TOTAL SYNTHESIS OF 14β-HYDROXY-8α,9α- AND 14β-HYDROXY-8α,9β-ESTRADIOLS

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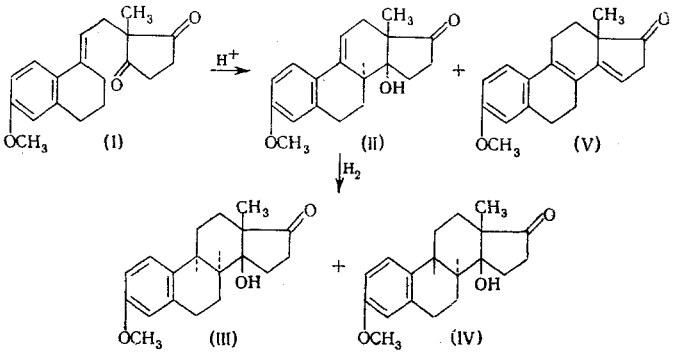
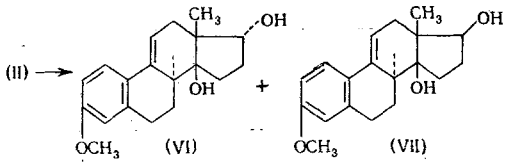
In a previous communication it was shown by us [1] that the cyclization product of 3-methoxy-$\Delta^{1,3,5(10),9(11)}$-8,14-seco-estratetraene-14,17-dione (I), and specifically the 3-methyl ether of 14β-hydroxy-$\Delta^{9(11)}$-dehydro-8α-estrone (II), can be isolated, the hydrogenation of which gave the 3-Me ethers of 14β-hydroxy-8α,9α- and 14β-hydroxy-8α,9β-estrone (III) and (IV).

In the present paper we studied the effect of the 14β-OH group on the stereochemistry of the reduction of the 17-CO group in ketone (II), and we also synthesized the 14β-hydroxy derivatives of the 17α- and 17β-estradiols, which are isomeric based on the B/C rings.



The initial problem was to develop the optimum conditions for the preparation of ketol (II). It was found that in the presence of CF_3COOH in benzene at 0°C the seco-diketone (I) gives a mixture of compound (II) and its dehydration product (V), from which ketol (II) is isolated in 22% yield by chromatographing on Al_2O_3.

To go from ketol (II) to the 14β-hydroxyestradiols it was necessary to reduce the 17-CO group. It proved that if $LiAlH_4$ is used the reduction proceeds stereospecifically to give 14β,17α-diol (VI) in 75% yield. The second isomer, corresponding to 14β,17β-diol (VII), was isolated in ~10% yield.



The reduction of ketol (II) using $NaBH_4$ is not as stereospecific, but it goes with the predominant formation of the 14β,17β-diol (VII), the yield of which is 48%; the isomeric 14β,17α-diol (VI) was isolated in 38% yield. The configuration of the OH groups in the diols was determined on the basis of comparing the IR, NMR, and mass spectral data. Thus, frequencies are observed in the IR spectra of the crystals of diols (VII) and (VI) that are characteristic for two OH groups, at 3440 and 3300 cm^{-1} for diol (VII), and at 3510 and 3400 cm^{-1} for diol (VI). In contrast to diol (VI), the presence of an intramolecular hydrogen

