

SYNTHESIS AND CHARACTERIZATION OF 8-HYDROXY-5,8,9,10-TETRAHYDRO-6H-BENZOCYCLOOCTEN-7-ONE, 5,6,9,10-TETRAHYDRO-BENZOCYCLO-OCTENE-7,8-DIONE AND 6,7,10,11-TETRAHYDRO-BENZOCYCLOOCTA- [b]QUINOXALINE

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Abstract

8-Hydroxy-5,8,9,10-tetrahydro-6H-benzocycloocten-7-one **3**, 5,6,9,10-tetrahydro-benzocyclooctene -7,8-dione **4** and 6,7,10,11-tetrahydro-benzocycloocta[b]quinoxaline **5** have been synthesised. The synthetic method involved modified acyloin cyclization of 3-[2-(2-ethoxycarbonyl-ethyl)-phenyl]-propionic acid ethyl ester **1** to 7,8-Bis-trimethylsilyloxy-5,6,9,10-tetrahydro-benzocyclo-octene **2** followed by acid-catalyzed hydrolysis furnished the acyloin **3**, and / or by oxidation with Jones reagent yielded to the α -diketone **4**. The corresponding quinoxaline **5** was prepared by the reaction of **4** α -diketone with benzene-1,2-diamine in acetic acid. The structure and spectral behavior of these molecules have been elucidated with molecular mechanical and quantum mechanical methods.

Introduction

A survey of literature on eight-membered rings and fused ones to aromatic molecules shows that these rings are one of the most difficult to prepare, due to their high steric energy and transannular effects.¹ Eight-membered cyclic compounds are found widely in nature and many biologically active cyclooctanoids natural products,² and synthetic compounds,³ have been studied. Cyclic α -diketones and quinoxalines are reported as intramolecular energy transfer,⁴ and pharmacological active compounds.⁵ In accordance to our interest for structural and spectral studies of new eight-membered fused rings to aromatic molecules, we have synthesized 8-hydroxy-5,8,9,10-tetrahydro-6H-benzocycloocten-7-one **3**, 5,6,9,10-tetrahydro-benzocyclo-octene-7,8-dione **4** and 6,7,10,11-tetrahydro-benzocycloocta [b]quinoxaline **5**.

Theoretical foundation for modern chemistry was laid more than 70 years ago and at this time it becomes possible, in principle, to use this for understanding how electrons,

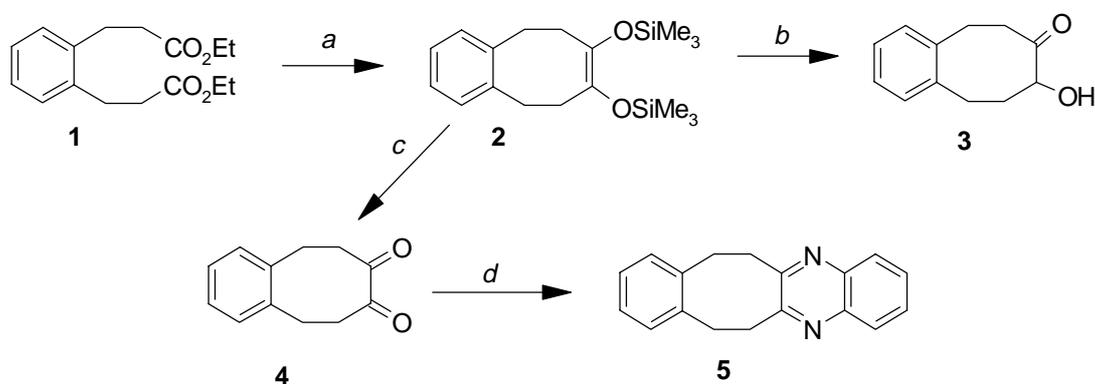
atoms, and molecules interact. Theoretical and empirical calculation methods like experimental or spectroscopic ones are helpful tools for elucidating structure and behavior of molecules, atoms, and electrons. In this work, for identification of structures and assigning signals in NMR spectra we have used MM+ molecular mechanics,⁶ AM1 (Austin Model 1) semiempirical quantum mechanics,⁷ and typed neglect differential overlap (TNDO)⁸ methods.

