47. Photochemical Rearrangement of a Steroidal α,β-Epoxylactone[1])

Photochemical Reactions, XI [1]

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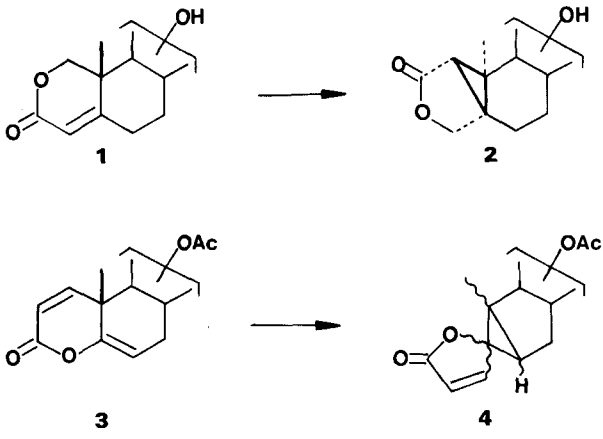
Summary

The UV. irradiation of 17β-acetoxy-4α,5α-epoxy-2-oxaandrostan-3-one (**7**) yields 17β-acetoxy-2-oxa-10 (5→4)*abeo*-4ξ(H)-androsta-3,5-dione (**11**). A non-photochemical synthesis of **11**, proceeding in lower yield, is also described.

Introduction. – As a part of a systematic study on the photochemical behaviour of heterocyclic steroids, we have recently reported that the α,β-unsaturated steroidal lactones undergo the 'type A rearrangement' (**1**→**2**) [2] *(Scheme 1)* or the di-π-methane rearrangement (**3**→**4**) [3], similar to their carbocyclic counterparts.

Another photochemical reaction, which has found wide application in the steroid field, is the rearrangement of α,β-epoxyketones to β-dicarbonyl isomers (**5**→**6**) [4] *(Scheme 2)*, so we extended our studies to the corresponding α,β-epoxylactone **7** *(Scheme 3)*.

Scheme 1



[1]) Communicated in part at the VIII[th] Conference on Isoprenoids, 9–15 September, 1979, Toruń (Poland). Part of the doctoral thesis of *A. Cánovas*, I.Q.S., Barcelona, 1980.

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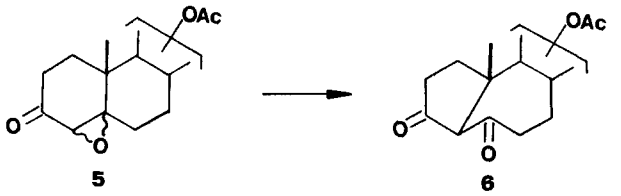
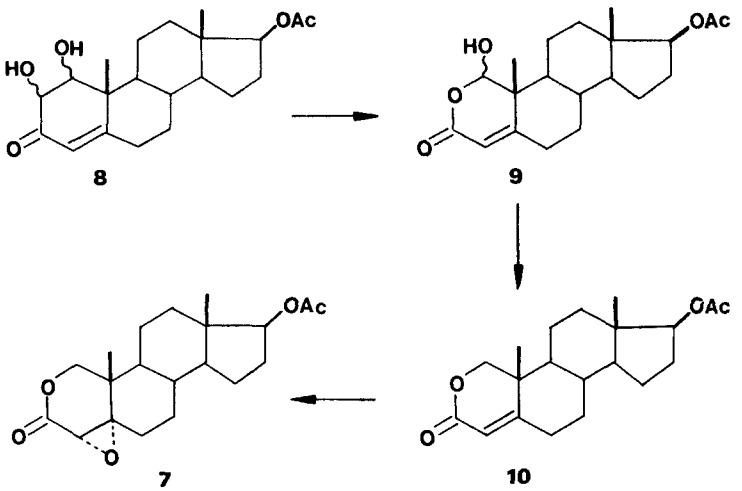
Scheme 2



Scheme 3



Preparation of **7** *(Scheme 3).* *cis*-Hydroxylation of 17β-acetoxy-1,4-androstadien-3-one with osmium tetroxide gave 17β-acetoxy-1ξ,2ξ-dihydroxy-4-androsten-3-one (**8**), together with its 4ξ,5ξ-isomer. On treatment with sodium metaperiodate, **8** was converted to the pseudo-acid **9**[2]), which was then reduced with sodium borohydride, in a two-phase system[3]), to the lactone **10**. Epoxidation of **10** with *m*-chloroperbenzoic acid furnished the epoxylactone **7** as a single isomer. The stereochemistry of the oxirane ring was established on the basis of its CD. data (λ_{max} = 232.2 nm, $\Delta\varepsilon = -7.800$)[4]). The three last steps were accomplished in quantitative yield[5]).