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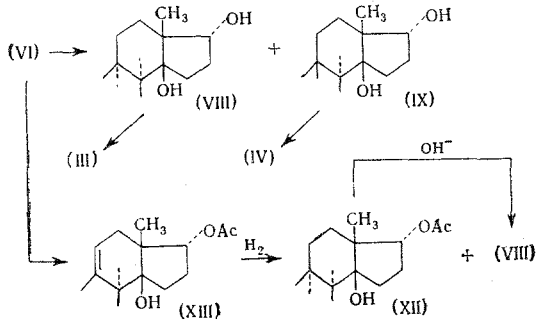
bond (IMHB) (frequencies of a free OH group at 3526 and 3616 cm^{-1}) was detected in the IR spectrum of diol (VII) in CCl_4, which indicates a cis-arrangement of the 14- and 17-OH groups [2]. The fragments $M-H_2O$ (282) and $M-2H_2O$ (264) are observed in the mass spectra of both diols. The ratio of the M^+/M^+-H_2O intensities is 3.4 for (VII), and 1.64 for diol (VI). On the basis of the data given in [3] regarding the predominant dehydration of axial carbinols under electron impact, diol (VII) can be assigned the 17β-axial, and diol (VI) the 17α-equatorial position of the OH group. A quadruplet with a center at 3.67 ppm and a halfwidth of 7.5 Hz is observed in the NMR spectrum of diol (VII), which also indicates an equatorial position of the proton at C-17. The NMR spectrum of diol (VI) has a multiplet in the 4.12 ppm region with a halfwidth of 10.2 Hz, which, together with the absence of a hydrogen bond when based on the IR spectral data, confirms the axial position of the proton at C-17.

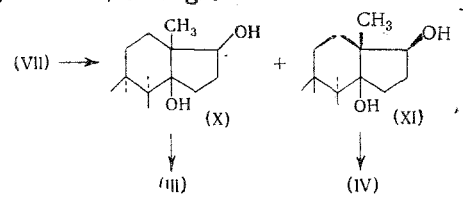
Next we studied the catalytic hydrogenation of the $\Delta^{9(11)}$ double bond in diols (VI) and (VII). It proved that the hydrogenation of diol (VI) proceeds stereospecifically to give the 3-Me ether of 14β-hydroxy-8α, 9α-estra-17α-diol (VIII) in 78% yield. The structure of the latter was proved by oxidation to the previously obtained ketol (III):



The presence of the epimeric 8α,9β-diol (IX) was proved in the following manner: the reaction mixture from the hydrogenation of diol (VI) was oxidized with CrO_3 in pyridine and the obtained mixture of ketols (III) and (IV) was separated by GLC. Based on the relative areas of the peaks, the amount of the 8α,9α-ketol (III) was 80%, and that of the 8α,9β-ketol (IV) was 20%.

In a similar manner the hydrogenation of 14β,17β-diol (VII) gave the corresponding 8α,9α-diol (X) in 90% yield. Employing GLC, the crude mixture was found to contain ~ 10% of the epimeric 8α,9β-diol (XI). The hydrogenation of the (VI) 17α-acetate (XIII) is exclusively stereospecific; here only the (VIII) acetate (XII) is formed, contaminated with a small amount of (VIII) due to acetolysis. The structure of the 17α-acetate (XII) was proved by saponification to diol (VIII).

Together with hydrogenation, we studied the reduction of the 9(11) double bond with sodium in liquid NH_3. In contrast to catalytic hydrogenation, the reduction of diol (VI) leads predominantly to compound (IX), with a trans-(8α,9β) coupling of the B/C rings.



Employing GLC (see above), we detected ~ 10% of the epimeric 8α,9α-diol (VIII) in the reaction mixture. A similar reduction of diol (VII) gave diol (XI) in quantitative yield.

As a result, employing various methods to reduce the 9(11) double bond in diols (VI) and (VII), it is possible to obtain either the 8α,9α- or 8α,9β-derivatives of the 14β-hydroxyestradiols in high yields. It is interesting to mention that for the 14β,17β-estradiols (X) and (XI), in contrast to the corresponding derivatives of the D-homo series [2], the formation of the IMHB depends on the configuration of the hydrogen at C-9. The formation of an IMHB (frequencies of a free OH group at 3537 and 3618 cm^{-1}) is observed in diol (X), which has an 8α,9α-configuration. The position of the absorption bands of the stretching vibrations of the OH groups in diol (X) makes it possible to conclude that the IMHB (ν_{OH} 3537 cm^{-1}) is formed via the reaction of the hydrogen of the 17β-hydroxyl group (secondary OH group) with the oxygen of the 14β-OH group (3618 cm^{-1}) [4]. The possibility of forming the IMHB in diol (X) is also clearly seen when the molecular models are examined, where a convergence of the OH groups is observed (distance ~ 2.4 Å). In diol (XI), with an 8α,9β-configuration, the IMHB is absent, despite the cis-arrangement of the OH groups. Actually, from the molecular models it can be seen that the distance between them is ~ 4.4 Å.

