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The lead tetraacetate oxidation of 5,10α-epoxyimino-5(10→1)*abeo*-1β(H)-5α-cholestan-3β-yl acetate*

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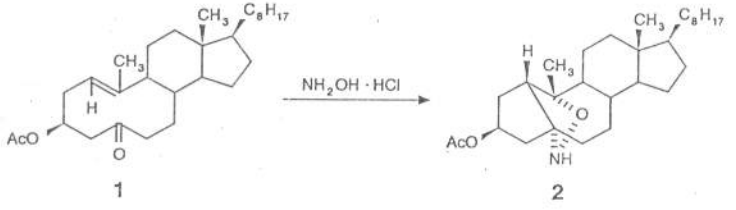
The lead tetraacetate oxidation of steroidal isoxazolidine **2** results in oxidative cleavage of the epoxymino bridge to give the nitro dirivatives **4** and **5** and the azoxy compounds **6** and **7**. A plausible mechanistic course for the observed oxidative processes involving intermediate formation of nitroso species is presented.

The lead tetraacetate (LTA) oxidations of various nitrogen-containing compounds (such as amines, amides, hydrazines, oximes, hydroxylamines,[1] unsubstituted isoxazolidine[2] and others) have been hitherto described. The results obtained have shown that the reaction course of these oxidations is particularly sensitive to the structure of the substrate and the reaction conditions used.

In the present paper we investigated the reactivity of a steroidal isoxazolidine (which in contrast to unsubstituted isoxazolidine is devoid of α-hydrogen with respect to the nitrogen atom), *i.e.*, 5α-epoxyimino-5(10→1)*abeo*-1β(H)-5α-cholestan-3β-yl acetate (**2**), when subjected to LTA oxidation under various experimental conditions.



1 2

Scheme 1

* Dedicated to the memory of Professor Milan D. Muškatirović

The steroidal isoxazolidine **2** was prepared by heating (*E*)-3β-acetoxy-5,10-secocholest-1(10)-en-5-one (**1**)[3] with hydroxylamine in the presence of a proton donor catalyst[4] (Sheme 1).

RESULTS AND DISCUSSION

The lead tetraacetate oxidation of isoxazolidine **2** was carried out in benzene solution at room temperature (in the presence of air, or under nitrogen, with stirring) using different substrate-to-oxidant mole ratios and different ways of their mixing (Table I). It was found that under these conditions isoxazolidine **2** underwent oxidative cleavage of the epoxyimino bridge to give (Sheme 2), in addition to a "non-polar fraction" **3** (which was not fully characterized), the nitro derivatives **4** and **5** and the azoxy compounds **6** and **7**. The yields of these products were dependent upon the oxidation conditions used (Table I). Thus, the best yields of the azoxy compounds **6** and **7** were obtained when an excess of the isoxazolidine **2** was present in the reaction mixture (experiment (iii)). Slow addition of LTA to isoxazolidine **2** had a similar effect (experiment (ii)*). On the other hand, with an excess of LTA the preferential product was the nitro derivative **4** (experiments (iv) and (v)). Besides, experiments (iiia) and (iva) carried out under nitrogen indicated that the absence of oxygen in the reaction media had practically no influence on product distribution. (However, it is important to point out that in these experiments the work-up procedure and separation of the products by column chromatography on SiO_2 was carried out without protection from air oxygen).

TABLE I. Products obtained by the lead tetraacetate oxidation of the isoxazolidine **2** in benzene solution.

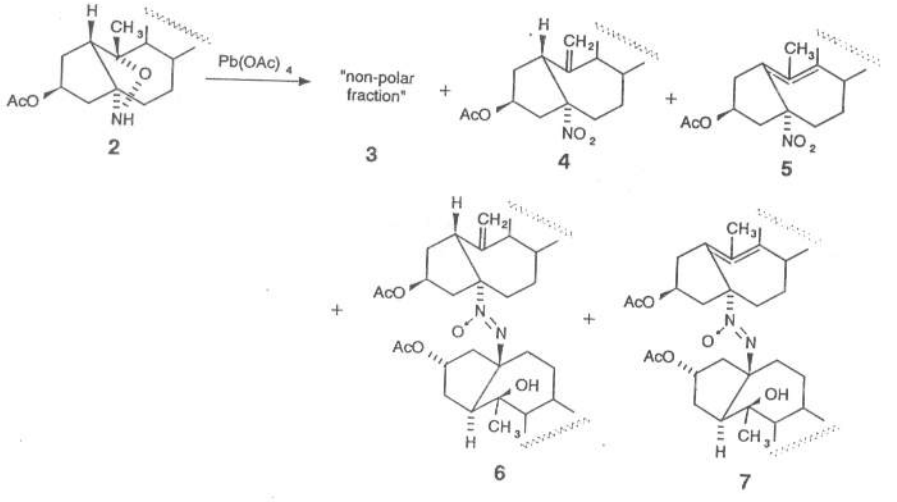
Mole ratio **2** / LTA	Conditions[b]	Yields (%) of reaction products[a]				
		3	**4**	**5**	**6**	**7**
1 : 1	(i) Mixed and stirred for 2 h	13	13	1	5	12
1 : 1	(ii) LTA slowly added to **2** (5 h)	5	10	1	11	21
2 : 1	(iii) Mixed and stirred for 5 h	6	11	1	16	28
	(iiia) As above under nitrogen	10	10	1	12	23
1 : 2	(iv) Mixed and stirred for 10 h	12	31	3	traces[c]	
	(iva) As above under nitrogen	14	28.5	2	traces[c]	
1 : 3	(v) **2** slowly added to LTA (5 h)	5	63	3-5	traces[c]	