Results and discussion

Synthesis

The synthetic scheme begins with the known diester **1**, 3-[2-(2-ethoxycarbonyl-ethyl)-phenyl]-propionic acid ethyl ester, which its preparation and modified acyloin cyclization has been reported previously.⁹ The resulting enediol bis-trimethylsilyl ether **2**, is relatively unstable and under subsequent acid-catalyzed hydrolysis,¹⁰ and/ or methanolysis in anhydrous methanol furnished the acyloin derivative **3** in good yield (95% and 73%, respectively).

Among the various methods, the Jones oxidation method known to be rapid with high yield, we have preferred this method and oxidation of enediol bis-trimethylsilyl ether **2** with Jones reagent¹¹ gave the desired α -diketone **4** which was purified by chromatography on silica gel (by 96% yield). Corresponding quinoxaline **5** was prepared by the reaction of benzene-1,2-diamine and the α -diketone in acetic acid. The crude product after workup was purified by two times recrystallizations from ethanol.¹² (Scheme 1)



Scheme-1 a) 5 eq. Na, 5 eq. TMSCl refluxing in Toluene, 6h; b) HCl 3N in Ether, 2h; c) Jones reagent in Acetone, 0 °C; d) Benzene-1,2-diamine refluxing in acetic acid.

Theoretical calculations

To obtain more detailed structural information and for assigning NMR spectral behavior of titled compounds we undertook molecular and quantum mechanical calculations using *HyperChem 4.5*¹³ and *ChemPlus*¹⁴ computer programs.

The problem of finding significantly populated conformations has been one of the major obstacles in studying conformationally flexible molecules. A number of algorithms for locating energy minima on a high-dimensional energy hypersurface have been proposed. They can be classified into two categories, random¹⁵ and systematic.¹⁶ While random generation is the method of choice for macromolecules, the application of a systematic method to a chain molecule (n rotatable bonds) is severely limited due to the fact that the number of trial conformations increases at the rate of 3^n .^{16a,b}

Eight-membered rings because of their low barrier of pseudorotation, are highly flexible and the conformation of the ring depends strongly on the number and nature of substituents. Molecular mechanics models are designed to provide good estimates of conformational energy differences, while the semiempirical molecular orbital models are not entirely satisfactory for this purpose.¹⁷ Determination of the conformations of title compounds, in order to allow finding the most favoured ones to use in *TNDO* calculations, were carried out by Metropolis Monte Carlo (*MMC*)¹⁸ search using *MM+* molecular mechanics by Polak - Ribiere¹⁹ conjugate gradient geometry optimization method. Then, according to our last studies,²⁰ we used AM1 semiempirical molecular orbital calculations for reoptimizing the favoured structures.

One of the major sources of perturbations in fused ring systems is strain and of the main parts of strain in medium rings is the transannular repulsion of the hydrogens of the CH_2 groups. Therefore replacement of such groups by heteroatoms or sp^2 hybridized carbon atoms would be expected to reduce the strain energy. There is a dearth of thermochemical information in this regard, but it is known that the presence of several (not just one) such elements facilitates ring closure.

In Monte Carlo searches that use the random walk, it is often necessary to raise the temperature used in the acceptance test to increase the probability of accepting a high energy conformation to cross a potential barrier. Temperature adjustment is typically

done after repeatedly finding the same duplicate conformation or repeatedly rejecting new conformations based on the Metropolis criterion. Rotation is used for acyclic bond dihedral angles and for dihedral angles in the cyclooctene ring, dihedral angles are rotated by the “torsional flexing” motion of Kolossvary and Guida,²¹ which effectively leads to new ring conformations while avoiding large atomic displacements that can decrease the efficiency of optimization. Since molecular flexibility is usually due to rotation of unhindered bond dihedral or torsion angles, with little change in bond lengths or bond angles, a frequent choice (used here) is to consider only the variation of bond torsion angles. These searches were done using the program *ChemPlus*. After the *MMC* search each conformation used as starting geometry for subsequent *MM+* with Newton - Raphson¹⁹ geometry optimization and semiempirical quantum mechanical *AMI* calculations using *HyperChem*, whereas the search shows that the most favored conformers of these compounds are as the following (Fig. 1):