EXPERIMENTAL METHOD

The TLC was run on plates covered with a bound layer of SiO_2. The melting points were determined on a Kofler block. The UV spectra (in alcohol) were taken on a Specord UV-VIS instrument. The IR spectra were taken on a UR-10 spectrophotometer as KBr pellets and in CCl_4.

The NMR spectra were taken on a JNM-4H100 instrument in $CDCl_3$ and in benzene; the mass spectra were recorded on an MX-1303 instrument, with direct insertion of the sample into the source. The GLC analysis was run on a Pye-Argon chromatograph, equipped with a 120 × 0.4 cm glass column that was packed with 5% XE-60° deposited on Chromatone N-AW-DMCS, 75-90 mesh; the temperature was 220°, and the argon flow rate was 50 ml/min.

Cyclization of 3-Methoxy-$\Delta^{1,3,5(10),9(11)}$-8,14-seco-estratetraene-14,17-dione (I). To a solution of 11 g of seco-diketone (I) in 110 ml of C_6H_6, cooled to 0-5°, was added 3.3 ml of 99.2% CF_3COOH solution. The mixture was stirred at 0-5° for 80 min, and then treated with ice water until neutral. The solution was evaporated to 1/4 volume and the residue was chromatographed on an Al_2O_3 column. From the benzene fraction we obtained 8.3 g of 3-methoxy-$\Delta^{1,3,5(10),8(9),14(15)}$-estrapentaene-17-one (V), mp 108-109° (from ether) [5]. From the ether fraction we isolated 2.4 g (22%) of ketol (II), mp 163-165° (from ether) [6].

Reduction of Ketol (II). a) A mixture of 5 g of ketol (II), 3.5 g of $LiAlH_4$, and 400 ml of absolute THF was refluxed for 75 min. After the usual workup and recrystallization of the residue from methanol we obtained 3.5 g of 3-methoxy-$\Delta^{9(11)}$-dehydroestra-14β,17α-diol (VI), mp 142-143°. The mother liquor from the separation of (VI) was chromatographed on a plate covered with a loose layer of SiO_2 (development with a 3:1 benzene—ether mixture). From the lower zone we isolated an additional 0.29 g of diol (VI), mp 142-143°. The total yield was 3.79 g (75%). Ultraviolet spectrum: λ_{max} 260 nm ($\log\varepsilon$ 4.17). Infrared spectrum (ν, cm^{-1}): 3510, 3400 (OH groups), 1650 ($\diagdown C = C \diagup$), 1610, 1570, 1500 (aromatic); (CCl_4, C $1.4 \cdot 10^{-3}$ M) 3626. Mass spectrum, m/e: 300 (M^+), 282 (M^+-H_2O), 264 (M^+-2H_2O), 249 (M^+-CH_3), 186, 171, 159. NMR spectrum (δ, ppm): 1.03 ($-CH_3$), 3.79 (OCH_3), 4.12 m ($\Delta W_{1/2}$ 10.2 Hz, 17β-proton), 6.13 m ($\diagdown C = CH$). From the upper zone we isolated 0.48 g (9.5%) of diol (VII), mp 153-154° (from methanol). After drying in vacuo over P_2O_5 the analytical sample had mp 173-175°. Ultraviolet spectrum, λ_{max} 262 nm, ($\log\varepsilon$ 4.38). Infrared spectrum (ν, cm^{-1}): 3440, 3300 (OH groups), 1650 ($\diagdown C = C \diagup$), 1610, 1573, 1500 (aromatic); (CCl_4, C $5.92 \cdot 10^{-4}$) 2616 (free OH) and 3526 (bound OH)). Mass spectrum, m/e: 300 (M^+), 282 (M^+-H_2O), 264 (M^+-2H_2O), 249, 186, 171, 161. NMR spectrum (δ, ppm); 1.12 (18-CH_3), 3.79 (OCH_3), 4.12 m ($\Delta W_{1/2}$ 7.5 Hz, 17α-H), 5.93 t (C = CH). Diol (VI) 17α-acetate (XIII), mp 150-151°C (from methanol). Ultraviolet spectrum, λ_{max} 260 nm ($\log\varepsilon$ 4.21). NMR spectrum (δ, ppm): 1.07 (18-CH_2), 2.03 (CH_3CO), 3.80 (OCH_3), 5.13 m (17β-H), 6.08 ($\diagdown C = C \diagup$).

