111. Photochemical Behaviour of 17β-Acetoxy-4-aza-1,5-androstadien-3-one: Photo-oxidation *vs.* Di-π-methane Rearrangement[1])

Photochemical Reactions IX [1]

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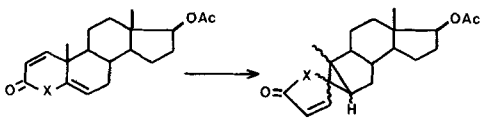
Summary

The irradiation of the title compound **6** with UV. light and under photosensitized oxidation conditions yields products which are characteristic of the photo-oxidation of the enamide moiety of **6**. In contrast to the situation encountered in the case of the irradiation of its carbocyclic and 4-oxa analogues **1** and **2**, respectively, no compound resulting from a di-π-methane rearrangement of the $\Delta^{1,5(6)}$-unsaturated system of **6** has been so far detected.

1. Introduction. – In the preceeding communication [1] we showed that the substitution of $H_2C(4)$ by an oxygen atom in the steroidal derivative **1** does not prevent the di-π-methane rearrangement of the $\Delta^{1,5(6)}$-dien system. Thus, UV. irradiation of lactone **2** yielded spiro-cyclic derivatives of type **4** [1] analogously to the behaviour of its carbocyclic counterpart **1** which gave **3** [2] *(Scheme 1)*.

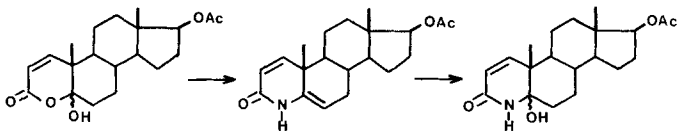
Scheme 1



1 X = CH_2 **3** X = CH_2
2 X = O **4** X = O

To investigate the influence of the heteroatom on the process, we have studied the photochemical behaviour of lactam **6** *(Scheme 2)*, the 4-aza analogue of ketone **1** and lactone **2**.

Scheme 2



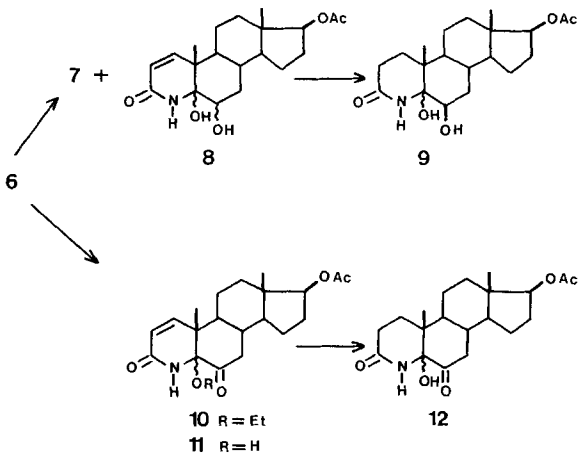
5 **6** **7**

[1]) Part of the doctoral thesis of *J. A. Vallet*, I.Q.S., Barcelona, 1978.

2. Synthesis and photolysis. – Conversion of 17β-acetoxy-5ξ-hydroxy-4-oxa-1-androsten-3-one (**5**) [1] with NH_3 under pressure yielded the desired lactam **6** in 22% yield besides the 5ξ-hydroxy-lactam **7** (42%)[2]).

The UV. irradiation ($\lambda = 254$ nm) of a 0.0030 M solution of **6** in benzene yielded a multicomponent mixture which decomposed to a great extent on chromatographic separation, but from which 11% of **6**, 4% of the 5ξ-hydroxy-lactam **7** and 8% of the dihydroxylactam **8** could be isolated, together with mixtures of unidentified products of very low polarity (11%) and of other highly unstable compounds (23%). In no case the formation of nitrogen containing spiro-cyclic derivatives of type **3** *(Scheme 1*, X = NH) was observed. The structure of **8**[2]) was confirmed by its catalytic hydrogenation to the known saturated dihydroxylactam **9** [3] *(Scheme 3)*.

Scheme 3



The photosensitized oxygenation of **6** with methylene blue as sensitizer afforded the hydroxy-oxo-lactam **11** (45%), together with a highly unstable compound (52%) for which the structure of the α-ethoxy-ketone **10** is temptatively proposed[3]) *(Scheme 3)*. The structure of **11**[2]) was also confirmed by its catalytic hydrogenation to the known saturated derivative **12** [4].