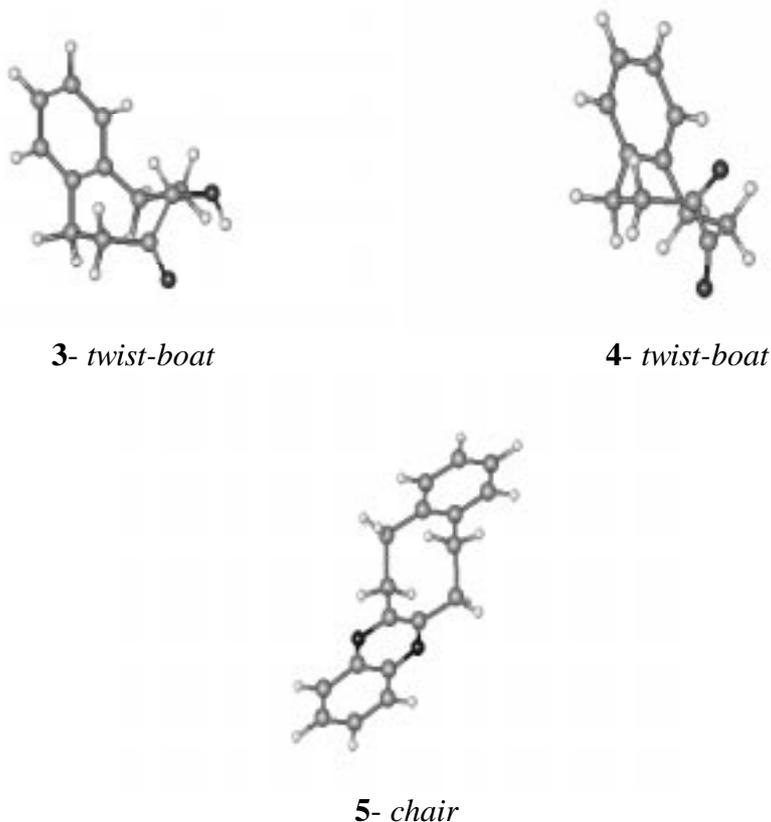


Fig. 1 The most favored conformers of title compounds.

Calculated results for each of the most favored structures are shown in Tables 1 and 2.

Table-1 Calculated results for each of the most favoured structures of 3, 4, and 5 using AM1 semiempirical molecular orbital method (Kcal/mol).

| <i>Calculation results</i> | <i>TB conformer of 3</i> | <i>TB conformer of 4</i> | <i>chair conformer of 5</i> |
|-------------------------------|--------------------------|--------------------------|-----------------------------|
| <i>Total Energy</i> | -54668.434 | -54014.509 | -67750.724 |
| <i>Binding Energy</i> | -2976.373 | -2848.054 | -4059.932 |
| <i>Isolated Atomic Energy</i> | -51692.062 | -51166.455 | -63690.792 |
| <i>Electronic Energy</i> | -320729.916 | -306866.683 | -306866.683 |
| <i>Core-Core Interaction</i> | 266061.482 | 252852.174 | 403922.371 |
| <i>Heat of Formation</i> | -77.147 | -53.031 | 75.720 |

Table-2 Calculated results for each of the most favoured structures of 3, 4, and 5 using MM+ molecular mechanics method (Kcal/mol).

| <i>Calculation results</i> | <i>TB conformer of 3</i> | <i>TB conformer of 4</i> | <i>chair conformer of 5</i> |
|-------------------------------|--------------------------|--------------------------|-----------------------------|
| <i>Bond stretching energy</i> | 0.695 | 0.864 | 0.891 |
| <i>Angle strain energy</i> | 1.849 | 1.579 | 2.186 |
| <i>Dihedral energy</i> | -0.950 | -1.929 | -6.444 |
| <i>Vdw energy</i> | 6.819 | 6.796 | 14.848 |
| <i>Stretch-bend energy</i> | 0.123 | 0.045 | 0.170 |
| <i>Electrostatic energy</i> | -0.925 | 6.241 | 1.249 |

Our theoretical study also shows that the calculated ^{13}C -NMR signals of benzocyclooctene parts of titled compounds of using TNDO/2 semiempirical quantum mechanical method are in good agreement with experimental data (see experimental data, Fig. 2 and Table-3).

