Pergamon

Tetrahedron Letters, Vol. 35, No. 38, pp. 7093-7096, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01466-3

Reaction of 7-Dehydrocholesteryl Acetate with RuO_4. First Isolation of a Cyclic Ruthenium (VI) Diester[1].

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Abstract. The reaction of 7-dehydrocholesteryl acetate (**1**) with RuO_4 has been performed in acetone-water at -60°C using an oxidant-substrate ratio of 1:1. The cyclic oxoruthenium (VI) diester **2**, likely an intermediate in the formation of 5α-cholest-7-en-3β,5,6α-triol 3-acetate (**3**) and 3β-acetoxy-5-hydroxy-5α-cholest-7-en-6-one (**4**), the final oxidation products of the steroidal substrate with RuO_4, has been isolated for the first time and characterized on the basis of spectral and chemical evidence.

Until recently it was believed that the reaction of ruthenium tetroxide with alkenes proceeded exclusively with the cleavage of the carbon-carbon double bond to give carbonyl compounds, namely ketones or carboxilic acids, and the reaction has mostly been carried out using catalytic amounts of the oxidant in the presence of a secondary oxidant such as sodium periodate in a biphasic system composed of CCl_4-CH_3CN-H_2O[2,3].

In contrast with previously reported results[4,5], we have recently found that when the reaction is conducted in acetone-water using an oxidant-substrate ratio of 1:1 in the absence of $NaIO_4$, the products are mainly 1,2-diols and/or α-ketols[6,7].

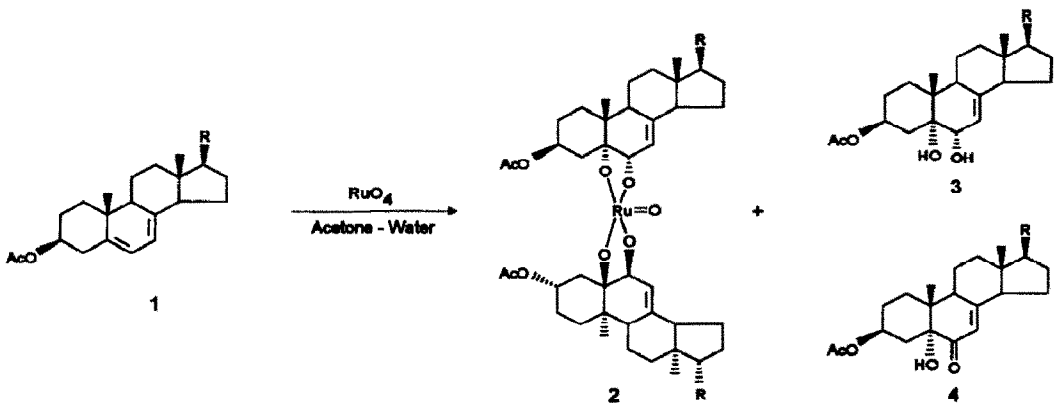
Although kinetic studies[3] had suggested that the scission of the carbon-carbon double bond could proceed *via* the formation of a cyclic ruthenium (VI) diester intermediate, no experimental support has been given to date for this hypothesis possibly due to the difficulty of isolating the unstable ruthenate esters in the previously used experimental conditions.

In this communication we wish to report that the reaction of 7-dehydrocholesteryl acetate (**1**) with RuO_4 in our experimental conditions indeed allowed us to isolate a ruthenium (VI) diester for which we propose the cyclic structure **2** on the basis of spectral and chemical evidence given below. Diester **2** is likely an intermediate compound in the formation of the 1,2-diol **3** and α-ketol **4**, the final oxidation products of 7-dehydrocholesterol with RuO_4, obtained along with compound **2** during the oxidation of the steroidal substrate (Scheme).

The reaction was performed as follows. A mixture of $RuO_2 \cdot 2H_2O$ (389 mg, 2.3 mmol) and $NaIO_4$ (2.9 g, 13.8 mmol) in 1:1 (v/v) acetone-water (55 mL) was stirred at room temperature. When the mixture became yellow (approximately 1h) the suspension was centrifuged and the supernatant was cooled to -50 °C and slowly added to a cooled (-50 °C) and stirred solution of 7-dehydrocholesteryl acetate (1 g, 2.3 mmol) in acetone (400 mL). TLC analysis of the reaction mixture performed immediately after the addition of the oxidant revealed the formation of the expected 1,2-diol **3** and α-ketol **4** along with two products

having greenish colours on the silica gel plate. Successive TLC analyses showed no further progress of the reaction