Photolysis of **7**. The UV. irradiation (λ = 254 nm) of a 0.0075 M dioxane solution of **7** yielded a mixture of starting material **7** (52%) and the β-ketolactone **11** (38%), together with traces of impurities of higher polarity (3%)[6]).

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[2]) Compound **9** has been detected as a very minor component in the ozonolysis mixture of 17β-acetoxy-1,4-androstadien-3-one [5].

[3]) When the reduction was carried out in aqueous methanol, a high proportion of the corresponding saturated lactone was obtained.

[4]) We thank Prof. Dr. *G. Snatzke*, Ruhr-Universität, Bochum, for the recording and interpretation of the CD. spectrum.

[5]) Spectral data of all new compounds are in good agreement with the proposed structures (see experimental part).

[6]) An analogous result was obtained when the irradiation was carried out in ethanol.

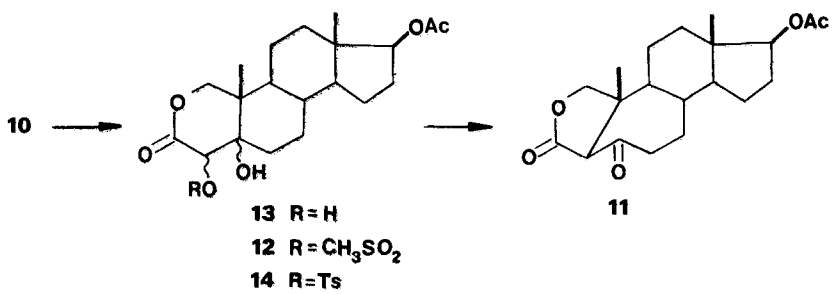
Non-photochemical preparation of the β-ketolactone **11** *(Scheme 4).* On the basis of the non-photochemical 10(5→4) rearrangement of 3-oxo and 3-deoxo steroids, described in the carbocyclic series [4] [6], the solvolysis of the 4-methanesulfonyloxy derivative **12** was examined.

Osmium tetroxide treatment of the lactone **10** yielded the *cis* diol **13** in 55% yield, from which the mesylate **12** was obtained quantitatively. All attempts to solvolyse **12** to **11** failed; either unchanged starting material or a mixture of several components was obtained from which no trace of **11** was detected (TLC.). However, refluxing the *cis* diol **13** with tosyl chloride in pyridine, yielded a complex mixture of compounds, from which the β-ketolactone **11**, formed presumably from the tosylate **14**, was isolated in 29% yield.

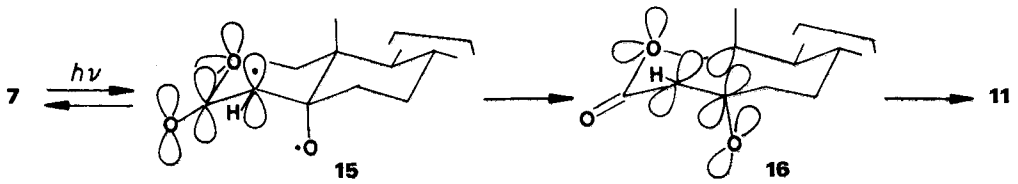
Discussion. – The photo-rearrangement **7**→**11** can be rationalised, assuming a formal similarity in the behaviour of the heterocyclic and the carbocyclic [4] compounds. The reaction sequence would proceed *via* a primary diradical **15**, which would rearrange through a transition state **16**, in a synchronous way, to **11** *(Scheme 5).*

The reaction here described is, to our knowledge, the first example of an α,β-epoxylactone giving rise to a stable β-ketolactone as a photo-product. In the previously described examples of α,β-epoxyesters irradiated with UV. light, β-keto-esters are only postulated as intermediates, but are not isolated, being unstable in UV. light [7]. Moreover, this is the first example of a steroidal lactone undergoing rearrangement to an *abeo*-structure, and, since it is known that some carbocyclic *abeo*-steroids exhibit anabolic activity, this reaction provides a route to comparable heterocyclic derivatives with possible pharmacological activity.