[a]All yields (average of at least 3 experiments) refer to crude products, separated by column chromatography on silica gel (yields after recrystallization or rechromatography were 10-20% lower). [b]For more details see Experimental. [c]The presence of these products was detected by ^{1}H-NMR.

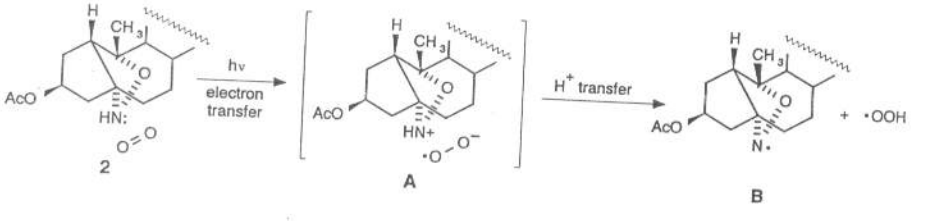
The structures of compounds **4-7** were deduced from their spectral characteristics (IR and ^{1}H-NMR spectra). They revealed that these LTA oxidation products were identical to those produced in the non-sensitized photooxygenation of the same isoxazolidine **2**.[5]

This finding indicated that the reaction courses of these two different oxidative processes could take place *via* the same intermediate. Namely, the photooxygenation

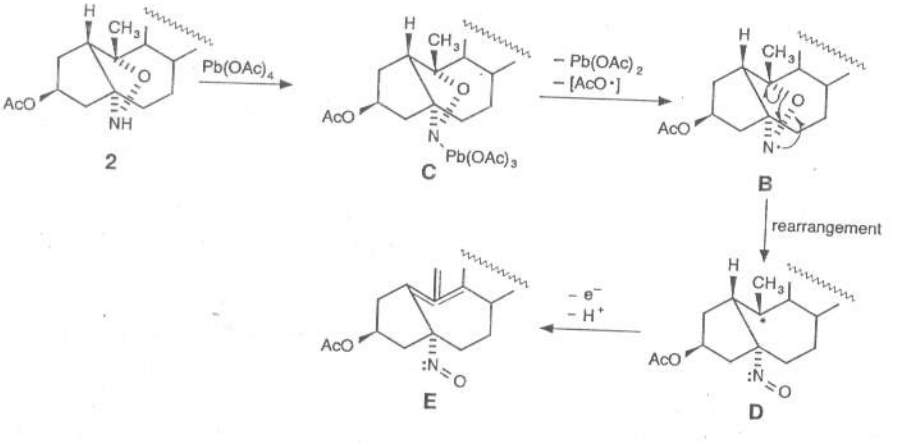
* Actually, under these conditions most of the reactions took place with isoxazolidine in excess.



Scheme 2.



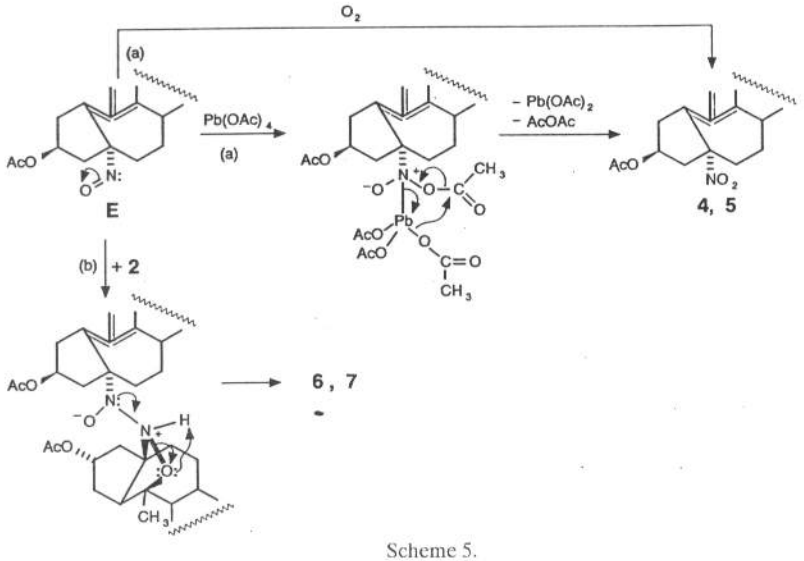
Scheme 3.