3. Conclusion. – Considering previously reported results [1] [2] it can be concluded that in going from carbocyclic to analogous heterocyclic systems the nature of the heteroatoms may play an important role in the photochemical behaviour of the different compounds. Thus, in the case of lactam **6** the influence of the enamide function predominates over the one of the $\Delta^{1,5(6)}$-unsaturated system, so that **6** undergoes photo-oxidation phenomena, which may be considered typical [4] of that chromophore, rather than a di-π-methane rearrangement as in the case of the enol-

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[2]) Spectral data support the structures of the new compounds (s. exper. part).

[3]) **10** decomposes when gently heated in acetone or after a few minutes in chloroform solution at room temperature. Its unstability prevented its further hydrogenation to the known saturated derivative [4].

lactone **2** [1]. Furthermore, the products obtained on UV. irradiation of **6** may be assumed to arise by a benzene sensitized process, since no reaction is observed on irradiation ($\lambda = 254$ nm or $\lambda \geq 280$ nm) in dioxane, despite the UV. absorption of **6**.

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Experimental Part

General remarks. S. [1]. The UV. irradiation was carried out at RT. with a low-pressure Hg lamp (NK 6/20, *Quarzlampen GmbH*, Hanau) in a typical immersion unit. For the photo-sensitized oxygenation a *Sylvania* 500 T 3Q/CI/U 220 V lamp and the same type of reactor were used, and a current of O_2 was introduced.

1. Preparation of 6. – *Conversion of* **5** *by* NH_3. To a solution of 801 mg of **5** [1] in 60 ml of dry tetrahydrofurane in a stainless steel tubular reactor, externally cooled with CO_2/acetone, an excess of liquid NH_3 was added. The closed reactor was kept at 78° for 14 h. Solvent evaporation *in vacuo* yielded 818 mg of a mixture of several components, which was chromatographed on silicagel. With ethyl acetate were eluted first 82 mg of a complex mixture of compounds of low polarity, then 176 mg of *17β-acetoxy-4-aza-1,5-androstadien-3-one* (**6**), m.p. 251–253° (dec.) after three crystallizations, $[\alpha]_D^{25} = -287°$ (0.25). – UV.: 213 (12,900), 295 (2,260). – IR.: 3170, 3090, 3050, 1730, 1685, 1680, 1675*s*, 1610, 1240. – ^{1}H-NMR.: 0.84 (*s*, $H_3C(18)$); 1.24 (*s*, $H_3C(19)$); 2.02 (*s*, $CH_3COO-C(17)$); 4.60 (*d*×*d*, $J = 9$, $J' = 7$, H–C(17)); 5.09 (*m*, H–C(6)); 5.78 (*d*×*d*, $J = 10$, $J' = 2$, H–C(2)); 6.65 (*d*, $J = 10$, H–C(1)); 7.70 (br., H–N(4)). – MS.: 329 (M^+).

$C_{20}H_{27}NO_3$ (329.44) Calc. C 72.92 H 8.26 N 4.25% Found C 72.75 H 8.29 N 4.23%

With ethyl acetate/methanol 9:1 343 mg of *17β-acetoxy-5ξ-hydroxy-4-aza-1-androsten-3-one* (**7**), were eluted, m.p. 248–253° (dec.) after four crystallizations, $[\alpha]_D^{25} = +203°$ (0.25). – UV.: 215 (9,200). – IR.: 3300, 1730, 1680, 1660, 1610, 1255. – ^{1}H-NMR.: 0.80 (*s*, $H_3C(18)$); 1.23 (*s*, $H_3C(19)$); 2.00 (*s*, $CH_3COO-C(17)$); 3.85 (*s*, HO–C(5)); 4.53 (*m*, H–C(17)); 5.92 (*d*×*d*, $J = 10$, $J' = 2$, H–C(2)); 6.28 (*d*, $J = 10$, H–C(1)); 7.01 (br., H–N(4)). – MS.: 347 (M^+).

$C_{20}H_{29}NO_4$ (347.46) Calc. C 69.13 H 8.41 N 4.03% Found C 69.01 H 8.45 N 3.99%

Finally, with ethyl acetate/methanol 4:1, 151 mg of a complex mixture of polar compounds were obtained.

