Formation of 2-oxatricyclo[4.3.1.$0^{3,8}$]decanes in intramolecular cyclization of α-halobicyclo[3.3.1]nonanones

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Transformations of α-chloro- and α-bromobicyclo[3.3.1]nonanones under conditions of the Favorskii reaction were studied. The interaction of dihalodiketones with MeONa gives 2-oxatricyclo[4.3.1.$0^{3,8}$]decane (oxaprotoadamantane) derivatives as a result of intramolecular cyclization, whereas 3-bromobicyclononanone undergoes only nucleophilic substitution of bromine.

Key words: α-halobicyclo[3.3.1]nonanones, 2-oxatricyclo[4.3.1.$0^{3,8}$]decane.

Interconversion of bridged bicyclic and cage tricyclic organic structures is of considerable interest as regards the design of organic molecules[1] as well as studies dealing with stereochemistry and reaction mechanisms.[2] In this work, we report on a quite unexpected intramolecular cyclization of dihalo-derivatives of bicyclo[3.3.1]nonane-2,6-dione under conditions of the Favorskii reaction.

The Favorskii rearrangement of α-haloketones is a relatively convenient method for the synthesis of carboxylic acids.[3] The use of this reaction in the series of bridged bicyclic structures for the synthesis of the corresponding bicyclic acids has been reported.[4,5] In order to continue the studies dealing with the Favorskii rearrangement of bicyclic α-haloketones, in the present work, we studied transformations of dichloro- and dibromobicyclo[3.3.1]nonane-2,6-diones under the action of MeONa. The halo-substituted diketones were prepared by halogenation of bicyclo[3.3.1]nonane-2,6-dione (**1**) with 2 equiv. of Br_2 or Cl_2.

It should be noted that the melting point of dibromo-derivative **2a** that we prepared (171—172 °C) differs substantially from that of the compound described previously (*cf.* Ref. 6: m.p. 165—166 °C). The main distinction between the synthetic procedures was duration of the reaction: in our study, the product was isolated 10 min after the addition of Br_2, whereas in the previous paper, the reaction was carried out for 3 h. Apparently, prolonged keeping of the reaction mixture led to epimerization of dibromoketone **2a** to give a mixture of diastereomers. This follows from the ^{1}H NMR spectrum in which the signals at δ 4.6 corresponding to the protons at C(3) and C(7) transform into a complex multiplet some time after the beginning of the reaction. In the ^{1}H NMR spectrum of dichlorodiketone **2b**, the signal at δ 5.2 shows up as a doublet of doublets, and the ^{13}C NMR spectrum contains signals for five carbon atoms of the bicyclic skeleton, in conformity with the symmetry of the molecule. To determine the configuration of the halogen atoms in the bicyclic molecule, we carried out bromination of ketone **1b** and found that under these conditions, the reaction yields the previously described[7] *exo*-bromoketone **2c**. Relying on these results, we ascribed di-*exo*-configuration to the halogen atoms in dibromo- and dichlorodiketones **2a,b** (*cf.* Ref. 8).

Dibromo- and dichlorodiketones **2a,b** react with MeONa under the conditions of the Favorskii reaction to give one product in each case (GLC); based on the spectral data, these products were identified as 4-halo-3-methoxy-2-oxatricyclo[4.3.1.$0^{3,8}$]decan-10-ones (**3a,b**) (oxaprotoadamantanones). The IR spectra of compounds **3a,b** contain absorption bands for C=O, C—Hal, and C—O groups. Characteristic signals in the ^{1}H NMR spectrum of compounds **3a,b** are a doublet with a spin-spin coupling constant of 5 Hz corresponding to the protons at the C(1) atom (which is in good agreement with the dihedral angles in a strained tricyclodecanone structure, one of which is 90° and the other 60°) and a doublet (in **3b**) or triplet (in **3a**) for the protons at C(4), which corresponds to dihedral angles of ~80° and 40° as a result of the transition of one of the six-membered rings into a boat conformation during cyclization. However, the multiplicities of signals indicate that the bromine atom in the structure of **3a** causes a greater distortion of the geometry of the tricyclodecanone skeleton. The ^{13}C NMR spectra of compounds **3a,b** exhibit 10 signals, which were assigned based on their multiplicities with incomplete spin–spin decoupling. The signals at δ 109 were assigned to the C(3) atom bound to two oxygen atoms. It is noteworthy that most of the ^{13}C chemical shifts for these two compounds are virtually

