Tetrahedron Letters No.30, pp. 3585-3590, 1966. Pergamon Press Ltd.
Printed in Great Britain.

14-HYDROXYDERIVATIVES OF dl-ESTRONE AND dl-D-HOMOESTRONE

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(Received 24 May 1966)

Earlier it was shown that cyclization of $\Delta^{1,3,5(10),9(11)}$-8,14-seco-estratetraene-3-ol-14,17-dione (I) and $\Delta^{1,3,5(10),9(11)}$-8,14-seco-D-homoestratetraene-3-ol-14,17a-dione (II) as well as of their methyl ethers (III) and (IV) results in formation of key compounds for synthesis of estrogenes of normal-(V), (VI) and D-homo-series(VII), (VIII)[1-5].

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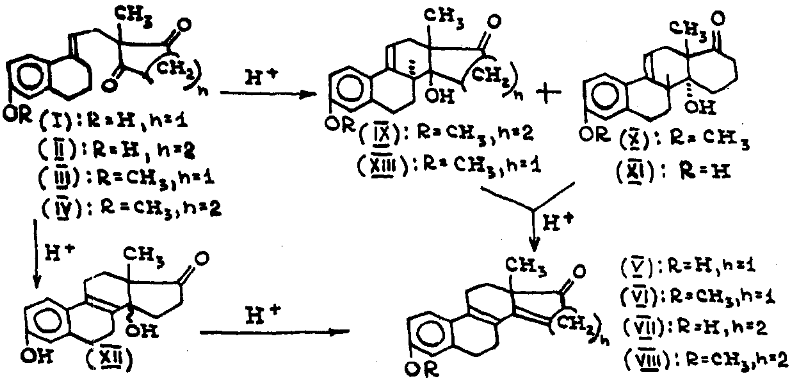
It was also found that in the course of cyclization of diketone (IV) two intermediate 14-hydroxysteroids (IX) and (X) were formed[6]. This fact confirms a suggestion on the mechanism of the reaction as aldol condensation in the presence of acids (see, e.g.[7]). The best yields / 36% of ketol (IX) and 20% of ketol (X)/ were obtained when acid resin "KU-2" was used as a cyclization agent.

Diketone (II) may be readely converted to dienone (VII) and it was possible to isolate 14-hydroxy-derivative (XI) using methyldihydroresorcinol as a cyclization agent. The cyclization of diketone (I) under similar conditions resulted in $\Delta^{1,3,5(10),8(9)}$-estratetraene-3,14-diol-17-one (XII) (λ max 275 mμ ; lg ε 4,18)[2].



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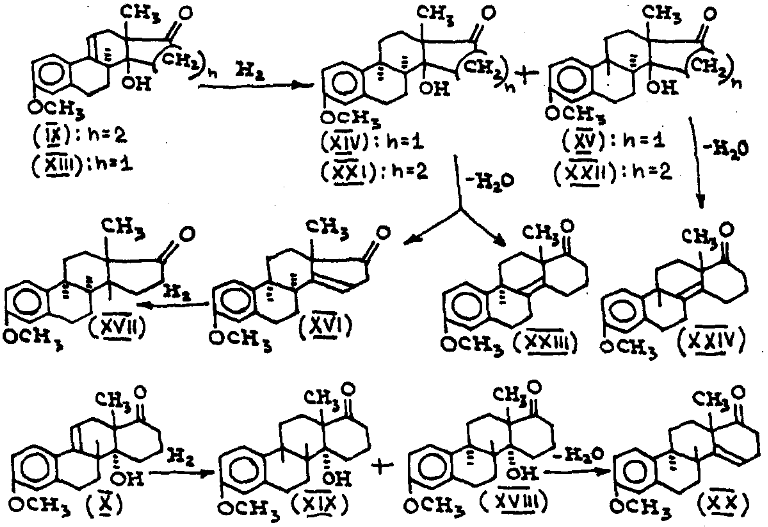
The cyclization of diketone (III) by perchloric acid at 15°C proceeded stereospecifically and gave only one isomer - 3-methoxy $\Delta^{1,3,5(10),9(11)}$-8α-estratetraene-14β-ol-17-one (XIII), m.p. 163-165° (from acetone-hexane 1:1), λ max 260 mμ (lg ε 4,3); IR-spectrum: 1610, 1733 (C=O), 3475 (-OH) cm^{-1}; mol. weight 298 (mass spectral data).



The hydrogenation of ketol (XIII) over 10% palladium on calcium carbonate yielded 79% of 3-methoxy-$\Delta^{1,3,5(10)}$-8α-estratriene-14β-ol-17-one (XIV) as a major product of the reaction, m.p. 182-183° (from acetone-hexane 1:1), λ max 278 mμ (lg ε 3,4); IR-spectrum: 1610, 1728 (C=O), 3440 (-OH) cm^{-1}; mol.weight 300 (mass spectral data).

