278. Photochemical Reactions. V [1]. Photo-oxidation of 17β-Acetoxy-4-aza-androst-5-en-3-one[1])

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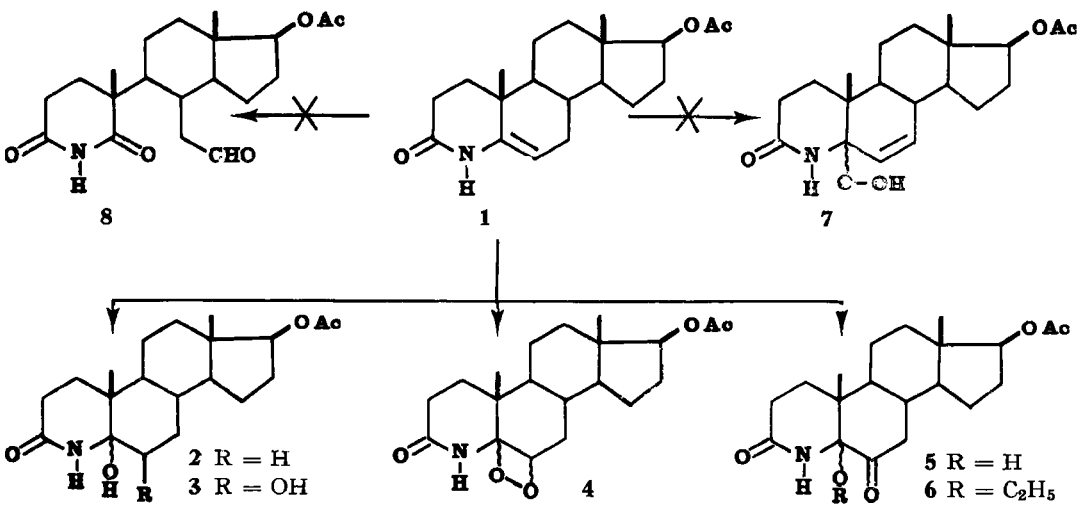
(6. X. 75)

Summary. The photo-oxidation of the title compound (**1**) is described. The isolated products are the result of a [2+2] oxygen addition to the olefinic double bond of the enamide.

In recent times, the photo-oxidation of the enamine function has received considerable attention [2]. These compounds suffer [2 + 2] siglet oxygen addition, with formation of unstable 1,2-dioxetanes, that ultimately yield carbonylic fragments. The decomposition of these dioxetanes are usually accompanied by luminiscence phenomena. On the other hand, oxidation products of enamides seem to play an important role in bioluminiscence phenomena [3]. For all this and considering the photoreactivity of the Δ^5 double bond in compound **1** [1], it was thought of interest to study its behaviour in photo-oxidation conditions.

When **1**, easily obtained from testosterone acetate [4], was irradiated during 12 h in benzene (Merck, analytical purity), with the light of a low-pressure Hg lamp, under a current of oxygen, a mixture of compounds was obtained, containing starting material (**1**, 9%), the hydroxy derivative **2** (5%), the diol **3** (16%), the dioxetane **4** (5%) and the keto-alcohol **5** (30%) (*Scheme 1*). All the structures were assigned on basis of the corresponding spectroscopic and analytical data[2]).

Scheme 1



[1]) Communicated in part at the XIV Reunión Bienal de la Real Sociedad Española de Física y Química, 24–29 September 1973, Oviedo (Spain) and at the Euchem Conference on Useful Preparative Aspects of Photochemistry, 1–5 September 1975, Ghent (Belgium).

[2]) The NMR.-, IR.-, UV.- and mass spectra of the new compounds are in good agreement with the proposed structures and will be reported only in the experimental part of this work.

With the purpose of finding more suitable conditions to obtain the assumed dioxetane **4**, the photosensitized oxygenation of **1** with methylene blue as sensitizer, was essayed, results being summarized in the Table (*cf. Scheme 1*).

Solvent	Time (min.)	Observed products
CH_3OH	60	Resinification
C_2H_5OH	60	One unstable product[a])
$CHCl_3/C_2H_5OH$ 95.5:0.5	75	**4** (4%) + **5** (41%) + **6** (23%)

[a]) Structure unknown: liberated I_2 when treated with NH_4I/CH_3OH.

As it was to be expected, in the specified aforementioned conditions, no products resulting from a water addition to the olefinic double bond (**1** → **2**) were observed. In one experiment, a new compound, identified as 17β-acetoxy-5-ethoxy-4-aza-androstan-3,6-dione (**6**), was isolated. In no case, the formation of allylic hydroperoxides or of carbonylic fragmentation products (**7** and **8**, see *Scheme 1*) was observed.