Scheme



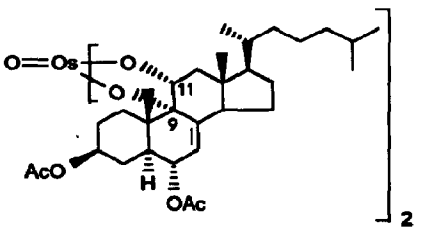
$R = C_8H_{17}$

which was therefore quenched by adding a few drops of isopropyl alcohol. Filtration of the reaction mixture afforded a grey solid which, by TLC analysis, was shown to be composed of the two coloured products[8]. Desiccation of this material followed by its HPLC separation (hexane-EtOAc, 82:18) gave pure **2** (48 mg, 2 % yield; hexane-EtOAc, 7:3, Rf=0.4) and a less polar product **5** (95 mg; 4 % yield; Rf=0.9 in the above mixture). The filtrate was taken to dryness to give a solid which was separated by column chromatography affording pure **3** (286 mg, 27 % yield) and **4** (560 mg, 53 % yield) identified by comparison with authentic specimens.

Both **2** and **5** proved to be unstable products but, while compound **5** when dissolved in $CDCl_3$ quickly transformed into **2**, the latter compound appeared to be more stable than **5** and survived in $CDCl_3$ solution for the time required for acquiring NMR data on a 400 MHz spectrometer. Nevertheless, only samples of **2** fresh from HPLC could be used for all the spectral studies and very often a repurification step was necessary after a prolonged NMR experiment. In fact, compound **2** slowly converts into **5** and, successively, into a mixture of **3** and **4** if left to stand in $CDCl_3$ solution.

Elemental analysis[9] and FABMS spectrum[10] established for **2** a molecular formula of $C_{58}H_{92}O_9Ru$ while treatement of **2** with saturated aqueous $NaHSO_3$ solution in dioxane gave diol **3**. ^1H- and ^{13}C-NMR spectra of **2**[10] indicated in the molecule the presence of the Δ^7 carbon-carbon double bond [^1H-NMR: δ 5.44 (H-7); ^{13}C-NMR: δ 144.81 (s, C-8), 116.96 (d, C-7)] and three oxygen-bearing carbons [δ 101.03 (s), 88.95 (d) and 69.85 (d)] one of them (δ 69.85) easily attributed to C-3.

Very useful in the structure elucidation of compound **2** was the observation of some striking NMR similarities observed between our compound and the C9-C11 steroidal cyclic osmim (VI) diester **6** recently synthesized in our laboratory[11]. In particular, the high chemical shift value of the two signals at δ 101.03 (C-5) and 88.95 (C-6) in the ^{13}C-NMR spectrum of **2** was strongly reminiscent of that exhibited by the carbon atoms geminal to osmium (C-9: δ 98.99; C-11: δ 89.21) in the osmate ester **6**. On the other hand, the proton spectrum of **2** when compared with that of diol **3** (its hydrolysis product) showed that the signal for H-6 (the proton vicinal to ruthenium) was downfield shifted at δ 4.99 in **2** (in **3** this proton resonated at δ 3.95). This chemical shift difference observed for H-6 in the proton spectra of ester **2** and diol **3** once again paralleled that observed for the proton (H-11) vicinal to osmium in compound **6** which in this product resonated at δ 5.39 while in the corresponding C9-C11 diol (its hydrolysis product) resonated upshifted at δ 4.47.These analogies in the NMR behaviour of the two compounds **2** and **6** suggested to us that compound **2** could be the ruthenate ester corresponding to diol **3**. Furthermore, the H-7 and H_{eq}-4 protons in **2** (H_{eq}-4: δ 1.77; H-7: δ 5.44) also underwent to displacements from their respective positions in the ^{1}H-NMR spectrum of diol **3** [Δδ (δ_2–δ_3) H_{eq}-4: -0.48; H-7: 0.43].



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The above data, when taken altogether, strongly suggested that a structural modification had occurred in the segment C4-C7 of **1** and thus that the new compound could be the cyclic ruthenate diester **2** derived from the attack of RuO_4 on the Δ^5 double bond of two molecules of **1** from their less-hindered α-faces as previously observed for the reaction of cholesteryl acetate with RuO_4[6]. The absence of hydroxyl bands in the IR spectrum of **2** and the multiplicities of the H_2-4 protons (H_{ax}-4: δ 1.94, dd, J=12.8 and 12.8 Hz; H_{eq}-4: δ 1.77, dd, J=12.8 and 4.7 Hz) further corroborated this structural hypothesis.