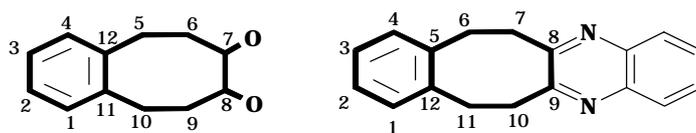


Fig. 2 Numbering system of title compounds

Table-3 TNDO/2 calculated ^{13}C -NMR chemical shifts (ppm).

| Molecule | 3 | 4 | 5 |
|----------|--------|--------|--------|
| C-1 | 132.66 | 132.52 | 132.76 |
| C-2 | 128.33 | 128.24 | 128.46 |
| C-3 | 128.24 | 128.27 | 128.38 |
| C-4 | 132.76 | 132.56 | 132.81 |
| C-5 | 24.10 | 24.70 | 134.88 |
| C-6 | 30.54 | 29.148 | 26.02 |
| C-7 | 179.71 | 176.72 | 23.14 |
| C-8 | 59.21 | 175.66 | 152.44 |
| C-9 | 24.48 | 30.40 | 152.45 |
| C-10 | 23.50 | 23.90 | 23.07 |
| C-11 | 133.74 | 133.51 | 26.04 |
| C-12 | 134.05 | 133.32 | 134.92 |

Conclusion

Based on available knowledge about the synthetic methods, we have deduced appropriate reaction conditions for the synthesis of medium sized (eight membered) ring compounds fused to benzene for synthesis of other derivatives. ^{13}C -NMR calculated signals show good agreement with experimental NMR results, and it seems that TNDO method is good tool for assignment of NMR signals, as well as for prediction of spectral behavior. It seems that scaling of calculations results can be adjusted results to experimental chemical shifts. An attractive extension of the above procedure is its application to easily prepare eight membered ring compounds fused to benzene and elucidate complicated systems.

Experimental

All manipulations till to preparation of enediol bis-trimethylsilyl ether **2** were performed under an atmosphere of purified argon and using gas/vacuum double manifold and standard Schlenk technique. DMSO, TMSCl and toluene were distilled from CaH_2 immediately prior to use. Elemental analyses: Carlo - Erba Modell 1104; IR: Bruker IFS

25; ^1H and ^{13}C NMR: Bruker AM - 400, Bruker AC - 200; MS: Varian MAT 311A, Varian MAT 111; melting points: Büchi SMP - 20; GC/MS: Top series 8000- Trio 1000 Fison Instruments .

8-Hydroxy-5,8,9,10-tetrahydro-6H-benzocycloocten-7-one (3). *a)* A threeneck, round bottom flask was fitted with a Friedrich condenser, a stirrer, and an addition funnel. Diethyl ether (100 mL) and the enediol bis-trimethylsilyl ether (**2**, 3.34 g, 10 mmol) was charged into the flask. The addition funnel was charged with HCl solution (3 N, 10 mL), then added dropwise to the flask, with stirring. The solution was refluxed and stirred for 2h, then the organic phase was washed with saturated calcium carbonate solution and water two times. The mixture was dried over MgSO_4 , and filtered. The resulting light yellow filtrate was evaporated with roto-evaporator and gave a golden yellow solid which was recrystallized from CHCl_3 (1.81 g, 9.5 mmol). The yield of **3** was 95%. *b)* Methanolysis of freshly distilled enediol bis-trimethylsilyl ether (**2**, 3.34 g, 10 mmol) in anhydrous methanol under argon in room temperature for 24 h after evaporation of solvent and volatile compounds gave a golden yellow viscose oil which was recrystallized from CHCl_3 (1.39 g, 7.3 mmol). The yield of the acyloin **3** was 73%. The m.p. 106°C , $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.75 (m, 1H), 2.20 (m, 1H), 2.74 (m, 2H), 2.87 (t, 2H, $J=6.1$ Hz), 3.12 (m, 2H), 4.31 (s, 1H), 7.18 (m, 4H); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ 215.20, 139.28, 138.69, 130.00, 129.23, 127.35, 127.22, 45.56, 36.82, 28.85, 27.41; EI MS 70 eV, m/z (relative intensity): 190 (44) [M^+], 172 (28), 146 (81), 129 (70), 117 (100), 104 (78), 91 (46), 77 (20), 58 (13), 39 (15). Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_2$ (190.24) C, 75.76; H, 7.42; Found C, 75.63; H, 7.65.

