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BROMINATION AND OXIDATION OF 2-OXAADAMANTANE

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A marked decrease in reactivity has been shown for oxaadamantane towards bromination and oxidation when compared with adamantane. The mono- and dihydroxy and acetoxy substituents in the products occupied positions in the molecule remote from the oxa bridge.

Despite the large number of substituted 2-oxaadamantanes [1-5], they have been obtained by cyclization of difficult to prepare bicyclic derivatives. There are only a few examples [6-8] of functionalization of the oxaadamantane molecule itself and other data concerning the chemical behavior of I are not found in the literature. Synthesis of oxaadamintane from bicyclo-[3.3.1]nonan-2,6-diol [9] has made it available preparatively and allowed us to investigate its behavior in the Ritter and Koch–Haaf reactions and in bromination and oxidation reactions [10, 11] already well known for adamantanes. Previously, there had only been a proposal [12] that the reactivity was lower than that of adamantane itself.

It is known that the reaction of adamantane with acetonitrile in the presence of sulfuric acid and t-BuOH leads to an 85% yield of N-(1-adamantyl)acetamide [13]. Compound I does not take part in this or the Koch–Haaf reaction [14]. It is also known that adamantane is quite readily brominated both as a result of nucleophilic substitution [15-17] and via a free radical mechanism [18-20] to give principally bridge mono- to tetra-substituted derivatives depending on the reaction conditions.

Reaction of I with bromine in CCl_4 at 20°C leads to an orange colored precipitate whose PMR spectrum shows a low field shift of 0.37 ppm for the protons next to the oxygen atom when compared with those protons in I. From elemental analysis, we propose that the structure is the complex $Br_2 \cdot I$ analogous to 1,4-dioxane [21, 22]. The UV spectrum of the complex shows a loss of the absorption bands of bromine and oxaadamantane (λ_{max} 228 and 235 nm respectively) and the appearance of a new, very intense charge transfer band ($n \rightarrow \sigma^*$) and 274 nm with absorbance log ε 4.83, not equal to the sum of the absorptions of the starting compounds at that wavelength. The complex is unstable to electron impact. The mass spectrum does not show a molecular ions peak but there are only seen peaks for the molecular ions of the starting materials (*m/z* M^+ 138 and 160) and their fragmentation products.

Through ionic bromination under very severe conditions (refluxing in bromine in the presence of $AlBr_3$ for 10 days) 4-bromo-2-oxaadamantane was isolated by chromatography from a mixture with unreacted I. In its IR spectrum, absorption bands for C=O, OH, and C=C were absent. The PMR spectrum showed broad singlet signals at 4.45 (1H, H–C–Br) and 3.90 ppm (2H, H–C–O) and a multiplet for adamantane skeletal protons at 1.50-2.46 ppm (10 H). The spectrum was identical to that obtained previously for 4,8-dibromo-2-oxaadamantane [23] (excluding integrated signal intensities), however, an exact assignment of the proton signal at C–Br (position 4 or 6) requires a more stringent proof. Ionic bromination under even more severe conditions (150°C, $AlBr_3$, 5 h in an ampul) led to tarring.

Hence we have shown that, in contrast to adamantane, compound I undergoes ionic bromination to give nonbridge products thus confirming a previous proposal [12] concerning the deactivation of positions 1 and 3 in oxaadamantane. The reason may be connected with a lowering of the resonance energy of stabilization of the carbocation with change of neighbouring CH_2 groups for oxygen. An analogous introduction of an electron acceptor substituent into the adamantane ring reportedly deactivates its bridgehead positions [24, 25].

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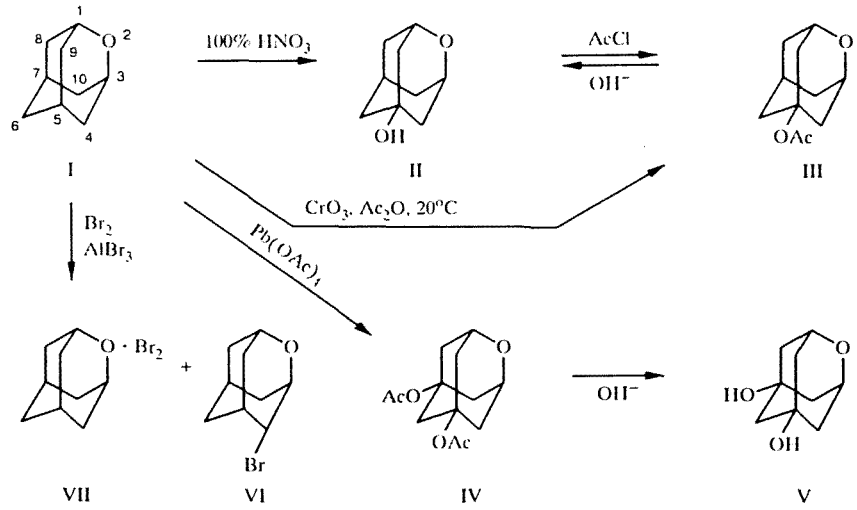
TABLE 1. Yields and Parameters for Compounds Obtained