The minor substance was 3-methoxy-$\Delta^{1,3,5(10)}$-8α,9β-estratriene-14β-ol-17-one (XV), m.p.139-140° (from acetone-

-hexane 1:1), λmax 278 mμ (lg ε 3,4); IR-spectrum: 1613, 1718 (C=0), 3475 (-OH) cm^{-1}; mol.weight 300 (mass spectral data).

Dehydration of ketol (XIV) (thionyl chloride, pyridine, -10°) produced 59% of 3-methoxy-$\Delta^{1,3,5(10),14(15)}$-8α,9α-estratetraene-17-one (XVI), m.p. 91-93° (from methanol); λmax 278 mμ (lg ε 3,4); NMR-spectrum: 1,25 ($-CH_3$), 3,82 ($-OCH_3$), 5,8 ($C=C^{-H}$) ppm.

The hydrogenation of dehydroestrone (XVI) over 10% palladium on calcium carbonate led to dl-9-iso-13-isoestrone methyl ether (XVII), m.p. 114-116°, which appeared to be identical in all respects (IR- and mass-spectra, mixed m.p.) with the sample of the substance obtained by Johnson[8] independently by a different method*.

The conversions described above unequivocally proved the 8α-configuration of hydrogen in the parent ketol (XIII). 14β-configuration of angular hydroxy group in (XIII) as well as "anti-cis" configuration of ketol (IX) and "anti-trans" configuration of ketol (X) were confirmed mass spectrometrically (details will be published elswhere).

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* We are extremely grateful to Professor W.S.Johnson (Wisconsin University, USA) who kindly carried out an identification of dl-9-iso-13-isoestrone methyl ether (IR-spectra and mixed m.p.).

The hydrogenation of ketol (X) over 10% palladium on calcium carbonate yielded 71% of 3-methoxy- $\Delta^{1,3,5(10)}$-D-homoestatriene-14α-ol-17a-one (XVIII); m.p. 187–189° (from ethylacetate); λ max 277 mμ (lg ε 3,2); IR-spectrum (CCl_4): 1607, 1707 (C=O), 3630 (-OH) cm^{-1}; mol.weight 314 (mass spectral data). Another reaction product was 3-methoxy-$\Delta^{1,3,5(10)}$-9β,8β-D-homoestratriene-14α-ol-17a-one (XIX); m.p. 154–156° (from ethylacetate); λ max 278 mμ (lg ε 3,3); IR-spectrum: 1606, 1683 (C=O), 3498 (-OH) cm^{-1} mol.weight 314 (mass spectral data).

The dehydration of ketol (XVIII) (thionyl chloride, pyridine, 3–10°) gave 3-methoxy- $\Delta^{1,3,5(10),14(15)}$-D-homoestratetraene-17a-one (XX) stable towards catalitic hydrogenation, m.p. 107–109° (from cyclohexane); λ max 278 mμ (lg ε 3,3); IR-spectrum: 1602, 1701 (C=O) cm^{-1}; mol. weight 296 (mass spectral data); NMR-spectrum: 1,3 ($-CH_3$), 3,85 ($-OCH_3$); 5,65 ($C{=}C{-}^{H}$) ppm.

The hydrogenation of ketol (IX) produced a mixture of 3-methoxy- $\Delta^{1,3,5(10)}$-8α,9β-D-homoestratriene-14β-ol-17a-one (XXII), m.p. 162–164° (from ethylacetate); λ max 277 mμ (lg ε 3,3); IR-spectrum: 1614, 1692 (C=O), 3500 (OH) cm^{-1}; mol.weight 314 (mass spectral data); and 3-methoxy- $\Delta^{1,3,5(10)}$-8α,9α-D-homoestratriene-14β-ol-17a-one (XXI), m.p. 217–219° (from methanol-ethylacetate 1:1), λ max 277 mμ (lg ε 2,4); IR-spectrum: 1609, 1688 (C=O), 3463 (-OH) cm^{-1}; mol. weight 314 (mass spectral data).

The dehydration of ketol (XXI) (thionyl chloride, pyridine, -10°) led to 3-methoxy-$\Delta^{1,3,5(10),8(14)}$-9α-D-homoestratetraene-17a-one (XXIII), m.p. 134-136° (from methanol), λ max 278 mμ (lg ε 3,3); IR-spectrum: 1610, 1705 (C=O) sm^{-1}; mol.weight 296 (mass spectral data); NMR-spectrum: 1,4 ($-CH_3$), 3,8 ($-OCH_3$) ppm; vinyl proton was absent.

Similarly ketol (XXII) was converted to 3-methoxy-$\Delta^{1,3,5(10),8(14)}$-9β-D-homoestratetraen-17a-one (XXIV), m.p. 95-97° (from methanol), λ max 278 mμ (lg ε 3,36); IR-spectrum: 1580, 1620, 1710 (C=O) cm^{-1}; mol.weight 296 (mass spectral data); NMR-spectrum: 1,52 ($-CH_3$), 3,95 ($-OCH_3$) ppm. Vinyl proton was absent.

Identification (and purity tests) of the products was carried out by means of thin layer binderless chromatography on Al_2O_3. For all products satisfactory elemental analyses were obtained.