

ANOMALOUS SPIRO- AND AROMATIZED 6-THIAESTROGENS<sup>1</sup>.

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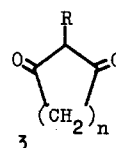
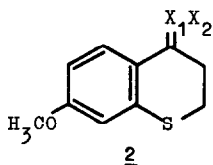
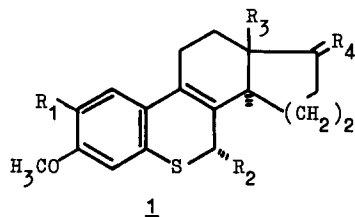
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Several of the 6-thiaestrogens 1 synthesized earlier in our laboratory<sup>4</sup> showed both chemically and physiologically remarkable properties. In order to investigate this typical behaviour more closely - especially to evaluate the substituent influence in both substrate i.e. vinyl alcohol 2a, as well as reactant i.e. diketone 3 - several variations were brought in of which the introduction of electronically different groups R in the diketone 3 led to some unexpected reaction products in the 6-thia series.

Following the scheme extensively described before<sup>5</sup> in the total synthesis of both carbocyclic as well as heterocyclic steroids, the oily vinyl alcohol 2a was converted into the crystalline isothiuroniumacetate 2b\* (m.p. 122-126°) in 90% yield.

Reaction with 2-acetylaminocyclopentane-1,3 dione 3a in 2-propanol-water 1:1<sup>6</sup> yielded diketone 4 (m.p. 176-178°). IR  $\gamma_{\max}^{\text{KBr}}$  3300 cm<sup>-1</sup> (NH) 1760, 1720, 1640 cm<sup>-1</sup> (C=O); UV  $\lambda_{\max}^{\text{EtOH}}$  317 (3,060) 278 (14,000) 247 (26,000) nm; NMR (CDCl<sub>3</sub>)  $\delta$  1,94 (CH<sub>3</sub>-C=O) 5,64 (C<sub>11</sub>-H, t). Cyclization of 4 with HCl-dioxane led to chloro-hydroxy ketal 5, obtained as a crystalline compound, which showed no C=O in the IR-spectrum, analyzed correctly for Cl and gave with water a strong acidic solution. Attempts to purify 5 by recrystallization from methanol yielded 6 (m.p. 227-229°). IR  $\gamma_{\max}^{\text{KBr}}$  3300 and 3450 cm<sup>-1</sup> (NH, OH), 1750, 1640 cm<sup>-1</sup> (C=O); UV  $\lambda_{\max}^{\text{EtOH}}$  318 (3,100) 295 (4,900) 253 (22,700) nm; NMR (C<sub>5</sub>D<sub>5</sub>N):  $\delta$  1,95 (CH<sub>3</sub>CO) 3,78 (C<sub>7</sub>-CH<sub>2</sub>).

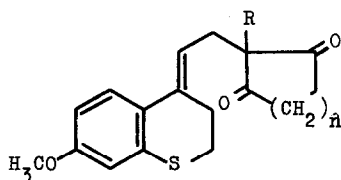
Upon heating the latter compound in dioxane-HCl, a simultaneous dehydration, loss of the aminoacetyl moiety and rearrangement took place resulting in the formation of the C-aromatized 6-thiaestrone 7 (m.p. 142,5-145°). IR  $\gamma_{\max}^{\text{KBr}}$  1690 cm<sup>-1</sup> (C=O) NMR (CDCl<sub>3</sub>)  $\delta$  centered round 2,72 and 3,10 (m, 2xCH<sub>2</sub>) 3,83 (OCH<sub>3</sub> and C<sub>7</sub>-CH<sub>2</sub>). 6.7-7.0 (2 ArH) 7.5-7.8 (3 ArH).


$$\underline{a} \quad X_1 = -CH = CH_2, X_2 = OH$$
$$\underline{b} \quad X_1X_2 = \text{CH}-\text{CH}_2-\text{S}-\text{C} \begin{array}{l} \nearrow \text{NH}_2^+ \\ \searrow \text{NH}_2^+ \\ \text{OAc}^- \end{array}$$

a R = NHAc, n=2

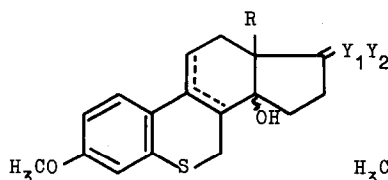
b R = NHAc, n=3

c R = Cl, n=2

$$\underline{d} \quad R = Cl, \quad n=3$$


4 R = NHAc n=2

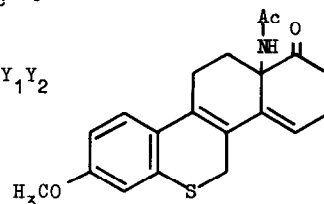
8 R = NHAc n=3



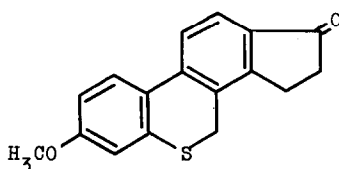
5  $\Delta 8,9$ , R = NHAc,  $Y_1$  = OH,  $Y_2$  = Cl