Compound	Empirical formula	Mp, °C (recrystallization solvent) or bp, °C (mm Hg)	yield, %
VII	$C_9H_{14}Br_2O$	158	48
II	$C_9H_{14}O_2$	268 (heptane)	47 (A), 65 (B)
III	$C_{11}H_{16}O_3$	126...130 (25)	35 (A), 90 (B)
IV	$C_{13}H_{18}O_5$	153...156 (25)	40
V	$C_9H_{14}O_3$	313...315 (heptane)	65
VI	$C_9H_{13}BrO$	113 (MeOH)	34

Closest in reactivity to oxaadamantane is adamantanone. In contrast to adamantane (which is readily oxidized by a range of reagents [26-29]) the behavior of I towards oxidation resembles adamantanone. Even when I was treated with 20% oleum (20°C, 3 h) or 25% HNO_3 (100°C, 5 h), 75 and 90% unreacted starting material was obtained. Chlorosulfonic acid broke up the oxaadamantane skeleton. Adamantane is oxidized only by 100% nitric acid (70 h, [29]). Treatment of II with the same reagent for 140 h at 20°C, with decomposition of the reaction mixture by refluxing with 40% sulfuric acid, gave 40% unreacted I. Preparative chromatographic separation then gave 5-hydroxy-2-oxaadamantane (II, 47% after recrystallization and distillation). Its IR spectrum showed a broad absorption for OH at 3200-3500 cm^{-1} and low intensity bands at 1020 and 1075 cm^{-1} for the ring C–O–C vibrations. The PMR spectrum showed signals for the 1-H and 3-H protons (broad singlet), the OH group and a skeletal multiplet in the ratio 2:1:11 respectively (see Table 2). Treatment of II with acetyl chloride gave 90% of the corresponding 5-acetoxy derivative III which could also be obtained in 35% yield by oxidation of I with CrO_3 in acetic anhydride (20°C, 60 h). Hydrolysis of the ester with 60% alcoholic KOH gave a 65% yield of II.



$Pb(OAc)_4$ is an efficient oxidant and it has been shown [24, 25] that its properties depend on the reaction conditions. Refluxing I with lead tetraacetate in glacial acetic acid (20 h) gave 53% unreacted I and 5,7-diacetoxy-2-oxa-adamantane (IV, 40%) after chromatographic separation. The IR and PMR spectra of IV (excluding integrated area ratios) were identical to those reported above for III. Hydrolysis of IV with aqueous KOH solution gave the dihydroxy derivative V.

Hence under quite forcing conditions it was possible to obtain mono- and di-substituted hydroxy and acetoxy derivatives of 2-oxaadamantane. However, even under more vigorous conditions (than for oxidation of adamantanone) oxidation does not go to completion. It affects only positions 5 and 7 of the skeleton removed from the oxygen bridge.

TABLE 2. Spectral Parameters for 2-Oxaadamantanes

Compound	IR Spectrum, cm^{-1}	PMR Spectrum, δ, ppm (CCl_4, TMS)
VII	1075, 1020 (C—O—C)	4,27 (2H, s, H—C—O), 1,30...2,26 (12H skeleton, m)
II	3220...3500 (OH), 1075, 1020 (C—O—C)	4,11 (2H, s, H—C—O), 3,30 (1H, s, OH), 1,32...2,48 (11H skeleton, m)
III	1745 (C=O), 1250 (ester), 1075, 1020 (C—O—C ring	4,08 (2H, s, H—C—O), 1,84 (3H, s, CH_3CO), 1,47...2,38 (11H skeleton, m)
IV	1745 (C=O), 1250 (ester), 1075, 1020 (C—O—C ring	4,08 (2H, s, H—C—O), 1,48 (6H, s, CH_3CO), 1,21...2,47 (10H skeleton, m)
V	3200...3500 (OH), 1075, 1020 (C—O—C ester)	4,10 (2H, s, H—C—O), 3,30 (2H, s, OH), 1,29...2,37 (10H skeleton, m)
VI	1050, 1020 (C—O—C ring	4,45 (1H, s, H—C—Br), 3,90 (2H, s, H—C—O), 1,50...2,46 (11H skeleton, m)

*In $CDCl_3$.

EXPERIMENTAL

PMR spectra were recorded on a Varian T-60 instrument with TMS internal standard. IR Spectra were taken on a UR-20 for Vaseline oil suspension or a thin film. UV spectra were recorded on a Specord-UV-vis for 10^{-5} molar solutions in ethanol solution. Mass spectra were taken on a Finnigan MAT-1125 instrument with ionization energy 80 eV. TLC and preparative column separations used Brockmann activity grade II alumina and Silpearl grade silica gel.