Compound **4** is stable in pure crystalline form, although it isomerized to **5** on SiO_2 column chromatography and was transformed into a mixture of **5** and **6** (*Scheme 1*), when heated with HCl in ethanol solution. Also, it slowly liberated I_2 when treated with NH_4I/CH_3OH and could be reduced with $NaBH_4$ to a highly polar compound, which decomposed easily. On the other hand, no chemiluminiscence was observed when **3** was heated[3]), nor the typical fragmentation to a dicarbonyl compound [2] (**4** → **8**) seemed to take place, a fact which can be related [5] to the lack of chemiluminiscence mentioned above.

A possible path to rationalize the formation of products **5** and **6** goes through the dioxetane **4**, which may isomerize to the keto-alcohol **5** or suffer a solvent attack with formation of an ethoxy-hydroperoxide (**9**), which then dehydrates to **6** (*Scheme 2*). These two processes, isomerization to a hydroxy-carbonyl derivative (**4** → **5**) and solvolysis (**4** → **9**), are not typical of dioxetanes, although they are well known in the case of 1,4-endoperoxides [6] and at least one example in the field of the enamines has been recently reported [2d].

We are grateful to PD Dr. *H. Wehrli*, Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, Zürich, for kindly supplying of starting material, for his help in recording of spectra, as well as for many stimulating discussions during the work. We also thank Prof. Dr. *K. Schaffner*, Organic Chemistry Department, University of Geneva, for spectroscopic services and Dr. *U. Burger* (Univ. Geneva), for ^1H- and ^{13}C-NMR. services.

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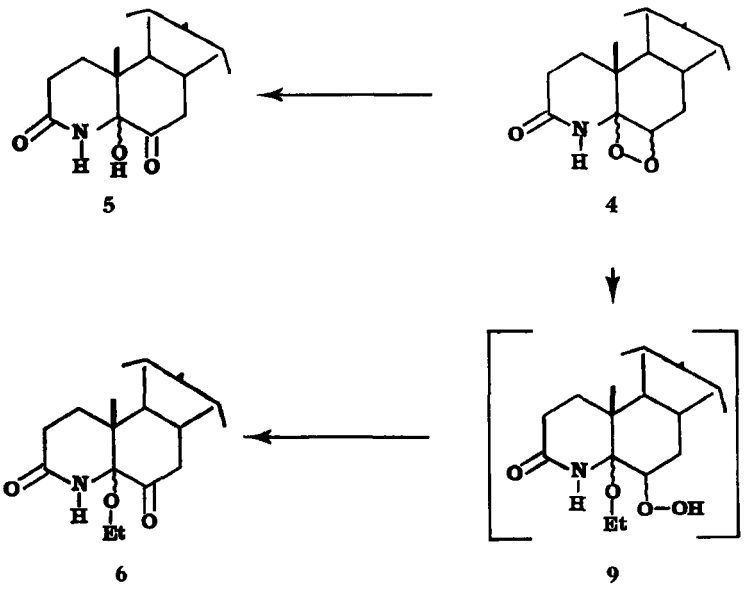
[3]) **4** melts with decomposition, giving a black tar.

Scheme 2



Experimental Part

For general remarks see [7]. The irradiations were carried out at room temperature, under a current of oxygen, with a low-pressure Hg lamp (NK 6/20, *Quarzlampen GmbH*, Hanau) disposed in typical immersion unit, or with a 200 watts *Phillips* tungsten lamp. Crystallizations are from acetone/petrol ether (b.p. 50–70°).

Irradiation of **1** *with UV.-light (low-pressure Hg lamp).* A solution of 905 mg **1** in 1 l benzene (Merck, analytical purity) was irradiated during 12 h. Solvent evaporation *in vacuo* yielded 1167 mg of a mixture of several components. Chromatography with chloroform/ethyl acetate/benzene/methanol 6:2:1:0.25 furnished 73 mg of impurities of very low polarity; 106 mg of starting material **1** [4] (identification through mixed m.p., TLC. and IR.-spectrum); and 61 mg of *17β-acetoxy-5ξ,6ξ-epidioxy-4-aza-androstan-3-one* (**4**), m.p. (two crystallizations) 192–195°[3]). – IR.: 3425, 3340, 3250, 1730, 1660, 1640, 1255. – ^{1}H-NMR.: 0.82 + 0.86, 2 *s*, $H_3C(18)$ + $H_3C(19)$; 2.05, *s*, C(17)—$OCOCH_3$; 3.11, *m*, H—C(6); 4.62, br., H—C(17); 6.58, br., NH. – MS.: $M^+ = 363$.