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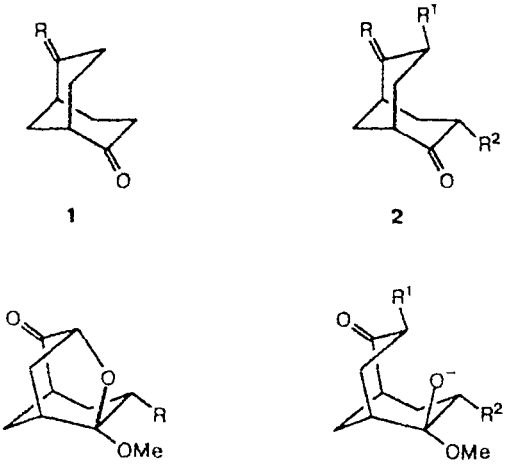
Scheme 1



1a: R = O **2a, 4a:** R = O, $R^1 = R^2$ = Br
1b: R = H_2 **2b, 4b:** R = O, $R^1 = R^2$ = Cl
3a: R = Br **2c:** R = H_2, R^1 = H, R^2 = Br
3b: R = Cl **2d:** R = H_2, R^1 = H, R^2 = OMe

identical, except for those corresponding to the carbon atoms bound to the halogen atoms.

The reaction of bromoketone **2c** with MeONa carried out under similar conditions also leads to one product, which was identified as methoxyketone **2d** based on spectral data. In this case, simple nucleophilic substitution of the halogen atom in the initial structure by a methoxy group occurs.

Thus, interaction of dihalodiketones **2a,b** with MeONa under conditions of the Favorskii reaction affords substituted 2-oxatricyclo[4.3.1.$0^{3,8}$]decanes **3a,b**, which are formed *via* intramolecular cyclization. The results obtained are in good agreement with the semibenzyl mechanism of the Favorskii rearrangement.[9] According to this mechanism, an attack of the base of the carbonyl group in position 2 gives the hemiketal anion **4**. This is followed by the attack at C(7) with replacement of the halogen atom and by intramolecular cyclization.

Experimental

IR spectra were obtained on a Specord M80 spectrometer for suspensions in Vaseline oil. NMR spectra were recorded on a Tesla BS 587A instrument (80 MHz for ^{1}H and 20 MHz for ^{13}C) using tetramethylsilane as the internal standard. Chromatography was carried out using silica gel L 100/160 (Chemapol).

General procedure for halogenation of bicyclo[3.3.1]nonane-2,6-dione (1a) and -2-one (1b). A solution of a halogen (0.06 or 0.03 mol) in the corresponding solvent (Br_2 in $CHCl_3$ or AcOH, Cl_2 in CH_2Cl_2) was added to a solution of a carbonyl compound (0.03 mol) in 200 mL of $CHCl_3$ or CH_2Cl_2 (in the case of ketone **1b**, in 60 mL of AcOH). The reaction mixture was kept for 10 min at 20 °C (in the case of chlorination, for 1 h at 0 °C), washed with water and with a 5% solution of $NaHCO_3$, and dried with Na_2SO_4, and the solvent was evaporated. The residue was purified by crystallization.

***exo,exo*-3,7-Dibromobicyclo[3.3.1]nonane-2,6-dione (2a).** Colorless crystals, yield 97%, m.p. 171—172 °C. Found (%): C, 34.95; H, 3.38; Br, 51.10. $C_9H_{10}Br_2O_2$. Calculated (%): C, 34.87; H, 3.25; Br, 51.55. IR, ν/cm^{-1}: 1750, 730. ^{1}H NMR, δ: 1.72—3.25 (m, 8 H); 4.58 (m, 2 H, CHBr).