Elemental analytical data for C and H agreed with that calculated. Constants and spectral data for II-VII are given in Tables 1 and 2.

Complex of 2-Oxaadamantane with Bromine (VII). Bromine (0.5 ml, 4.5 mmole) in CCl_4 (2.5 ml) was added dropwise with stirring to a solution of oxaadamantane (200 mg, 1.5 mmole) in CCl_4 (4 ml) cooling the reaction mixture with iced water. Stirring was continued for 0.5-1 h and the precipitate filtered and washed with cold CCl_4 to give the orange complex of VII (220 mg).

4-Bromo-2-oxaadamantane (VI). Bromine (3 ml) was added to a mixture of oxaadamantane I (200 mg, 1.5 mmole) and $AlBr_3$ (300 mg) and the whole heated for 80 h at 60°C. The mixture was cooled, CCl_4 (5 ml) added, and the orange precipitate (130 mg) was filtered. After vacuum distillation the material had mp 158°C and had spectral data identical to complex VII. The filtrate was washed with saturated $Na_2S_2O_5$ solution, water, and saturated NaCl solution and dried (Na_2SO_4). TLC (Al_2O_3, benzene) showed the presence of oxaadamantane I (R_f 0.56) and VI (R_f 0.72). Column chromatography of the oily residue gave starting I (50 mg, 25%) and 4-bromo-2-oxaadamantane (VI, 79 mg).

5-Hydroxy-2-oxaadamantane (II). A. with cooling to 0°C and stirring, oxaadamantane (270 mg, 2 mmole) was added to 100% nitric acid (2.5 ml) such that the temperature did not exceed 15°C. The product was stirred at room temperature for 140 h, heated at 60°C for 1.5 h, and nitric acid distilled off *in vacuo*. Water (1 ml) and sulfuric acid (96%, 0.4 ml) were added to the residue and it was heated for 1 h at ~100°C, cooled, neutralized with aqueous NaOH solution (30%), and extracted with chloroform. The extract was washed with water, saturated NaCl, dried with $MgSO_4$, and concentrated *in vacuo*. After chromatography on aluminium oxide (35 × 2.5 cm column, eluent ethyl acetate–hexane, 3:1), the residue gave an unidentified substance (20 mg, R_f 0.98), unreacted I (100 mg, 40%), and II (90 mg, purified by recrystallization and vacuum distillation).

B. 5-Acetoxy-2-oxaadamantane (100 mg) was hydrolyzed under the conditions given in [30] using a threefold excees of 60% ethanolic KOH solution to give an oily residue (80 mg). Preparative chromatography on thick layer Silpearl silica gel plates (18 × 24 cm, 1 mm layer, eluent ethylacetate–hexane,3:1) gave ester III (37 mg) and II (32 mg), identical to that reported above.

5-acetoxy-2-oxaademantane (III). A. Chromium trioxide (1.5 g, 14.5 mmole) in acetic anhydride (10 ml) was added gradually over 1 h to oxaadamantane (300 mg, 2.2 mmole) in acetic anhydride (6 ml). After 60 h the mixture was neutralized with saturated sodium carbonate solution, extracted with CH_2SO_4. Evaporation of solvent gave a viscous liquid (280 mg).

Preparative chromatography on Al_2O_3 (eluent chloroform) then gave an unidentified hydrocarbon fraction (75 mg, bp 193-196°C, found, %: C 85.6, H 14.4%, IR spectrum: 2900-3000, 1470, 1380 cm^{-1}) as well as I (79 mg) and the acetoxy product III (85 mg).

B. A mixture of alcohol II (70 mg) and acetyl chloride (2 ml) was refluxed for 3 h. Excess reagent was distilled *in vacuo* and the residue was redistilled *in vacuo* to give III (80 mg), identical to that reported above.

5,7-Diacetoxy-2-oxaadamantane (IV). Glacial acetic acid (4.2 ml) was added to a mixture of oxaadamantane (I, 300 mg, 2.2 mmole) and lead tetraacetate (1.3 g, 2.9 mmole). The mixture was refluxed for 20 h, neutralized with saturated sodium carbonate solution, and extracted with ether. The extract was washed with water, saturated NaCl solution, and dried with $MgSO_4$. Removal of solvent *in vacuo* gave an oily residue (420 mg). Chromatography on an Al_2O_3 column (eluent chloroform–hexane, 1:1) gave oxaadamantane (I, 160 mg) and product IV (225 mg).

5,7-Dihydroxy-2-oxaadamantane (V) was obtained from IV (130 mg) by hydrolysis with a sixfold excess of 60% KOH solution in ethanol [30]. Yield 90 mg. A separation similar to that described above for the mono hydroxy- and acetoxy-oxaadamantanes II and III gave starting ester (IV, 20 mg) and product V (48 mg) which was purified by recrystallization and distillation *in vacuo*.

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