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Regioselectivity of the bromination of 1-oxo-1,2,3,4-tetrahydronaphthalene and 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene, and thiabiscyclanones synthesis on their basis

ALEXEI N. PANKRATOV[1*], OLGA V. FEDOTOVA[1], ANTONINA V. BARABANOVA[1], TAT'YANA V. ALYONKINA[2] and YURI YU. ELISEEV[2]

[1]*Department of Chemistry, N. G. Chernyshevskii Saratov State University, 83 Astrakhanskaya Street, Saratov 410012, Russia (e-mail: pankratovan@chem.sgu.ru) and* [2]*Russian Antiplague Research Institute "Microbe", 46 Universitetskaya Street, Saratov 410005, Russia*

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Abstract: On the basis of quantum chemical (PM3 and RHF/6-31G*) study, the regioselectivity of the bromination of 1-oxo-1,2,3,4-tetrahydronaphthalene (**1**) and 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**2**) at their alicyclic and aromatic fragments was quantum chemically substantiated and confirmed experimentally. It was found that the above compounds undergo aromatic at the α-methylene position. The conditions for bromination at the positions 5, 8 of benzannelated ring were established. For the first time, non- and 2,2'-dibromosubstituted with respect to the oxo group bis(6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphth-2-yl) sulphides (**7, 8a, b**) were obtained. The latter were found to show promise as stabilizing agents for the storage of cholera sera.

Keywords: 1-oxo-1,2,3,4-tetrahydronaphthalene, bromination, reactivity, quantum chemical study, sulphur-containing 1,5-diketones.

INTRODUCTION

The chemical properties of methylenebiscyclanones have been studied extensively.[1,2] However, information on the preparation and reactivity of thiabiscyclanones is scarce.[3,4] The presence of a sulphur atom and a condensed aromatic fragment in the diketones structure not only influences their chemical behaviour, but also allows these compounds, as well as their transformations products, to be regarded as potentially biologically active compounds.[5,6] In this sense, the synthesis of previously unknown thiabiscyclanones – bis(1-oxo-1,2,3,4-tetrahydronaphth-2-yl) sulphides, including halogen substituted ones, containing a condensed aromatic ring, seemed to be of interest. For this purpose, it was considered that 2-bromosubstituted ketones, in particular, 1-oxo-tetrahydronaphthalenes, could be the most convenient starting materials.

* Author for correspondence

COMPUTATIONAL METHODS AND EXPERIMENTAL

Quantum chemical computations.

The electronic structure of the molecules, thermodynamic characteristics of the theoretically feasible bromination σ-complexes, as well as the cationic localization energies were computed by means of the PM3 (Parametric Method 3) method,[7] with software of the MOPAC package.[8,9] The preliminary optimization was realized by the molecular mechanics method using the MMX procedure with software of the *PCMODEL* complex.[10] Mulliken charges on the atoms were computed *ab initio* by means of the RHF (Restricted Hartree - Fock) method[8] in the 6-31G* basis with software of the *Hyper Chem* package [HyperChem (TM), Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, U.S.A.]. The frontier electron density values in the HOMO of the different atoms in the molecules are based on data of RHF/6-31G* computations.

Syntheses.

Compound (***1***) was synthesized according to a known[11] technique.

Compound (***3***). A solution of 0.96 ml (18.7 mmol) of bromine in 5 ml of chloroform was added dropwise under stirring to a solution of 3 g (17 mmol) of 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**2**) in 30 ml of a mixture of diethyl ether and chloroform (1 : 1 v/v). The reaction mixture was stirred at room temperature for 3 h, left to stand overnight, washed with water, $NaHCO_3$, water, dried over $MgSO_4$ and the solvents evaporated. The crystals which formed were recrystallized from 2-propanol. Yield, 1.98 g (45 %), m.p. 101–102 ºC. Anal: Calcd. for: $C_{12}H_{13}BrO$; C, 56.92, H, 5.14, Br, 31.62. Found: C, 57.04, H, 5.08, Br, 31.97.

Compounds (***5, 6a, b***). These compounds were synthesized analogously to bromide **3** with reagents **1**, **2** and bromine using a mole ratio of 1 : 2. The crystals which formed were filtered, washed with hexane. (**5**) Yield, 9.00 g (35 %), m.p. 56–57 ºC. Anal: Calcd. for: $C_{10}H_8Br_2O$; C, 39.47, H, 2.63, Br, 52.63. Found: C, 39.25, H, 2.51, Br, 51.94. (**6a, b**) Yield, 2.80 g (40 %), m.p. 132–133 ºC. Anal: Calcd. for: $C_{12}H_{11}Br_3O$; C, 35.03, H, 2.61, Br, 58.82. Found: C, 35.45, H, 2.54, Br, 58.24.