Scheme 4



Scheme 5



Experimental Part

General remarks: [3].

Preparation of 7. – *17β-Acetoxy-1ξ,2ξ-dihydroxy-4-androsten-3-one* (**8**). To a solution of 10.17 g of 1-dehydrotestosterone acetate in 150 ml of *t*-BuOH, a solution of 2.30 g $KClO_3$ in 90 ml H_2O and 70 ml *t*-BuOH, and 1 g OsO_4 was added, with external cooling. The mixture was left at RT. in the dark during 25 days; after dilution with ether, it was worked up as usual, washing with aqueous $NaHSO_3$ and $NaHCO_3$ solutions, yielding 10.84 g of a mixture. Chromatography with cyclohexane/ethyl acetate 1:1 furnished 1.69 g of starting material (identified by mixed m.p., TLC. and IR. spectrum), followed by 5.17 g of *17β-acetoxy-4ξ,5ξ-dihydroxy-1-androsten-3-one* [9] (identified by mixed m.p., TLC. and UV., IR., NMR. and mass spectra). The third fraction contained 3.24 g of the 1ξ,2ξ-dihydroxy compound **8**, m.p. 240–242° after 3 crystallizations; $[\alpha]_D^{24} = +79.6°$ (1.00). – UV.: 242 (12,310). – IR.: 3448, 1725, 1672, 1250. – ^{1}H-NMR.: 0.85 (*s*, $H_3C(18)$); 1.26 (*s*, $H_3C(19)$); 2.00 (*s*, AcO–C(17)); 2.8+3.4 (br., HO–C(1) + HO–C(2)); 4.00, 4.40 (*AB*-system, $J_{AB} = 3$, H–C(1), H–C(2)); 4.58 (*m*, H–C(17)); 5.75 (*s*, H–C(4)); after D_2O addition, the signals at 2.8 and 3.4 disappeared. – MS.: 362 (M^+).

$C_{21}H_{30}O_5$ (362.47) Calc. C 69.59 H 8.34% Found C 69.69 H 8.40%

The fourth fraction, 0.61 g, was a complex mixture not further investigated.

Cleavage of **8** *with sodium metaperiodate.* To a solution of 2.38 g of **8** in 500 ml of ethanol, 11.85 g of sodium metaperiodate in 200 ml of water were added. The mixture was stirred at RT. for 16 h. Solvent evaporation *in vacuo* and the usual work-up with ethyl acetate, yielded 2.35 g of *17β-acetoxy-1ξ-hydroxy-2-oxa-4-androsten-3-one* **9** [5], m.p. 221–222° after 3 crystallizations. – UV.: 227 (12,100). – IR.: 3360, 3030, 1700, 1625, 1260, 1230. – ^{1}H-NMR.: 0.84 (*s*, $H_3C(18)$); 1.20 (*s*, $H_3C(19)$); 2.05 (*s*, AcO–C(17)); 4.60 (*m*, H–C(17)); 5.20 (br., HO–C(1)); 5.40 (*s*, H–C(1)); 5.67 (*s*, H–C(4)); after D_2O addition, the signal at 5.20 disappeared. – MS.: 331 ($M^+ - OH$).

Reduction of **9** *with sodium borohydride.* To 160 mg of **9** in 10 ml of $CHCl_3$, a solution of 200 mg of $NaBH_4$ in 20 ml H_2O was added. The mixture was left at RT. for 30 min under vigorous stirring. After acidification with HCl, extraction as usual yielded 157 mg of *17β-acetoxy-2-oxa-4-androsten-3-one* (**10**), m.p. 157–157.5° after 3 crystallizations; $[\alpha]_D^{20} = +13.3°$ (0.30). – UV.: 223 (9,400), 270 (1,100). – IR.: 3020, 1715, 1620, 1230. – ^{1}H-NMR.: 0.80 (*s*, $H_3C(18)$); 1.22 (*s*, $H_3C(19)$); 2.07 (*s*, AcO–C(17)); 4.00, 4.30 (*AB*-system, $J_{AB} = 12$, $H_2C(1)$); 4.60 (*m*, H–C(17)); 5.65 (*s*, H–C(4)). – MS.: 332 (M^+).