The 17β-acetate of diol (VII), mp 61-70°, is unstable and decomposes during recrystallization and chromatographing.

b) With stirring, a mixture of 5 g of ketol (II), 200 ml of absolute THF, and 7 g $NaBH_4$ was heated up to the boil, 17.5 ml of 5% NaOH solution was added, and the stirring under reflux was continued for 20 h. After the usual workup, extraction with ether, and removal of the solvent, the residue was chromatographed preparatively on SiO_2 plates (development with a 3:1 benzene—ether mixture). From the upper zone we isolated 1.9 g (38%) of diol (VII), mp 153-154°. From the lower zone we isolated 2.4 g (48%) of diol (VI), mp 141-143°.

Hydrogenation of Diol (IV). A solution of 300 mg of diol (VI) in 25 ml of absolute THF was hydrogenated in the presence of 10% $Pd/CaCO_3$ until the H_2 absorption ceased (1 mole). After the usual workup and recrystallization from ether we obtained 155 mg of diol (VIII), mp 141-144°. The analytical sample had up 142-144° (from methanol). After distilling off the solvent the mother liquor, which, based on the GLC data, contained two isomers [(VIII) and (IX)], was preparatively chromatographed on a plate covered with a loose layer of SiO_2; a double development was run using a 3:1 benzene—ether mixture. From the lower zone we isolated an additional 80 mg of (VIII), mp 141-144° (total yield 78%). Ultraviolet spectrum, λ_{max} 280, 287 nm ($\log\varepsilon$ 3.24; 3.22). Infrared spectrum (ν, cm^{-1}): 3400 and 3530 (OH groups), 1610, 1578, 1500 (aromatic); (CCl_4, C $3.37 \cdot 10^{-4}$), 3637, 3628 (free OH group). Mass spectrum, m/e: 302 (M^+), 284

(M^+-H_2O), 266 (M^+-2H_2O), 251, 173, 161. NMR spectrum (δ, ppm): 1.06 (18-CH_3), 3.74 (OCH_3), 4.26 m ($\Delta W_{1/2}$ 14 Hz, 17β-H). From the upper zone we isolated 54 mg (18%) of diol (IX) with mp 145-147°.

Oxidation of Diol (VIII). A solution of 40 mg of diol (VIII) in 0.4 ml of absolute pyridine was added to a solution of 43 mg of CrO_3 in 0.6 ml of pyridine, the mixture was allowed to stand at 20° for 16 h, and after the usual workup we obtained 38 mg of ketol (III) with mp 175-176°, which in its melting point and retention time (GLC) was identical with an authentic specimen [6].

A similar oxidation of the reaction mixture from the hydrogenation of diol (VI), with subsequent GLC analysis, gave two peaks, which were identified as being ketol (III) (80%) and ketol (IV) (20%).