***exo,exo*-3,7-Dichlorobicyclo[3.3.1]nonane-2,6-dione (2b).** Colorless crystals, yield 90%, m.p. 183—185 °C. Found (%): C, 48.56; H, 4.60; Cl, 32.42. $C_9H_{10}Cl_2O_2$. Calculated (%): C, 48.90; H, 4.56; Cl, 32.07. IR, ν/cm^{-1}: 1755, 710. ^{1}H NMR ($(CD_3)_2CO$), δ: 1.7—2.73 (m, 6 H); 2.85 (m, 2 H); 5.2 (dd, 2 H, CHCl, J = 11 Hz, 10 Hz). ^{13}C NMR ($CDCl_3$), δ: 201.7 (2 C); 58.2 (2 C); 44.7 (2 C); 37.7 (2 C); 31.6 (1 C).

***exo*-3-Bromobicyclo[3.3.1]nonane-2-one (2c).** Colorless crystals, yield 94%, m.p. 74—75 °C (*cf.* Ref. 7).

Interaction of halobicyclo[3.3.1]nonanones 2a—c with sodium methoxide (general procedure). A solution of MeONa (0.025 mol) in 30 mL of anhydrous MeOH was added to a solution of halobicycloketone **2a—c** (0.01 mol) in 100 mL of anhydrous MeOH. The reaction mixture was kept for 1 h at 20 °C and neutralized with 2 *M* HCl. Then it was poured into a double volume of water and extracted with chloroform (3×80 mL). The combined extracts were dried with Na_2SO_4, concentrated, and chromatographed using chloroform as the eluent.

***endo*-4-Bromo-3-methoxy-2-oxatricyclo[4.3.1.$0^{3,8}$]decan-10-one (3a).** Colorless crystals, yield 57.5%, m.p. 94—96 °C. Found (%): C, 46.32; H, 4.84; Br, 30.34. $C_{10}H_{13}BrO_3$. Calculated (%): C, 46.01; H, 5.02; Br, 30.60. IR, ν/cm^{-1}: 1740 (C=O); 1120, 710. ^{1}H NMR (CCl_4), δ: 2.85—1.53 (m, 8 H); 3.3 (s, 3 H, OMe); 4.26 (d, 1 H, J = 5 Hz); 4.6 (t, 1 H, J = 6 Hz). ^{13}C NMR ($CDCl_3$), δ: 209.2 (s, C(10)); 109.1 (s, C(3)); 83.8 (d, C(4)); 49.1 (q, OMe); 44.5 (d, C(1)); 43.9 (d, C(8)); 39.9 (d, C(6)); 38.9 (t, C(5)); 35.1 (t, C(9)); 29.3 (t, C(7)).

***endo*-4-Chloro-3-methoxy-2-oxatricyclo[4.3.1.$0^{3,8}$]decane-10-one (3b).** Colorless crystals, yield 65%, m.p. 81—82 °C. Found (%): C, 55.29; H, 6.03; Cl, 16.74. $C_{10}H_{13}ClO_3$. Calculated (%): C, 55.44; H, 6.05; Cl, 16.36. IR, ν/cm^{-1}: 1735 (C=O); 1120, 720. ^{1}H NMR (CCl_4), δ: 2.75—1.5 (m, 8 H); 3.3 (s, 3 H, OMe); 4.3 (d, 1 H, J = 5 Hz); 4.55 (d, 1 H, J = 7 Hz). ^{13}C NMR ($CDCl_3$), δ: 208.98 (s, C(10)); 109.2 (s, C(3)); 83.9 (d, C(4)); 53.1 (d, C(1); 49.2 (q, OMe); 44.3 (d, C(8)); 39.6 (d, C(6)); 38.8 (t, C(5)); 35.1 (t, C(9)); 29.8 (t, C(7)).

3-Methoxybicyclo[3.3.1]nonan-2-one (2d). Yield 65%, b.p. 105—107 °C (17 Torr), n_D^{25} 1.4955. Found (%): C, 71.05; H, 9.21. $C_{10}H_{16}O_2$. Calculated (%): C, 71.39; H, 9.60. IR, ν/cm^{-1}: 1720, 1130. ^{1}H NMR (CCl_4), δ: 1.26—2.55 (m, 12 H); 3.35 (s, 3 H, OMe); 3.57—3.7 (m, 1 H, H(3)).

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