Anodic Oxidations of α-Santonine in Acetonitrile.

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Abstract: Some anodic oxidations of α-santonine using different experimental conditions were performed on a Pt electrode in acetonitrile medium. Four main products were obtained: 14-hydroxy-α-santonine, 4,5-epoxy-α-santonine, 14-acetamide-α-santonine and α-santonic acid. These oxidations were important since there are few methods to oxidize the allylic methyl groups attached to α,β-unsaturated ketones.

Introduction.

The α-santonine structure 1, possesses an α,β-α',β'-unsaturated ketone and a lactone as main functional groups. The electrochemistry of this groups, can occur by either, electroreduction or electrooxidation. The first santonine electroreduction realized in 1959, was performed in order to obtain some polarographic determinations (1-3).

The aim of this communication, was to make anodic oxidations of α-santonine in acetonitrile to establish a procedure to use, in order to modify other natural compounds with related structures. The experimental results, afforded new isolated products with different structure modifications than the previously reported (4).

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Results and Discussion.

Different concentrations of α-santonine and electrolyte as well as applied charge (Coulombs, C) were used to perform the preparative electrolysis. All experimental conditions used in this work are displayed in Scheme 1.

After the α-santonine electrolysis, the reaction mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and purified by column chromatography over silica gel using ethyl acetate/hexane (60:40) as eluent.

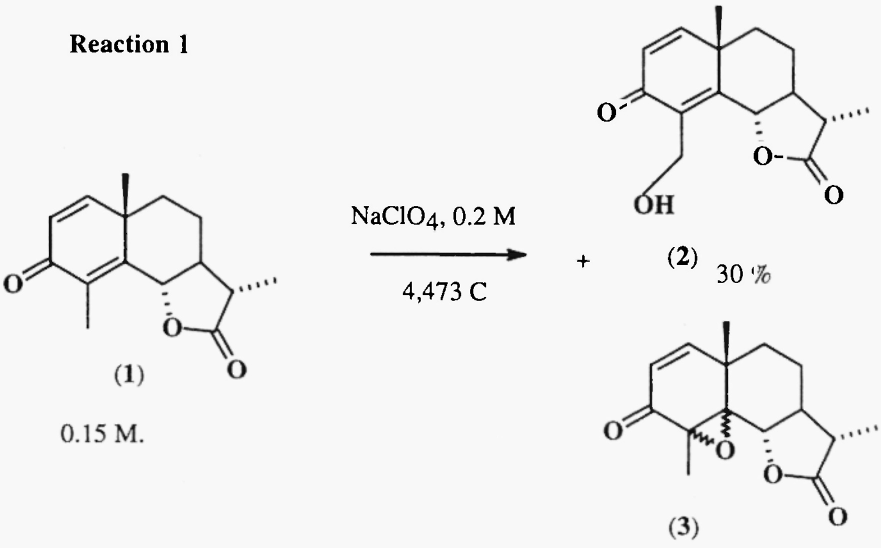
The obtained 14-hydroxy-α-santonine $\underline{2}$ (5) from reaction 1 is explained because of the alcohol formation can occur according to the Eberson and Nyberg report (6). Here, the generated nitrilium salt reacts with water to yield $\underline{2}$ in an anodic substitution reaction. This behavior suggests that the electrolytic medium contains as little as 3 % of water. In the reaction, the 4,5-epoxy-α-santonine $\underline{3}$ (7) was also formed. The mechanism pathway for this reaction is unknown; however, it was previously reported that this product is formed in the anodic oxidation of α,β-unsaturated ketones (4).

The applied charge in reaction 1, was higher than the theoretically calculated to oxidize the specified amount of substrate. Then, a high fraction of this charge is involved in a non-faradaic charge consumed by other species in the solution. Nevertheless, compounds $\underline{2}$ and $\underline{3}$ were isolated in 60% yield after purification.

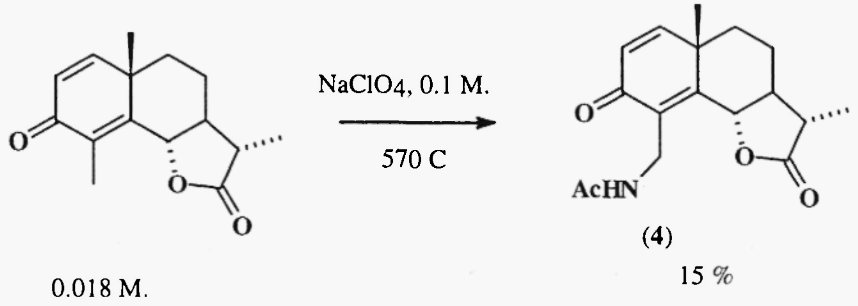
The formation of 14-acetamide-α-santonine $\underline{4}$ (8) in reaction 2, is explained according to the proposed Takahashi´s *et al* pathway (4), to oxidize the allylic methyl group attached on the α,β-unsaturated ketones. Three main steps are required: first, the transference of one-electron from the α-santonine to the anode; where this electron is provided from the unsaturated ketone moiety yielding a radical cation on the methyl group. This must be the active species that under an electrophilic substitution process, reacts in a second step with the (solvent) acetonitrile to produce a nitrilium salt, which is further hydrolyzed to the acetamide derivative (6). Whereas, acetyl derivatives are formed when acetate ions are present in the electrolytic medium (4).