Scheme 4.

of isoxazolidine **2** was considered to involve (Scheme 3) an initial electron transfer from substrate to molecular oxygen to give the exciplex **A**, which upon internal proton-transfer was tranformed to the isoxazolidine radical **B** (and hydroperoxide radical).

In the LTA oxidation, this isoxazolidine radical **B** could be produced by homolysis of the N – Pb bond in the initialy formed N-lead triacetate[1] **C** (Scheme 4). The further fate of this species could be as follows. Its rearrangement to the more stable 5-nitroso C(10) radical **D** followed by one-electron oxidation (by acetate radical) and proton elimination results in the formation of the nitroso intermediate **E**, from which all the products isolated can be derived. Thus the nitroso group can undergo (Scheme 5) (a) either oxidation (by air oxygen and/or LTA) to give the nitro derivatives **4** and **5**, or (b) coupling with the isoxazolidine **2** (when present in excess) to give azoxy derivatives **6** and **7**.



Scheme 5.

Although the nitroso intermediate **E** (either in monomeric or dimeric form) has not been isolated in the pure state, its presence (probably in the "non-polar fraction" **3**) is substantiated by the following observations: (1) upon treatment of the isoxazolidine **2** with LTA in benzene, the mixture rapidly turned blue (due to the appearance of nitroso compounds.[6]). The blue colour gradually faded in the course of the reaction or upon exposure to air. (2) The blue coloured solution showed an absorption maximum at 682 nm (characteristic for nitroso monomers[7]). (3) When the "non-polar fraction" **3**, immediately after elution from the column, was mixed with an equimolar amount of isoxazolidine **2** in benzene (containing a catalytic amount of acetic acid) and the mixture was stirred at room temperature for 24 h, it gave (upon column chromatography on SiO_2) the nitro compounds **4** and **5** (in a total yield of 18%) and the azoxy derivatives **6** and **7** (in 6.5% and 11% yield, respectively).

Finally, the difference in product distribution observed in differently performed experiments (Table I) can also be explained in terms of the above mechanistic scheme.

The coupling reaction of **E** to the azoxy compounds **6** and **7** which requires the participation of unreacted isoxazolidine molecules (as in experiments (ii) and (iii)), is favoured when an excess of isoxazolidine **2** is present in the reaction mixture. On the contrary, in the presence of an excess of LTA (as in experiments (iv) and (v)), the concentration of unreacted isoxazolidine molecules is considerably lowered; therefore, the coupling reaction is suppressed and the competing oxidation to the nitro derivative **3** becomes the main process.

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EXPERIMENTAL

General. Removal of solvents was carried out under reduced pressure. Preparative column chromatography: silica gel 0.063-0.200 mm. TLC: control of reactions and separation of products on silica gel G (Stahl) with benzene/EtOAc 9:1 or 7:3, detection with 50% aqueous H_2SO_4. M. ps. uncorrected. Absorption spectrum: Super Scan 3. IR spectra: Perkin Elmer 337 spectrophotometer. ^{1}H-NMR spectra at 100 MHz: Varian AH 100 spectrometer. Light petroleum refers to the fraction boiling at 40-60 °C.

Lead tretraacetate oxidations of isoxazolidine **2**. – (i) To a solution of **2** (460 mg, 1 mmol) in dry benzene (100 ml) was added LTA (490 mg, 1 mmol + 10% excess) and the mixture was stirred at room temperature for 2 h.

(ii) To a stirred solution of **2** (460 mg, 1 mmol) in dry benzene (30 ml), a suspension of LTA (490 mg, 1 mmol + 10% excess) in dry benzene (90 ml) was gradually added through a dropping funnel at room temperature for 3 h and stirring continued for another 2 h.

(iii) A mixture of **2** (460 mg, 1 mmol) and LTA (245 mg, 0.5 mmol + 10% excess) in dry benzene (100 ml) was stirred at room temperature for 5 h.