$C_{20}H_{28}O_4$ (332.44) Calc. C 72.26 H 8.49% Found C 72.27 H 8.89%

Epoxidation of **10**. To a solution of 4.40 g of **10** in 900 ml of $CHCl_3$, 32 g of *m*-chloroperbenzoic acid were added. The mixture was stirred at 40° for 120 h. The usual work up, washing with aqueous solution of $NaHCO_3$, yielded 4.58 g of *17β-acetoxy-4a,5a-epoxy-2-oxaandrostan-3-one* (**7**), m.p. 213–214° after 4 crystallizations; $[\alpha]_D^{20} = -32.5°$ (0.35). – UV.: 202 (2,000), 270 (1,700). – CD.: CH_3CN *c* (mg/g) = 0.3130; path length = 0.1: 232.2 (–7,800); 195.0 (–0,387). – IR.: 3020, 1745, 1725, 1240, 1230, 1040. – ^{1}H-NMR.: 0.80 (*s*, $H_3C(18)$); 1.15 (*s*, $H_3C(19)$); 2.00 (*s*, AcO–C(17)); 3.30 (*s*, H–C(4)); 3.80, 4.15 (*AB*-system, $J_{AB} = 10$, $H_2C(1)$); 4.56 (*m*, H–C(17)). – MS.: 348 (M^+).

$C_{20}H_{28}O_5$ (348.44) Calc. C 68.94 H 8.10% Found C 69.09 H 8.31%

Photolysis of 7. – A solution of 423 mg of **7** in 160 ml of dioxane (*Carlo Erba*, analytical purity) was irradiated during 78 h with a low-pressure Hg lamp. Solvent evaporation *in vacuo* yielded 425 mg of an oil, mixture of 2 main components. Chromatography on silica gel *Merck* ('reinst'), with benzene/ethyl acetate 15:1, furnished, first 220 mg of starting material **7** (identification by mixed m.p., TLC. and IR. spectrum). The second fraction consisted of 159 mg of *17β-acetoxy-2-oxa-10(5→4)*abeo-*4ξ(H)-androsta-3,5-dione* (**11**), m.p. 161–162° after 3 crystallizations; $[\alpha]_D^{20} = -36.3°$ (0.38). – UV.: 202 (2,800), 262 (6,300); after addition of one drop of 0.1N NaOH: 202 (6,600), 290 (12,880); Fe^{3+} complex (3.1 mg of **11** in 5 ml of 3.7. 10^{-3}M solution of $FeCl_3$ in ethanol): 540 (200). – IR.: 1750, 1710, 1665, 1655, 1265, 1210, 1180. – ^{1}H-NMR.: 0.81 (*s*, $H_3C(18)$); 1.21 (*s*, $H_3C(19)$); 2.05 (*s*, AcO–C(17)); 3.75 (*s*, H–C(4)); 4.00 (*s*, $H_2C(1)$); 4.65 (*m*, H–C(17)); 11.20 (*s*, HO–C(6)); the relative values of the integral curves of the signals at 3.75 and 11.20 are lower than one; after D_2O addition, the signal at 11.20 disappeared. – MS.: 348 (M^+).

$C_{20}H_{28}O_5$ (348.44) Calc. C 68.94 H 8.10% Found C 68.70 H 8.14%

The third fraction, 12 mg of a mixture of polar components, was not further investigated.

Non-photochemical preparation of 11. – *17β-Acetoxy-4ξ,5ξ-dihydroxy-2-oxaandrostan-3-one* (**13**). To a solution of 408 mg of **10** in 150 ml of ether, 300 mg of OsO_4 were added, with external cooling. The mixture was left for 16 h at RT. in the dark. After dilution with ether, it was extracted as usual, washing with aqueous solution of $NaHSO_3$, to yield 433 mg of a mixture which was chromatographed with cyclohexane/ethyl acetate 2:1. The first fraction consisted of 77 mg of a mixture, not further investigated. The second fraction furnished 238 mg of **13**, m.p. 238–240° after 4 crystallizations; $[\alpha]_D^{20} = +76.2°$ (0.20). – IR.: 3460, 3350, 1730, 1235, 1025. – ^{1}H-NMR.: 0.80 (*s*, $H_3C(18)$); 0.98 (*s*, $H_3C(19)$); 2.00 (*s*, AcO–C(17)); 3.00 (br., HO–C(4)+HO–C(5)) disappeared after D_2O addition; 4.15, 4.25 (*AB*-system, $J_{AB} = 11$, $H_2C(1)$); 4.48 (*s*, H–C(4)); 4.50 (*m*, H–C(17)). – MS.: 366 (M^+).