In reaction 3, the effect of both the applied charge and the electrolyte concentration used for the santonine oxidation was analyzed. In this reaction, the mechanism is different compared with that of the acetamide formation, because the electron extraction localizes the radical cation on the carbonyl oxygen. Thus, it is stabilized by resonace after a proton loss from C-6 yielding an intermediate that is furthermore oxidized promoting the lactone

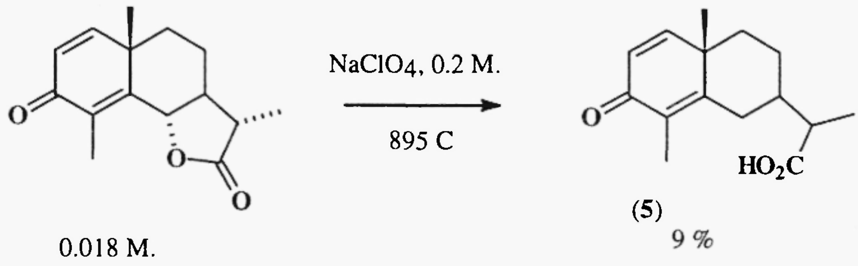
Reaction 1



Reaction 2



Reaction 3



Experimental conditions, for the anodic oxidation of α–santonine performed on a Pt electrode in acetonitrile. Constant potential electrolysis at 1.6 V. Vs SCE.

ring cleavage offering the α-santonic acid 5 (9). Evidently the electrolyte concentration is important to stabilize the intermediate on the reaction medium.

Because of the α,β-α',β'-unsaturated ketones and the lactone moieties are present in some steroid structures it is important to study the electrooxidation of the α-santonine since the results may be applied to achieve anodic oxidation of steroids.

Conclusion.

The above results showed that different experimental conditions can be used to perform anodic oxidations of α-santonine offering different products and might be applied for the transformation of other molecules with α,β-α',β'-unsaturated ketones. Additionally the oxidation of the allylic methyl group is important, since there are few methods to perform this reaction.

References

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(5) ^{1}H NMR ($CDCl_3$, δ): 6.74 (1H, d, J=10 Hz, H-1), 6.28 (1H, d, J=10 Hz, H-2), 4.82 (1H, d/sp, H-6), 4.81 (2H, s/sp, H-14), 2.43 (1H, q, H-11), 1.98 (3H, d, J=6.9 Hz, H-13), 1.85 1(D_2O) (1H, br s, H-O), 1.50-2.20 (2H, m, H-7,8,9), 1.38 (3H, s, H-15); IR (Film) 1774, 1662, 2998 cm^{-1}.

(6) L. Eberson and K. Nyberg. *Tetrahedron Lett.* **22**, 2389 (1966).

(7) ^{1}H NMR ($CDCl_3$, δ): 6.75 (1H, d, J=10 Hz, H-1), 5.89 (1H, d, J=10 Hz, H-2), 4.50 (1H, d, J=11 Hz, H-6), 1.85-2.25 (2H, m br s, H-8,9), 1.73 (3H, s, H-14), 1.29 (3H, s, H-15), 1.25 (3H, d, J=7 Hz, H-13); IR (film): 1785, 1687, 2889 cm^{-1}.

(8) ^{1}H NMR ($CDCl_3$, δ): 6.75 (1H, d, J=10 Hz, H-1), 6.25 (1H, d, J=10 Hz, H-2), 6.19 (1H, s, H-N), 4.85 (1H, d, J=12, H-6), 4.20 (2H, dd, H.14), 2.5 (1H, q, H-11), 1.88 (3H, s, H-16), 1.46-2.10 (2H, m, H-8,9), 1.38 (3H, s, H-15), 1.30 (3H, d, J=7.2, H-13); IR(film): 3456, 1788, 1710, 1668, 1458 cm^{-1}.

(9) ^{1}H NMR ($CDCl_3$, δ): 6.71 (1H, d, J=10 Hz, H-1), 6.25 (1H, d, J=10 Hz, H-2), 5.75 (1H, br s, COOH), 2.5-3.1 (2H, m, H-7,8,9), 1.98 (3H, s, H-14), 1.25 (3H, d, J=6 Hz, H-13), 1.19 (3H, s, H-15); IR(film) 1654, 1714, 2978 cm^{-1}.

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