(iiia) To a stirred solution of **2** (460 mg, 1 mmol) in dry benzene (100 ml) through which nitrogen was bubbled was added LTA (245 mg, 0.5 mmol + 10% excess) and the mixture was stirred under nitrogen for 5 h.

(iv) A mixture of **2** (460 mg, 1 mmol) and LTA (980 mg, 2 mmol + 10% excess) in dry benzene (100 ml) was stirred at room temperature for 10 h. Excess LTA was destroyed with ethylene glycol.

(iva) To a stirred solution of **2** (460 mg, 1 mmol) in dry benzene (100 ml) through which nitrogen was bubbled for 20 min was added LTA (980 mg, 2 mmol + 10% excess) and the mixture was stirred for 10 h. Excess LTA was destroyed with ethylene glycol.

(v) To a stirred suspension of LTA (1.47 g, 3 mmol + 10% excess) in dry benzene (50 ml), a solution of **2** (460 mg, 1 mmol) was gradually added through a dropping funnel at room temperature for 3 h and stirring continued for another 2 h. Excess LTA was destroyed with ethylene glycol.

General work-up and separation procedures

The above reaction mixtures were diluted with diethyl ether, washed with water, saturated aq. $NaHCO_3$ solution and water, dried and evaporated to dryness.

The resulting mixtures were separated by column chromatography using benzene/light petroleum (7:3), benzene, and benzene/EtO_2 (in various proportions) as eluents. Benzene/light petroleum (7:3) eluted the "non-polar fraction" **3**. Benzene eluted the nitro derivatives **4** and **5**. Elution with benzene/Et_2O (99:1) afforded the azoxy compound **6**. Benzene/Et_2O (96:4) eluted the azoxy product **7**. More polar fractions contrained unresolvable complex mixtures which were not investigated further.

"Non-polar fraction" **3**. Oil. λ_{max} 682 nm.

*5-Nitro-5(10→1)*abeo-*1β(H)-5α-cholest-10(19)-en-3β-yl acetate* (**4**). M.p 143 °C (from MeOH) (Ref. 5, m.p. 143 °C). The IR and ^{1}H-NMR spectra were identical to those reported in Ref 5.

*5-Nitro-5(10→1)*abeo-*5α-cholest-9(and/or 1(10))-en-3β-yl acetate* (**5**). Oil (Ref. 5, oil). Spectral data identical to those reported in Ref. 5.

*5[3β-Acetoxy-5(10→1)*abeo-*1β(H)-5α-cholest-9(and/or 1(10))-en-5*-ONN-*azoxy*]-*10α-hydroxy-5(10→1)*abeo-*1β(H)-cholestan-3β-yl acetate* (**6**). M.p. 172-173 °C (from acetone) (Ref. 5, m.p. 173 °C). The IR and ^{1}H-NMR spectra were identical to those reported in Ref. 5.

*5[3β-Acetoxy-5(10→1)*abeo*-1β(H)-5α-cholest-10(19)-en-5*-ONN-*azoxy*]-*10α-hydroxy-5(10→1)*abeo*-1β(H)-cholestan-3β-yl acetate* (**7**). M.p. 112-114 °C (from MeOH) (Ref. 5, m.p. 114 °C). The IR and ^{1}H-NMR spectra were indentical to those reported in Ref. 5.

Reaction of "non-polar fraction" **3** *with isoxazolidine* **2**. – Fraction **3** immediately after elution from the column (70 mg) and isoxazolidine **2** (70 mg) were dissolved in benzene (50 ml) to which two drops of acetic acid were added and the mixture was stirred at room temperature for 24 h. The usual work-up and column chromatography afforded a mixture of nitro derivatives **4** and **5** (13 mg, 18%), azoxy compound **6** (9 mg, 6.5%) and azoxy product **7** (15 mg, 11%).

ИЗВОД

ОЛОВО-ТЕТРААЦЕТАТНА ОКСИДАЦИЈА 5,10α-ЕПОКСИИМИНО-5(10→1)*abeo*-1β(H)-5α-ХОЛЕСТАН-3β-ИЛ-АЦЕТАТА

МИЛАН ДАБОВИЋ, ИВАН ЈУРАНИЋ, ЉУБИНКА ЛОРЕНЦ и МИХАИЛО Љ. МИХАИЛОВИЋ

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Дејством олово-тетраацетата на стероидни изоксазолидин **2** врши се оксидативно раскидање његовог епоксиимино моста, при чему се граде нитро-деривати **4** и **5**, и азокси-једињења **6** и **7**. У раду је приказан могући механистички ток запажених оксидативних процеса у коме учествује нитрозо интермедијер.

(Примљено 8. септембра 1994)

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