$C_{20}H_{29}NO_5$ (363.44) Calc. C 66.09 H 8.04 N 3.85% Found C 66.34 H 8.32 N 3.62%

A further fraction consisted of 352 mg of *17β-acetoxy-5ξ-hydroxy-4-aza-androstan-3,6-dione* (**5**), m.p. (three crystallizations) 235–236°. – IR.: 3380, 3220, 1760, 1730, 1660, 1630, 1245. – ^{1}H-NMR.: 0.79 + 0.82, 2 *s*, $H_3C(18)$ + $H_3C(19)$; 2.07, *s*, C(17)—$OCOCH_3$; 4.62, br., H—C(17); 5.54, br., HO—C(5); 7.16, br., NH. – MS.: $M^+ = 363$.

$C_{20}H_{29}NO_5$ (363.44) Calc. C 66.09 H 8.04 N 3.85% Found C 66.15 H 8.00 N 3.79%

At last, 63 mg of the hydroxy derivative **2** [1] and 181 mg of the diol **3** [1] were eluted (identification in both cases, through mixed m.p., TLC. and IR.-spectrum).

Photosensitized oxidation of **1** *(tungsten lamp).* – 1) *In methanol.* A solution of 551 mg **1** and 8 mg methylene blue in 600 ml methanol, was irradiated during 1 h. After solvent evaporation *in vacuo*, the residue was diluted in ether and washed with water several times, until complete decoloration. Evaporation *in vacuo* of the organic phase, previously dried on sodium sulfate, yielded a very complex resinic material, which could not be separated by the conventional chromatographic methods.

2) *In ethanol.* A solution of 604 mg **1** and 8 mg methylene blue in 600 ml ethanol, was irradiated during 1 h. The same extraction procedure specified above, yielded one main product, which

liberated I_2 when treated with NH_4I/CH_3OH and decomposed spontaneously and during several attempts of purification.

3) *In chloroform/ethanol.* 13 mg of methylene blue in 5 ml ethanol were added to 1.0 g **1** in 1 l chloroform. The solution was irradiated during 75 min. The same extraction procedure specified above, yielded 1280 mg of a mixture of three main products. Chromatography with benzene/chloroform/ethyl acetate 1:1:1[4]) furnished, after 71 mg of impurities of very low polarity, 294 mg of *17β-acetoxy-5ξ-ethoxy-4-aza-androstan-3,6-dione* (**6**), m.p. (three crystallizations) 220–222°. – UV.: 240 (918). – IR.: 3210, 3105, 1740, 1730, 1685, 1255, 1240. – NMR.: 0.78 + 0.80, 2 *s*, $H_3C(18)$ + $H_3C(19)$; 1.16, *t*, $J = 7$, CH_3 (5-ethoxy); 2.90–3.60, *m*, CH_2 (5-ethoxy); 4.66, br., H—C(17); 6.80, br., NH; after D_2O addition, the signal at 6.80 disappeared; the presence of a 6-oxo function was further confirmed by ^{13}C-NMR. spectroscopy: signal at 205.3 ppm. – MS.: $M^+ = 391$.

$C_{22}H_{33}NO_5$ (391.49) Calc. C 67.49 H 8.50 N 3.58% Found C 67.76 H 8.66 N 3.46%

A further fraction consisted of 56 mg **4** (identification, after three crystallizations, through mixed m.p., TLC. and IR.-spectrum). At last, 519 mg **5** were eluted (identification through mixed m.p., TLC. and IR.-spectrum).

Thermal conversion of **4** *into* **5** + **6**. A solution of 22 mg **4** in 6 ml ethanol and 2 drops conc. HCl, was refluxed during 1 h. Extraction by the usual method, yielded a mixture of several components. Chromatography with benzene/chloroform/ethyl acetate 1:1:1 furnished 6 mg **6** (identification, after one crystallization, through TLC., IR.- and mass spectra) and 11 mg of **5** + **4** (TLC.), that afforded a pure sample of **5** after three crystallizations (identification through mixed m.p., TLC. and IR.-spectrum).

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[7] *J. Repollés, F. Servera & J.-J. Bonet,* Helv. *57,* 2454 (1974).

4) This mixture is not appropriate for TLC. control, for which benzene/chloroform/methanol/triethylamine 15.55:4.00:0.50:0.45 should be used.