$C_{20}H_{30}O_6$ (366.46) Calc. C 65.55 H 8.25% Found C 65.33 H 8.26%

The third fraction, 98 mg of a mixture of polar compounds, was not further investigated.

17β-Acetoxy-5ξ-hydroxy-4ξ-mesyloxy-2-oxaandrostan-3-one (**12**). To 65 mg of **13** dissolved in 1 ml of pyridine, 0.1 ml of methanesulfonyl chloride was added. The mixture was stirred for 15 min at RT., then poured on ice/$NaHCO_3$ and extracted with ether as usual, to yield 71 mg of **12**, m.p. 188–189° after 3 crystallizations; $[\alpha]_D^{20} = +40.7$ (0.98). – UV.: end absorption. – IR.: 3470, 1750, 1725, 1355, 1245, 1170. – ^{1}H-NMR.: 0.80 (*s*, $H_3C(18)$); 0.95 (*s*, $H_3C(19)$); 2.00 (*s*, AcO–C(17)); 2.60 (br., HO–C(5)) disappeared after D_2O addition; 3.35 (*s*, CH_3SO_3–C(4)); 4.10, 4.25 (*AB*-system, $J_{AB} = 11$, $H_2C(1)$); 4.50 (*m*, H–C(17)); 5.42 (*s*, H–C(4)). – MS.: 384 ($M^+ - CH_3COOH$); 365 ($M^+ - CH_3SO_2$).

$C_{21}H_{32}O_8S$ (444.48) Calc. C 56.74 H 7.25% Found C 57.02 H 7.58%

Treatment of **13** *with tosyl chloride.* To 28 mg of **13** dissolved in 5 ml of pyridine, 30 mg of tosyl chloride were added. The mixture was refluxed for 3 h and, after cooling, poured on ice/$NaHCO_3$. Ether extraction yielded 31 mg of a mixture which was chromatographed on silica gel *Merck* ('reinst') with cyclohexane/ethyl acetate 2:1. The first fraction yielded 9 mg of **11** (identified by mixed m.p., TLC. and IR. spectrum). The second fraction consisted of 8 mg of a mixture of 2 components. The third fraction gave 6 mg of the starting material **13** (identified through mixed m.p., TLC. and IR. spectrum). Finally, the fourth fraction, 7 mg of a mixture of 2 components, was eluted. The second and fourth fractions were not further investigated.

REFERENCES

[1] Part X: *C. Brosa & J.-J. Bonet,* Afinidad, *36,* 223 (1979).
[2] *V. Ferrer, J. Gómez & J.-J. Bonet,* Helv. *60,* 1357 (1977).
[3] *J.A. Vallet, J. Boix, J.-J. Bonet, M.C. Briansó, C. Miravitlles & J.L. Briansó,* Helv. *61,* 1158 (1978).
[4] *C. Lehmann, K. Schaffner & O. Jeger,* Helv. *45,* 1031 (1962); *H. Wehrli, C. Lehmann, P. Keller, J.-J. Bonet, K. Schaffner & O. Jeger,* ibid. *49,* 2218 (1966).
[5] *O.R. Rodig & G. Zanati,* J. org. Chemistry *33,* 914 (1968).
[6] *Y. Mazur & M. Nussim,* J. Amer. chem. Soc. *83,* 3911 (1961).
[7] *M. Tokuda, M. Hataya, J. Imai, M. Itoh & A. Suzuki,* Tetrahedron Letters *1971,* 3133; *J.D. Coyle,* chem. Rev. *78,* 97 (1978).
[8] *G. Hüppi, Frl. G. Eggart, S. Iwasaki, H. Wehrli, K. Schaffner & O. Jeger,* Helv. *49,* 1986 (1966); *G. Hüppi,* Doctoral Thesis, E.T.H., Zürich 1967.