Compound (***7***). A solution of 4.05 g (16 mmol) of $Na_2S{\cdot}9H_2O$ in 10 ml H_2O was added dropwise to a solution of 6.8 g (30 mmol) of 2-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene (**4**) in 35 ml of 2-propanol. The reaction mixture was stirred at room temperature for 30 min. The crystals which formed were filtered, washed with water and diethyl ether. Yield, 3.90 g (74 %), m.p. 125–126 ºC. Anal: Calcd. for: $C_{20}H_{18}O_2S$; C, 74.54, H, 5.59, S, 10.04. Found: C, 75.01, H, 5.45, S, 9.64.

Compounds (***8a, b***). A solution of 0.84 g (3.3 mmol) of $Na_2S{\cdot}9H_2O$ in 10 ml of 2-propanol was added dropwise to a solution of 1.5 g (6 mmol) of tribromides **6a,b** in 15 ml of a mixture of 2-propanol and chloroform (3 : 1 v/v). The reaction mixture was stirred at room temperature for 12 h, washed with water, dried with $MgSO_4$, and the solvent removed by distillation. The oil which formed was purified by column chromatography on silica gel L 100/160, the eluent was hexane. Yield, 1.3 g (31 %), m.p. 120–122 ºC. Anal: Calcd. for: $C_{24}H_{22}Br_4SO_2$; C, 41.49, H, 3.17, Br, 46.13, S, 4.61. Found: C, 41.67, H, 3.47, Br, 45.93, S, 4.14.

Reaction control and substance identification.

The ^{1}H-NMR spectra were recorded on a Varian FT 80 A spectrometer (at 80 MHz) in $CDCl_3$, using TMS as the internal standard. The IR spectra were determined using a Specord M-80 spectrophotometer in vaseline oil and hexachlorobutadiene. Control over progress of the reaction and the purity of the obtained substances was performed by the TLC method (Silufol UV-254, hexane – diethyl ether – chloroform, 3 : 1 : 1 v/v/v, detection with iodine vapour).

*Determination of the effect of sulphides **7, 8a, b** with respect to preventing growth of saprophytes colonies in initial sera.*

All the assays with the serum samples were performed under non-sterile conditions allowing, therefore, their contamination with saprophytic microflora. The capability of the reagents to prevent growth of microbial saprophytes was studied using "Dry nutrient medium for controlling over sterility (thioglycolic)" manufactured in Russia. One ml of each serum sample was distributed in 6 tubes each containing 20 ml of thioglycolic medium. Three tubes were incubated at a temperature of 30 to 35 ºC for detecting anaerobic microorganisms, and the other 3 tubes at 20 to 25 ºC searching for fungi and bacteria with a growth opti-

mum in this temperature range. The incubations were performed for 14 days or longer, being periodically observed. The results were obtained visually (macroscopic observation), and in the cases of the appearance of microorganisms, microscopic investigations were carried out after 14 days.

RESULTS AND DISCUSSION

The first step of the bromination of 1-oxo-1,2,3,4-tetrahydronaphthalene (**1**) and 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**2**) at position 2 of the cyclohexenone ring is assumed to be enolization of the substrate.

Using the PM3 method,[7] the electronic structure of molecules of ketones **1** and **2** and their enolic tautomers (**1e**, **2e**) was computed. As can be seen from Table I, in which the standard values of the heat of formation (ΔH_f), entropy (S), free energy of formation (ΔG_f), and the dipole moments (μ), of the isolated molecules **1** and **2** are presented, the oxo tautomers are preferred considerably in terms of energy. This is in agreement with the gaseous-phase IR spectrum of 1-oxo-1,2,3,4-tetrahydronaphthalene.[12]

Differences in the heats and free energies of formation between the enolic and ketone tautomers of substances **1**, **2** are quite similar. Also, there is a substantial decrease in the polarity of the molecules of both compounds on enolization. These factors serve as a basis for explaining the similar behaviour of substrates **1**, **2** in the bromination reaction at the cycloalkenone fragment. An argument supporting this explanation is the similarity of the *ab initio* (RHF/6-31G*)[8] computed Mulliken charges on the C2 atom, the site of bromination of the non-aromatic ring, and also of the charges on the hydrogen atoms bound to C2 (Table II).