2. Photolysis of 6. – 2.1. *UV. irradiation of* **6**. A solution of 0.995 g of **6** in 1 l of benzene (*Merck*, analytical purity; approx. water content 0.03%), was irradiated for 57 h under nitrogen (not absolutely free of traces of oxygen). Solvent evaporation *in vacuo* at RT. yielded 1.203 g of a highly complex mixture, which was chromatographed on silicagel. With benzene/ethyl acetate 7:3 133 mg of a complex mixture of compounds of low polarity were eluted. With benzene/ethyl acetate 1:1 130 mg of impure starting material **6** were obtained, which were purified by prep. TLC. (benzene/chloroform/methanol/triethylamine 16:4:2:1) and identified by mixed m.p., TLC. and IR. spectrum. The third fraction, eluted with benzene/ethyl acetate 1:3, contained 282 mg of a mixture of several components, which decomposed on an attempt to further separate them by chromatography. With ethyl acetate 181 mg of a mixture of **7** (25%) and **8** (75%) were eluted, which could be separated by prep. TLC. (benzene/chloroform/methanol/triethylamine 16:4:2:1). **7** was identified by mixed m.p., TLC. and IR. spectrum. *17β-Acetoxy-5ξ,6ξ-dihydroxy-4-aza-1-androsten-3-one* (**8**). M.p. 201–203° after two crystallizations. – UV.: 213 (12,000). – IR.: 3540, 3280, 1720, 1675, 1655, 1605, 1255. – MS.: 363 (M^+). – The ^{1}H-NMR. spectrum couldn't be recorded due to the low solubility of the compound in the usual solvents. The elemental analysis wasn't carried out since the sample decomposed during its further purification (crystallization).

Catalytic hydrogenation of **8**. 22 mg of **8** in 30 ml of ethanol were added to 40 mg of Pd/C in ethanol. After hydrogen uptake the catalyst was filtered off and the solvent evaporated *in vacuo* to yield 20 mg of *17β-acetoxy-5ξ,6β-dihydroxy-4-aza-androstan-3-one* (**9**) [3] containing traces of several compounds. **9** was purified by prep. TLC. (benzene/acetone 3:2) and identified by TLC., IR. and MS.

2.2. *Photosensitized oxygenation of* **6**. A solution of 364 mg of **6** and 14 mg of methylene blue in 370 ml of chloroform/ethanol 99.5:0.5 was irradiated for 5 min. After solvent evaporation *in vacuo* the residue was diluted in ether and washed several times with water until complete decolorization. Evaporation of the dried (Na_2SO_4) organic phase *in vacuo* yielded 380 mg of a mixture of two compounds, which were separated by their different solubility in ethyl acetate. To the soluble portion (163 mg of the crude mixture) temptatively the structure of *17β-acetoxy-5ξ-ethoxy-4-aza-1-androsten-3,6-dione* (**10**) was attributed. – IR.: 3400, 3270, 3100, 1730, 1700, 1680, 1655, 1630, 1610. – ^{1}H-NMR.: 0.83 (*s*, H_3C(18)); 1.15 (*t*, CH_3CH_2O–C(5)); 1.45 (*s*, H_3C(19)); 2.05 (*s*, CH_3COO–C(17)); 3.50 (*m*, CH_3CH_2O–C(5)); 4.58 (*m*, H–C(17)); 5.5, 6.5 (*AB* system, disturbed by coupling with H–N(4), H–C(2), H–C(1)); 7.0 (br., H–N(4)); moreover, the spectrum shows signals due to an experimentally observed decomposition of **10** in $CDCl_3$. The remarkable unstability of the compound prevented its further analysis.

The insoluble material was chromatographed with benzene/ethyl acetate 1:9 giving 34 mg of **10** (TLC.) and 171 mg of *17β-acetoxy-5ξ-hydroxy-4-aza-1-androsten-3,6-dione* (**11**). – UV.: 213 (12,000). – IR.: 3440, 3360, 3240, 1735, 1675, 1610, 1240. – ^{1}H-NMR.: 0.82 (*s*, H_3C(18)); 1.28 (*s*, H_3C(19)); 2.02 (*s*, CH_3COO–C(17)); 4.40 (*m*, H–C(17)); 5.20 (br., HO–C(5)); 5.90 (*d*×*d*, J'=10, J=2, H–C(2)); 6.48 (*d*, J=10, H–C(1)); 7.18 (br., H–N(4)). – MS.: 361 (M^+). **11** decomposed on crystallization, therefore no m.p. and elemental analysis were obtained.

Catalytic hydrogenation of **11**. 40 mg of **11** in 30 ml of ethanol were hydrogenated over 90 mg of Pd/C. Working-up as usual (s. above) yielded 41 mg of a mixture of several compounds. Chromatography with ethyl acetate furnished first 12 mg of a mixture of compounds of low polarity and then 25 mg of *17β-acetoxy-5ξ-hydroxy-4-aza-androstan-3,6-dione* (**12**), identified by TLC., IR. and MS.

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