6  $\Delta 8,9$ , R = NHAc,  $Y_1 Y_2 = 0$

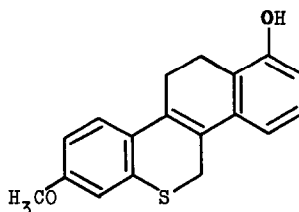
12  $\Delta_{9,11}$ ,  $R = Cl$ ,  $Y_1 Y_2 = 0$



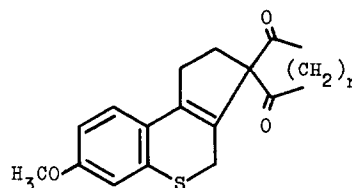
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7



10



11 n=2

13 n=3

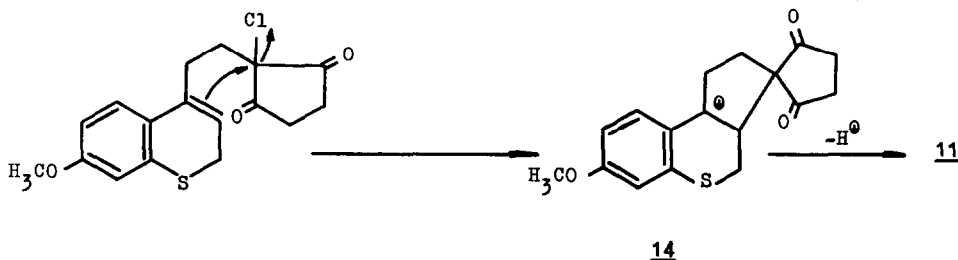
In the analogous reaction series starting with 2-acetylaminocyclohexane-1,3 dione 3b oily 8 was obtained, IR  $\gamma_{\text{max}}^{\text{CHCl}_3}$  3500  $\text{cm}^{-1}$  (NH) 1720, 1700, 1660  $\text{cm}^{-1}$  (C=O), NMR ( $\text{CDCl}_3$ )  $\delta$  1,92 ( $\text{CH}_3\text{-C=O}$ ) 5,61 ( $\text{C}_{11}\text{-H}$ , t), which upon cyclization in dioxane-HCl afforded the bisdehydro-D-homo-steroid 2 (m.p. 232-234°). IR  $\gamma_{\text{max}}^{\text{KBr}}$  3450 (NH), 1710, 1630 (C=O), UV  $\lambda_{\text{max}}^{\text{EtOH}}$  338 (10.000) 320 (11.000) 275 (27.600) 271 (26.000 sh), NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  1,80 ( $\text{CH}_3\text{-C=O}$ ) 3,50 ( $\text{C}_7\text{-CH}_2$ ) 6,18 ( $\text{C}_{15}\text{-H}$ , t).

To investigate the eventual aromatization of ring-C **9** was heated with acid for a prolonged period of time which, however, gave the ring D-aromatized phenol **10** (m.p.

145-150°); IR  $\gamma_{\text{max}}^{\text{KBr}}$  3400  $\text{cm}^{-1}$  (OH), NMR ( $\text{CDCl}_3$ )  $\delta$  3,70 ( $\text{C}_7\text{-CH}_2$ , m) 6,6-7,4 (6 ArH) as the exclusive product, the formation of which might be rationalized in terms of the lower energy content of the resulting conjugated system.

In connection with previous work on ring C-aromatization in the carbocyclic series<sup>7</sup> upon reaction of chlorodiketones with vinylalcohols further work in this direction was pursued. Although the reaction of 2b with diones 3c and 3d did not lead to addition products (formation of dimeric products, understandable when dienes are involved<sup>6</sup>) reaction was observed when 2a and 3c were heated in xylene. TLC analysis of the total reaction mixture did not reveal even a single trace of ring C-aromatic products, however, from the reaction mixture a compound was isolated, (m.p. 222-225°), which according to its spectral data possessed structure 11. IR  $\gamma_{\text{max}}^{\text{KBr}}$  1740, 1710  $\text{cm}^{-1}$  ( $\text{C=O}$ ), UV  $\lambda_{\text{max}}^{\text{EtOH}}$  270 (8.600) 236 (30.000) nm; NMR ( $\text{CDCl}_3$ )  $\delta$  1,99 (2 protons, t) 2.5-3.2 (8 protons).