TABLE I. Computed characteristics of compounds **1**, **2** and their hydroxy tautomers **1e**, **2e**

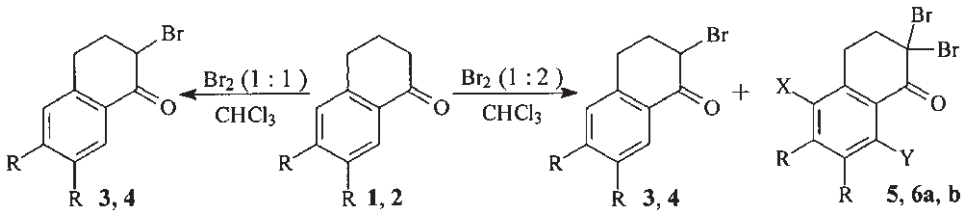
Compound	ΔH_f/4.184 kJ/mol	S/4.184 J/(mol K)	ΔG_f/4.184 kJ/mol	μ/D
1	–24.28	91.06	6.46	2.96
1e	–14.53	91.33	16.13	0.944
2	–42.36	108.19	2.70	3.08
2e	–32.42	108.03	12.69	0.539

TABLE II. Mulliken charges on the atoms of 1-oxo-1,2,3,4-tetrahydronaphthalene (**1**) and 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**2**) molecules

Molecule	Charge on atom								
	C1	C2*	C3	C4	C5	C6	C7	C8	O
1	0.552	–0.408	0.178	–0.335	–0.241	–0.176	–0.219	–0.167	–0.554
2	0.553	–0.407	0.177	–0.332	–0.263	0.037	0.006	–0.204	–0.558

* Charges on the hydrogen atoms at C2 in molecule **1** are 0.192 and 0.209, and in molecule **2**, 0.191 and 0.207

The occurrence of the above reaction route was confirmed experimentally for both carbonylic compounds **1**, **2** (Scheme 1).



R = X = Y = H (**1**, **4**, **5**); R = CH_3 (**2**, **3**, **6a**, **b**); X = Br, Y = H (**6a**); X = H, Y = Br (**6b**)

Scheme 1.

It was shown that the bromination of 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene **2** in a mixture of diethyl ether and chloroform (1 : 1 v/v) using a 1 : 1 mole ratio of the reactants proceeds in the same manner as for homolog **1**,[11] affording 2-bromo-6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**3**) in a yield of 45 %.

In order to explain the reactivity of compounds **1**, **2** with respect to electrophilic attack at the aromatic ring, a simulation of the reaction barriers was performed stipulating that the reaction occurs *via* the σ-complex stage,[13–16] the energy of such an intermediate being close to the energy of the transition state (localization approximation).[13–16] The heats and free energies of formation of the theoretically feasible σ-complexes of the bromination of the aforementioned substrates for substitution at all positions of the ring are presented in Table III.

TABLE III. Thermodynamic characteristics of the σ-complexes of the bromination of compounds **1**, **2** according to PM3 data

Compound	Position	ΔH_f/4.184 kJ/mol	S/4.184 J/(mol K)	ΔG_f/4.184 kJ/mol
1	5	176.37	102.78	209.04
1	6	180.76	103.99	213.07
1	7	174.41	102.70	207.10
1	8	181.13	101.96	214.04
2	5	153.21	114.99	201.66
2	8	156.89	114.66	205.44

The values of the cationic localization energy (Table IV) were computed:[13,15]

$$\Delta\Delta H_f = \Delta H_f(A) + \Delta H_f(Br^+) - \Delta H_f(ABr^+),$$
$$\Delta\Delta G_f = \Delta G_f(A) + \Delta G_f(Br^+) - \Delta G_f(ABr^+),$$

where A is a substrate from the hydronaphthalenone series, ABr^+ is σ-complex of the aromatic bromination reaction. For the electrophilic bromonium cation Br^+, the experimental values of $\Delta H_f(Br^+)/4.184 = 301.184$ kJ/mol and $\Delta G_f(Br^+)/4.184 = 292.523$ kJ/mol[17] were used. The higher is the cationic localization energy, the lower is the activation energy of the process.[16]

The computed cationic localization energies (Table IV) show that the probability of electrophilic attack by bromine at the different aromatic ring positions of ketone **1** changes in the order: 7 > 5 > 6 > 8.