5,6,9,10-Tetrahydro-benzocyclo-octene-7,8-dione (4). The Jones reagent is a solution of chromic acid and sulfuric acid in water, we have prepared a standard solution by dissolving 26.72g of chromic trioxide in 23 mL concentrated sulfuric acid diluted with water to a volume of 100 mL. An oxidation of enediol bis-trimethylsilyl ether **2** was carried out by titrating a stirred solution of **2** (3.34 g, 10 mmol) in 20 mL acetone at 0°C with the standard solution of Jones reagent. The mixture after titration separates into a green lower layer of chromium salts and an upper layer, which is an acetone solution of

oxidation product. This solution after neutralization with 20% NaOH solution, addition of MgSO₄, separation of organic layer, and evaporation of solvent gave a golden yellow viscose oil which was purified by chromatography on silica gel with dichloromethane (1.80 g, 9.6 mmol). The yield of diketone **4** was 96%. IR (neat): ν_{max} . 3016, 1705 (C=O), 759 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.8 (t, J= 6.5 Hz, 4H), 2.95 (t, J= 6.5 Hz, 4H), 7.2 (m, 4H, ArH) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 207.42, 137.78, 130.35, 128.19, 41.50, 28.73 ppm; EI MS 70 eV, m/z (relative intensity): 188 (20) [M⁺], 145 (15), 118 (61), 104 (25), 91 (27), 73 (43), 58 (41), 43 (100). Anal. Calcd. for C₁₂H₁₂O₂ (188.22) C, 76.57; H, 6.43; Found C, 76.43; H, 6.57.

6,7,10,11-Tetrahydro-benzocycloocta-[b]quinoxaline (5). A twoneck 100 mL flask was fitted with a condenser and a stirrer. Benzene-1,2-diamine (1.18 g, 12 mmol), the α -diketone (**4**, 1.9 g, 10 mmol) in 20 mL acetic acid, pured into the flask and the solution was refluxed and stirred for 30 minutes. Then, the reaction mixture was cooled to 25°C and added 50 mL cold water. The product extracted with ether (3 × 20 mL) and then the organic phase was washed with saturated calcium carbonate solution and water two times. The mixture was dried over MgSO₄, and filtered. The resulting light yellow filtrate was evaporated with roto-evaporator and gave brown solid, which was purified with two times recrystallizations from ethanol (2.24 g, 8.6 mmol). The yield of the quinoxaline **5** was 86%. ¹H NMR (400 MHz, CDCl₃): δ 3.24 (t, J= 7.1 Hz, 4H), 3.45 (t, J= 7.1 Hz, 4H), 6.93 (m, 4H, ArH), 7.53 (q, 2H), 7.84 (q, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 156.60, 140.89, 138.71, 129.97, 128.77, 128.43, 126.81, 36.93, 32.85 ppm; EI MS 70 eV, m/z (relative intensity): 260 (67) [M⁺], 245 (100), 169 (7), 130 (9), 115 (10), 91 (6), 77 (7). Anal. Calcd. for C₁₈H₁₆N₂ (260.33) C, 83.04; H, 6.19; Found C, 82.89; H, 6.07.

Theoretical Calculations. The structure of **3**, **4** and **5** were drawn in 2D and was converted to 3D using *HyperChem*, and pre-minimized by Polak - Ribiere geometry optimization using MM+. The MMC search was carried out using this structure with MM+ and Polak - Ribiere geometry optimization using ChemPlus. This search was performed with range for acyclic or ring torsion variation $\pm 10 - 120$, Random Walk, and Metropolis Criterion use T= 300 K, switch to 400 K. The structures which were found by

MMC, were reminimized by Newton - Raphson optimization using MM+. In our semiempirical AM1 calculations we used each of these structures as the starting points for the optimization jobs and subsequently obtained structures were used in assigning NMR signals with TNDO calculations. Energy minimizations were performed until the absolute value of the largest partial derivative of energy with respect to the coordinates was below $0.01 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$. All calculations were performed on a Pentium 166 MHz computer.

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Povzetek

Pripravili smo 8-hidroksi-5,8,9,10-tetrahidro-6*H*-benzociklookten-7-on **3**, 5,6,9,10-tetrahidro-benzo-ciklookten-7,8-dion **4** in 6,7,10,11-tetrahidro-benzociklookta[*b*]kinoksalin **5**. Spojine smo pripravili z modificirano aciloinsko ciklizacijo etilnega estra 3-[2-(2-etoksikarbonil-etil)-fenil]-propionske kisline **1** v 7,8-bis-trimetilsilaniloksi-5,6,9,10-tetrahidro-benzociklo-okten **2**. S sledečo kislinsko katalizirano hidrolizo smo dobili aciloin **3**, ki smo ga oksidirali z Jones reagentom v α -diketon **4**. Ustrezni kinoksalin **5** smo pripravili z reakcijo spojine **4** z benzendiaminom v očetni kislini. Strukture in spektroskopske lastnosti spojin smo potrdili tudi z molekularnomehanskimi in kvantnomehanskimi izračuni.