The formation of the spirocompound 11 is presumably occurring via the following scheme



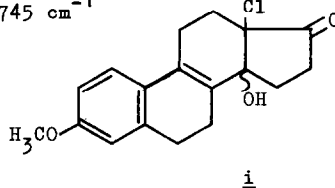
The enhanced stabilization (S.participation) of the  $\text{C}^{\ominus}$ -ion in 14 may account for the relatively greater nucleophilicity of the  $\text{C}_8\text{-C}_9$  double bond, and therefore explain the direct expulsion of the chlorine atom. Major improvement in the yield of 11 was reached when the reaction was carried out in nitromethane at 120°<sup>10</sup>, but again no formation of 7 could be observed. However, upon carrying out the addition at 90°, the formation of a second product, the chloro-hydroxy ketone 12 was noted (m.p. 111.5-121°)

(decomp.); IR  $\gamma_{\text{max}}^{\text{CHCl}_3}$  1730  $\text{cm}^{-1}$  (C=O); UV  $\lambda_{\text{max}}^{\text{EtOH}}$  245 (46.900) 270 (19.600) 310 (2.600) nm; NMR ( $\text{CDCl}_3$ )  $\delta$  3,26 ( $\text{C}_7\text{-CH}_2$ ) 5,71 ( $\text{C}_{11}\text{-H}$ , t) - no formation of 11 at this temperature - which could not be converted to 7 or 11 upon treatment with either acid or base. Finally, the chlorocyclohexanedione 3d, did not give rise to addition product with vinyl-alcohol 2a upon reaction in refluxing xylene or DMF. In refluxing nitromethane however, the homologous spirocompound 13 was formed (m.p. 220-223°). IR  $\gamma_{\text{max}}^{\text{KBr}}$  1720, 1690  $\text{cm}^{-1}$  (C=O); UV  $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$  270 (9.000) 238 (31.000) nm; NMR ( $\text{CDCl}_3$ )  $\delta$  1,59 ( $\text{C}_{16}\text{-CH}_2$ , s) 3,25 ( $\text{C}_7\text{-CH}_2$ , m).

Further conversion of these interesting spirocompounds will be described in our full paper.

#### References:

- \* Satisfactory elemental analyses and spectral data - in so far not reported directly - have been obtained for all crystalline compounds.
- 1. Part XVII in the series "Heterocyclic Steroids". For part XVI see W.N. Speckamp, J.G. Westra and H.O. Huisman, Tetrahedron, in press.
- 2. Part of the forthcoming thesis of W.M.B. Könst, University of Amsterdam.
- 3. To whom all correspondence should be addressed.
- 4. J.G. Westra, W.N. Speckamp, U.K. Pandit, H.O. Huisman, Tetrahedron Letters, 2781 (1966).
- 5. J. Weill-Raynal, Bull.Soc.Chim.Fr., 4561 (1969).
- 6. C.H. Kuo, D. Taub, N.L. Wendler, J.Org.Chem., 33, 3126 (1968).
- 7. T.B. Windholz, B. Arison, R. Brown, Tetrahedron Letters, 34, 3331 (1967).
- 8. A characteristic for the symmetrical spirodiketostructure is the large upfield shift of the S-CH<sub>2</sub> protons, due to a shielding by the two carbonyl functions, which according to model studies are perfectly located<sup>9</sup> to exert a maximum influence, each on one of the S-CH<sub>2</sub> protons.
- 9. J.W. ApSimon, P.V. Demarco, D.W. Mathieson, W.L. Craig, A. Karim, L. Saunders and W.B. Whalley, Tetrahedron, 26, 119 (1970).
- 10. The analogous experiment in the carbocyclic series afforded also the Cl-OH ketone 1, m.p. 122° (decomp.); IR  $\gamma_{\text{max}}^{\text{KBr}}$  3520  $\text{cm}^{-1}$  (OH) 1745  $\text{cm}^{-1}$  (C=O); UV  $\lambda_{\text{max}}^{\text{EtOH}}$  278 (19.400) nm.



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