TABLE IV. Enthalpies ($\Delta\Delta H_f$) and free enrgies ($\Delta\Delta G_f$) of cationic localization on bromination at different positions of the aromatic ring of molecules **1**, **2**

Compound	Position	$\Delta\Delta H_f$/4.184 kJ/mol	$\Delta\Delta G_f$/4.184 kJ/mol
1	5	100.53	89.94
1	6	96.14	85.91
1	7	102.50	91.89
1	8	95.77	84.94
2	5	105.61	93.56
2	8	101.93	89.78

Furthermore, the frontier electron density of the highest occupied molecular orbital (HOMO) of the different atoms of molecules **1** and **2** were computed. With respect to molecule **1**, the above quantities for C5–C8 carbon atoms are equal to 0.085, 0.011, 0.163 and 0.075, respectively. For the C5 and C8 atoms of molecule **2**, the corresponding values are 0.011 and 0.025. It is interesting to note that the reactivity series for the different positions of molecule **1** predicted by such static indices such as charges on atoms (Table II) and electron density of the HOMO, appears to be 5 > 7 > 6 > 8 and 7 > 5 > 8 > 6, respectively. The dynamic reactivity index, cationic localization energy, should obviously lend credibility to a greater extent, since the perturbation theory[18] is not completely applicable to the reaction under study. Nevertheless, all three just mentioned indices indicate a greater rate of electrophilic reaction with participation of position 5 of molecule **1** as compared to position 8.

With respect to 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**2**), in which the positions 6 and 7 are occupied, the indices $\Delta\Delta H_f$, $\Delta\Delta G_f$ and the charges on the atoms give an analogous result: 5 > 8, in contrast to the electron density of the HOMO.

The said regularities of the reactivity of compound **1**, in terms of the predominant participation of positions 5 and 8 of the molecule, are in compliance to views[14,15] on the consistent *meta* orientation of carbonyl-containing substituents, and *ortho*, *para* orientation of the cycloalkyl fragment. Furthermore, when considering the comparative reactivity in the series of compounds **1**, **2** to bromination at positions 5 and 8, non-occupied in both molecules, attention is drawn to the fact that for either of the two positions 5 or 8, more negative charges on the atoms and greater values of $\Delta\Delta H_f$, $\Delta\Delta G_f$ are observed in the case of compound **2** in comparison with **1**.

Therefore, the activation energy for bromination of 6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene (**2**) is lower than for its non-methylated homolog **1**.

Taking into account the information[14,15] on kinetic control of electrophilic aromatic substitution reactions, it could be expected that the product yields of the bromination of the aromatic ring would be higher for compound **2** than for compound **1**.

This quantum chemical supposition is confirmed by our obtained experimental data. Thus, with a two-fold mole excess of bromine in the medium diisopropyl ether – chloroform (1 : 1 v/v), ketone **1** gives a mixture of 2-bromo and 2,2- dibromo substituted 1-oxo-1,2,3,4-tetrahydronaphthalenes (**4, 5**) after 24 h. For the oxo compound **2**, the reaction is complete within 1 h, which is a testimony of the enhanced nucleophilicity of compound **2** as compared to the homolog **1**, with the formation of, along with monobromo derivative **3**, a mixture of the isomers 2,2,5- and 2,2,8-tribromo-1-oxo-1,2,3,4-tetrahydronaphthalenes (**6a, b**). The bromosubstituted ketone **3**, being an intermediate in the synthesis of compounds **5**, **6a, b**, was identified in the reaction mixtures by thin layer chromatography (TLC). Bromination of a condensed aromatic ring is evidenced by ^{1}H-NMR spectroscopy data. In the ^{1}H-NMR spectra, the signals of the protons at the C5 and C8 atoms appear at 6.96 p.p.m. and 7.85 p.p.m., respectively; the shift of the proton signal at the C8 position toward a weaker field is obviously related to the deshielding effect of the electron-acceptor substituent. Methylene and methyl protons signals are observed as a multiplet at 2.23–2.29 p.p.m. and a singlet at 1.52 p.p.m., respectively. The ratio for the isomers **6a** and **6b** calculated on the basis of the comparison of the integral intensities of the aromatic protons signals at C5 and C8 is equal to 1.2:1.

Consequently, the substrate selectivity for the bromination of compounds **1**, **2** is controlled by the static reactivity index, charge on the atom, and the dynamic index, cationic localization energy.

