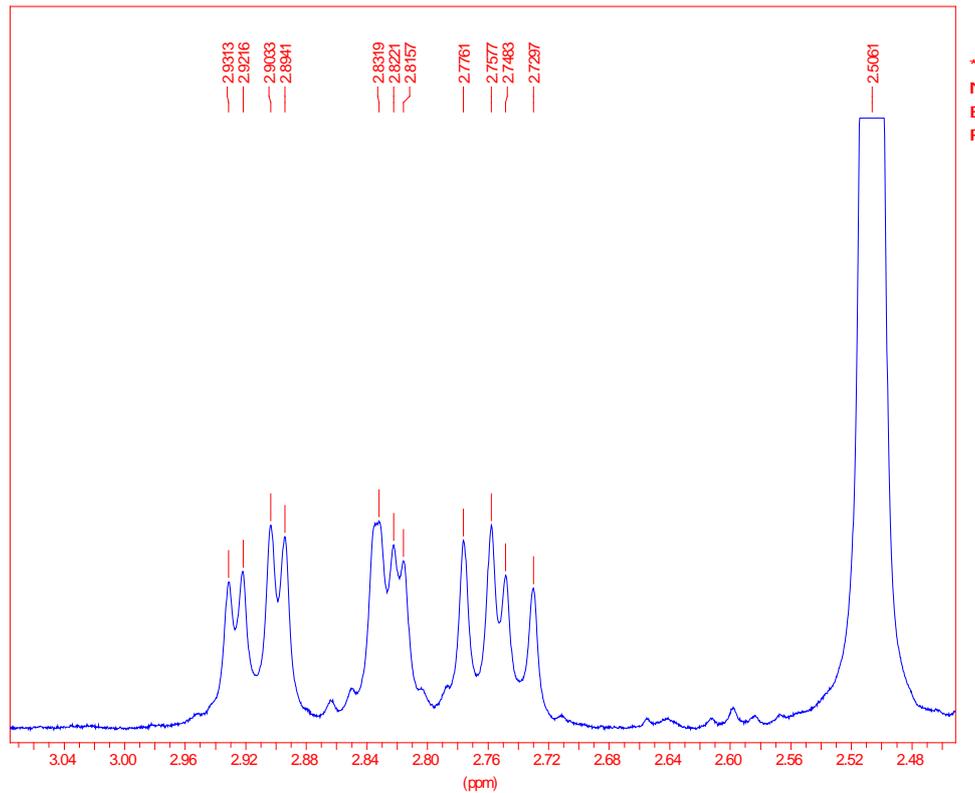
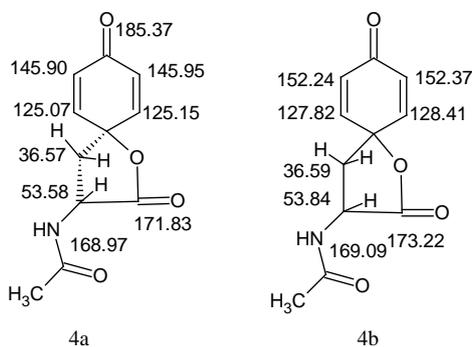


Figure 6. Fragment of the spectrum ^1H NMR (2.9 - 2.7 ppm) from a signal from group CH_2 of structure **4**.



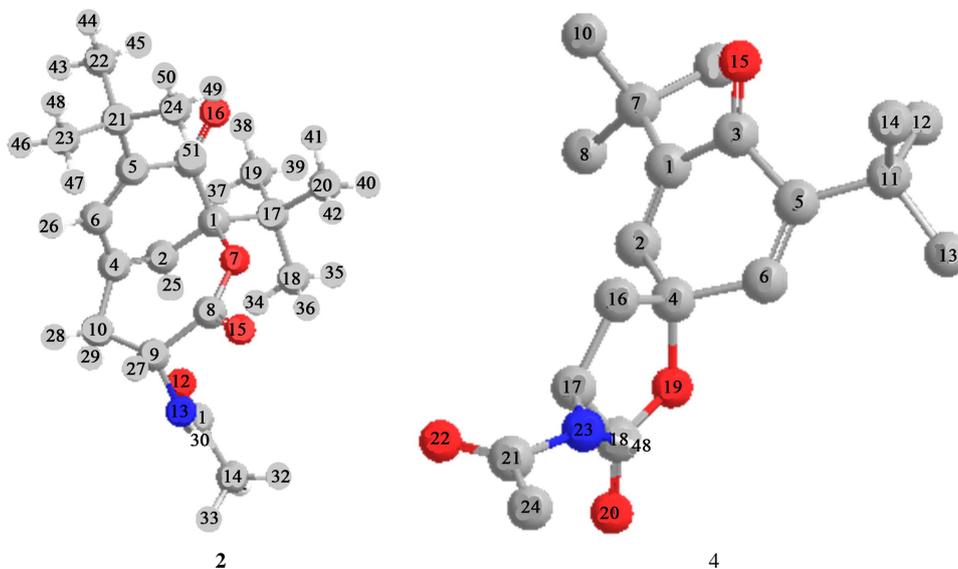
Scheme 3. Isomers of compound **4**.

One of the possible factors influencing allocation of frequencies in spectrums ^1H and ^{13}C NMR can be asymmetry because of influence *tert*-butyl groups on geometrical parameters.

Path comparison of structures **2** and **4** by method of Hartree-Fock (UHF) on energy formations the result is received: (H_f°) for **2** $H_f^\circ = -179.3$ -for **4** $= -144.4 \text{ kcal}\cdot\text{mol}^{-1}$, values of charges on atoms of oxygen [**2**, O (15) $q = -0.58$; **4**, O (15) $q = -0.59$].

Distinctions in charges on atoms of carbeneum in a hexatomic cycle [**2**, C (1) $q = -0.02$, **4**, C (1) $q = +0.3$].

Angle between a plane of hexatomic cycle and communication C=O (15), for **2** [C (2)-C (1)-(O)-(16)] ω hailstones = 27.6° , for **4** [C (2) - C (1)-O (15)] ω hailstones = 26° .



A calculates of enthalpies (H_f°) and of entropies (S_f°) for structures **2** and **4** have appeared comparable (**2**, $H_f^\circ = 17.5 \text{ kcal}\cdot\text{mol}^{-1}$, $S_f^\circ = 182.3 \text{ unite}\cdot\text{cal}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$; **4**, $H_f^\circ = 17.1 \text{ kcal}\cdot\text{mol}^{-1}$, $S_f^\circ = 174.9 \text{ unite}\cdot\text{cal}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$). These results in of set with calculation of geometry of structures **2** and **4** specifies in dynamic isomerism possibility.

4. Conclusion

At oxidative ring, the formation is produced in process interaction of 2-(N-acetylamine)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid with oxygen in the presence of alkali and 2,4-di-*tert*-butylbicyclo(4,3,1)deca-4,6-dien-8-(N-acetylamine)-3,9-dion-1-oxa and 6,8-di-*tert*-butyl-3-(N-acetylamine)-spiro(4,5)deca-1-oxa-5,8-di-en-2,7-dione are formed. The interrelation of results by oxygen depends on temperature. These results may be impotent for investigation of components during reactions 2-(N-acetylamine)-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionic acid in the conditions of biological researches.

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