On this basis, it seems likely that ruthenium in the diester **2** could adopt a square-based pyramidal five-coordination, as done by osmium in several osmate esters like oxobis(ethane-1,2-diolato)osmium(VI)[12], in which the metal is connected to the C-5 and C-6 carbons of each of the two steroidal units through a couple of oxygen bridges in such a way that the four oxygens of the two chelating ester ligands constitute the base of the pyramid, the fifth (apical) coordination position being occupied by the remaining oxygen required by the molecular formula of **2**. At this stage, however, it is not possible to decide with certainty which of two possible square-based pyramidal arrangements possessing a two-fold axis (the axis of the Ru=O bond), one with the oxygen of the Ru=O group directed towards the two A rings of the molecule, the other having this atom protruding in the direction of the B/C/D ring portion of the two steroids units, both accounting for the presence of only one set of signals observed in the ^{1}H- and ^{13}C-NMR spectra of **2**, corresponds to our compound; albeit the latter structure seems to be preferred on

account of the large downfield shift suffered by the H-7 proton in **2** relative to its value in **3** ($\Delta\delta$= 0.53 ppm) possibly due to the vicinity in the space with the Ru=O grouping as estimated by the examination of a molecular model of **2**.

In order to clarify this point and to definitively confirm the structure of **2** a number of attempts aimed at obtaining crystals of **2** suitable for X-ray analysis were made but, unfortunately, all were unsuccessful mostly due to decomposition of the product during the crystallization stage. Nonethless, studies are in progress both to crystallize **2** and to establish the structural relationship between **2** and the more labile product **5** which, though has not yet been studied as a pure compound, seems to have a structure very similar to that of **2**, as indicated by ^{1}H- and ^{13}C-NMR spectra of a sample enriched in this compound.

To the best of our knowledge compound **2** represents the first ruthenate ester ever synthesized.

Acknowledgements. This research was supported by a grant from MURST. Mass spectral data were provided by the "Servizio di Spettrometria di Massa del CNR e dell'Università di Napoli". Throughout the NMR work the facilities of the "Centro di Metodologie Chimico-Fisiche dell'Università di Napoli" were used.

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8. Compounds **2** when taken to dryness has a red coral colour while compound **5** has a brownish one which is reminiscent of that of an osmate ester.
9. **2**: $[\alpha]_D$= -122.2 (c= 0.2, $CDCl_3$); FTIR (film) ν_{max} 1733, 1245, 1027 and 955 cm^{-1}; UV ($CHCl_3$) λmax 365 nm (ε=3136); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.44 (1H, bs, H-7), 4.99 (1H, bd, J= 2.2 Hz, H-6), 4.91 (1H, m, H_α-3), 2.05 (1H, bd, J= 8.5 and 8.5 Hz, H-14), 1.94 (1H, dd, J= 12.8 and 12.8 Hz, H_{ax}-4), 1.93 (3H, s, acetate), 1.77 (1H, dd, J= 12.8 and 4.7 Hz, H_{eq}-4), 1.24 (3H, s, H_3-19), 0.91 (3H, d, J= 6.0 Hz, H_3-21), 0.86 (6H, d, J= 6.6 Hz, H_3-26 and H_3-27), 0.57 (3H, s, H_3-18); ^{13}C-NMR ($CDCl_3$, 100.1 MHz) δ 169.52 (s), 144.81 (s), 116.96 (d), 101.03 (s), 88.95 (d), 69.85 (d), 55.99 (d), 54.23 (d), 43.41 (s), 42.23 (d), 41.79 (s), 39.49 (t), 39.09 (t), 37.62 (t), 36.07 (d), 36.03 (t), 31.11 (t), 28.01 (d), 27.87 (t), 26.97 (t), 23.77 (t), 22.81 (t), 22.79 (q), 22.54 (q), 21.32 (q), 21.23 (t), 18.82 (q), 18.82 (q), 12.03 (q); FABMS spectrum contained significant ion clusters at *m/z* 1014, through 1021 (MH^+-16), 941 through 945, (M^++2Na-2CH_3COOH-16), 919 through 923 (M^++Na-2CH_3COOH-16).
10. Anal. calcd for $C_{58}H_{92}O_9Ru$: C, 67.30; H, 8.96; O, 13.92; Ru, 9.77. Found: C, 66.96; H, 8.84; O, 13.64; Ru, 10.52. Microanalyses were performed at the Analytische Laboratorien, Gummerrsbach, Germany.
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(*Received in UK* 23 *June* 1994; *revised* 25 *July* 1994; *accepted* 29 *July* 1994)