For compound **2**, using the above indices, the positional selectivity is also described. Under the condition of kinetic control of the reaction,[14,15] the quantitative proportion of 5- (**6a**) and 8- (**6b**) bromo derivatives established experimentally (1.2 : 1) corresponds to a higher rate of bromination at position 5 against the electrophilic attack at the carbon atom at position 8 of the ring. This experimental fact is in agreement with the more negative charge on the C5 atom and larger values of $\Delta\Delta H_f$, $\Delta\Delta G_f$ for the corresponding σ-complex formation compared to the analogous characteristics involved in substitution at the C8 atom of molecule **2**.

Thus, the yields of the bromination products of compounds **1**, **2** are comparable semiquantitatively with the $\Delta\Delta H_f$, $\Delta\Delta G_f$ values and the charges on atoms.

The results obtained using the commonly accepted terms of the perturbation theory, attest that the reaction under study is closer to a charge-controlled one than to a frontier-controlled one. At the same time, the bromination of an aromatic ring in general is a case of the interaction between a soft Lewis base (aromatic system) and a soft acid (bromine-containing electrophilic species). On the other hand, it is known[14,19] that a soft-soft interaction is frontier-controlled, and hard-hard one is charge-controlled.

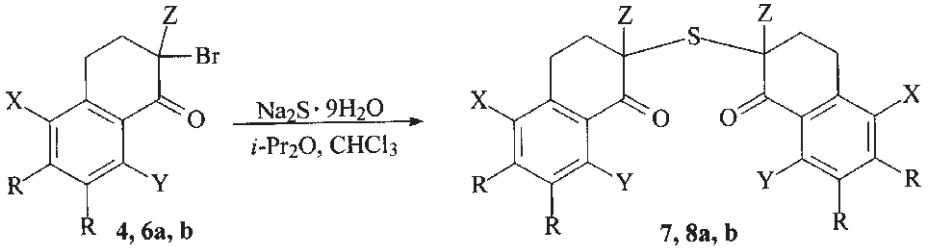
The contradiction is eliminated by taking into consideration the following points.

1. Notions on charge-controlled and frontier-controlled processes are not completely adequate for describing reactions with an essential redistribution of chemical bonds.

2. The hardness of the aromatic system in an α-tetralone molecule is enhanced due to the presence of an electron-acceptor carbonyl substituent.

3. An electrophilic species becomes more hard as its charge increases. The results of the present work testify indirectly that the reacting species (*i.e.*, bromonium ion Br^+) is positively charged.

The synthesized bromosubstituted compounds, 1-oxo-1,2,3,4-tetrahydronaphthalenes (**4, 6a, b**), give the corresponding bis(1-oxo-1,2,3,4-tetrahydronaphth-2-yl) sulphides (**7, 8a, b**) under the action of sodium sulphide (Scheme 2).



R = X = Y = Z = H (**4**, **7**); R = CH_3, X = Z = Br, Y = H (**6a**, **8a**); R = CH_3, Y = Z = Br, X = H (**6b**, **8b**)

Scheme 2.

For 2-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene **4**, the reaction proceeds in methanol or 2-propanol to form the product - hitherto unknown bis(1-oxo-1,2,3,4-tetrahydronaphth-2-yl)sulphide (**7**) in yields of 20 and 74 %, respectively. In 2-propanol, besides the increased product yield, the duration of the reaction was 30 min instead of 3 h, necessary in methanol. The dioxosulphide **7** was stable in air and did not require additional purification, in constrast to 2,2'-dicyclohexanonyl sulphide, which had to be stored in the cold.[4]

TABLE V. Physico-chemical characteristics of the synthesized compounds

No.	^{1}H-NMR Spectrum (δ/p.p.m.)	IR Spectrum (ν/cm^{-1})
3	7.85 (1H, *s*, Harom, C8), 6.96 (1H, *s*, Harom, C5), 4.62 (1H, *t*, J_{H-H} = 6.0 Hz, CH), 2.22–2.84 (4H, *m*, $2CH_2$), 2.21 (6H, *s*, $2CH_3$)	3022, 2948 (C–H), 1610 (C–C), 1674 (C=O), 628 (C–Br)
5	7.25–8.07 (2H, *m*, Harom), 2.95 (4H, *m*, $2CH_2$)	3024, 2932 (C–H), 1596 (C–C), 1696 (C=O), 620 (C–Br)
6 a, b	7.85 (1H, *s*, Harom, C8), 6.96 (1H, *s*, Harom, C5), 2.23–2.97 (4H, *m*, $2CH_2$), 1.52 (6H, *s,* $2CH_3$)	3025, 2944 (C–H), 1608 (C–C), 1696 (C=O), 628 (C–Br)
7	7.25–8.07 (8H, *m*, $2C_6H_4$), 4.02 (2H, *t*, J_{H-H} = 6.3 Hz, 2CH), 2.95 (4H, *m*, $2CH_2$), 2.30 (4H, *m*, $2CH_2$)	3024, 2932 (C–H), 1598 (C–C), 1674 (C=O)
8 a, b	7.19 (1H, *s*, Harom, C8), 6.96 (1H, *s*, Harom, C5), 2.60 (8H, *m*, $4CH_2$), 1.54 (12H, *s*, $4CH_3$)	3024, 2922 (C–H), 1600 (C–C), 1696 (C=O), 625 (C–Br)

The synthesis of halogen-containing 1,5-diketones is rare, being restricted to only few examples,[20,21] in all the cases the substances were obtained by direct halogenation

of dioxo compounds. For the first time we have obtained representatives of new series of halogen-containing 1,5-diketones – bis(2,5-dibromo- and bis(2,8-dibromo-6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphth-2-yl) sulphides (**8a**, **b**) with conservation of the ratio of 1.2 : 1 by the reaction between tribromo substituted 1-oxo-1,2,3,4-tetrahydronaphthalene **6a**, **b** and $Na_2S{\cdot}9H_2O$ in 2-propanol and chloroform (3 : 1 v/v) medium.

The composition and structure of the obtained compounds were confirmed by the data from elemental analysis, as well as IR and ^{1}H-NMR spectroscopy (Table V).

The compounds **7**, **8a**, **b** were tested in respect to non-adsorbed semiproducts of cholera agglutinating sera 01 Inaba and Ogawa isolated by hyperimmunization of horses with O-antigens of Vibrio cholerae biotype EltTor.

The pH values of the sera were determined potentiometrically using a Ionomer Universal EV-74 instrument at a temperature of 25 ± 2 ºC. On addition of the dioxo compounds **7**, **8a**, **b**, the pH varied only slightly, whereas addition of chinosol and boric acid (as standards) changed the pH values of the sera in the acidic direction. Protein was assayed by a spectrophotometric method using a SF-46 spectrophotometer at wavelengths of 260 nm (to take into account the absorption of nucleotide compounds) and 280 nm (to take into account the absorption of aromatic amino acids). The protein contents were calculated from a nomogram.[22] It was shown that the addition of reagents **8a**, **b** to serum prevents the development of saprophytes for 6 months, whereas the presence of the diketone **7** in serum does not affect the growth of microflora, which confirms that bis(2,5-dibromo- and bis(2,8-dibromo-6,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphth-2-yl)sulphides **8a**, **b** show promise as stabilizing agents for the storage of bacteria at various kinds of collection centers.

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ИЗВОД

РЕГИОСЕЛЕКТИВНОСТ ПРИ БРОМОВАЊУ 1-ОКСО-1,2,3,4-ТЕТРАХИДРОНАФТАЛЕНА И 6,7-ДИМЕТИЛ-1-ОКСО-1,2,3,4-ТЕТРАХИДРОНАФТАЛЕНА И СИНТЕЗА ТИЈАБИСЦИКЛАНОНА НА ЊИХОВОЈ ОСНОВИ

ALEXEI N. PANKRATOV, OLGA V. FEDOTOVA[1], ANTONINA V. BARABANOVA[1], TAT'YANA V. ALYONKINA[2] and YURI YU. ELISEEV[2]

[1]Department of Chemistry, N. G. Chernyshevskii Saratov State University, 83 Astrakhanskaya Street, Saratov 410012, Russia and [2]Russian Antiplague Research Institute "Microbe", 46 Universitetskaya Street, Saratov 410005, Russia

Квантнохемијским израчунавањима (PM3 и RHF/6-31G*) подржано је, а експериментално и потврђено региоселективно бромовање 1-оксо-1,2,3,4-тетрахидронафталена (**1**) и 6,7-диметил-1-оксо-1,2,3,4-тетрахидронафталена (**2**) на њиховим алицикличним одн. ароматичним фрагментима. Показано је да бромовање наведених једињења настаје у α-метилен-

ском положају. Утврђени су услови за бромовање у положају 5,8 бензенанелираног прстена. По први пут су добијени несупституисани и 2,2´-дибромосупституисани деривати у односу на оксо групу бис(6,7-диметил-1-оксо-1,2,3,4-тетрахидронафт-2-ил) сулфида (**7**, **8a**, **b**). Изгледа да се ово последње наведено једињење може употребити као стабилизациони агенс за серуме колере.

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