Hydrogenation of (VI) 17-Acetate (XIII). A solution of 500 mg of (XIII) in 30 ml of absolute THF was hydrogenated in the presence of 10% $Pd/CaCO_3$ until the H_2 absorption ceased (1 mole). After the usual workup we obtained 359 mg of 17-acetate (XII), mp 195-200°. We isolated an additional 70 mg of (XII) from the upper zone by the preparative separation of the mother liquors on a plate covered with a loose layer of SiO_2 (development with a 3:1 benzene—ether mixture). The analytical sample had mp 198-200° (from methanol), and the yield was 86%. Ultraviolet spectrum, λ_{max} 278 nm (log ε 3.44). Infrared spectrum, (ν, cm^{-1}): 3550 (OH), 1730 (CH_3COO), 1610, 1510, 1580, 1500 (aromatic). Mass spectrum, m/e: 344 (M^+), 326 (M^+-H_2O), 266, 251, 174, 158. NMR spectrum (δ, ppm): 1.04 (18-CH_3), 2.02 (CH_3CO), 3.75 (OCH_3), 5.2 m (17β-H). From the upper zone we isolated 50 mg (8%) of diol (VIII) with mp 142-144° (does not depress the mixed melting point with an authentic specimen).

Saponification of Acetate (XII). A solution of 76 mg of acetate (XII) in 2 ml of 10% alcoholic KOH solution was let stand for 1 h, and after the usual workup we obtained 58 mg of diol (VIII) with mp 142-144°, which was identical with an authentic specimen.

Reduction of Diol (VI) with Sodium in Liquid NH_3. To 75 ml of liquid NH_3, which had been distilled over Na, at −50 to −60° was added a solution of 50 mg of diol (VI) in 35 ml of absolute ether and 20 ml of absolute THF. To the obtained solution was added 2.55 g of Na (in small pieces), the mixture was stirred at the same temperature for 30 min, and 0.8 g of NH_4Cl was added cautiously. After evaporation of the NH_3,the residue was treated with water (at −5 to 0°) and then extracted with ether. The ether extract was neutralized with solid CO_2, washed with water, and dried over $MgSO_4$. After distilling off the solvent we obtained 596 mg (85%) of diol (IX) with mp 143-148°. The analytical sample had mp 145-147° (from methanol). Ultraviolet spectrum: λ_{max} 278, 287 nm log ε 3.62; 3.55). Infrared spectrum (ν, cm^{-1}); 3610, 3563, 3500 (OH), 1610, 1580, 1505 (aromatic); (CCl_4, C $1.3 \cdot 10^{-3}$) 3631 (OH). Mass Spectrum, m/e: 302 (M^+), 284 (M^+-H_2O), 266 (M^+-2H_2O), 251, 187, 159. NMR spectrum (δ, ppm): 0.96 (18-CH_3), 3.77 (OCH_3), 4.01 m (17β-H).

The oxidation of diol (IX) with CrO_3 in pyridine gave an 84% yield of ketone (IV) with mp 138-140° (from ethanol), which in its melting point and retention time (GLC) was identical with the previously obtained sample [6].

Hydrogenation of Diol (VII). A solution of 1 g of diol (VII) in 50 ml of absolute THF was hydrogenated in the presence of 10% $Pd/CaCO_3$ until the H_2 absorption ceased (1 mole). After the usual workup we obtained 900 mg (90%) of diol (X) with mp 140-141° (from ether). Ultraviolet spectrum: λ_{max} 280, 285 nm (log ε 3.33; 3.43). Infrared spectrum (ν, cm^{-1}); 3520, 3410 (OH), 1610, 1585, 1503 (aromatic); (CCl_4, C $1.24 \cdot 10^{-4}$) 3618 (free OH) and 3537 (bound OH). Mass spectrum, m/e: 302 (M^+), 284 (M^+-H_2O), 266 (M^+-2H_2O), 252, 173, 160. NMR spectrum (δ, ppm): 1.02 (18-CH_3), 3.62 (OCH_3). The oxidation of the mixture from the hydrogenation of diol (VII), with subsequent GLC analysis, gave two peaks, which were identified as being ketol (III) (90%) and ketol (IV) (10%).

The oxidation of diol (X) with CrO_3 in pyridine gave ketol (III) in 96% yield, mp 175-176°, which was identical with an authentic sample.

Reduction of Diol (VII). The reduction of 0.2 g of diol (VII) was run under the conditions described for the reduction of diol (VI) (0.3 g of Na, 30 ml of liquid NH_3, 20 ml of absolute ether, 10 ml of absolute THF, and 0.21 g of NH_4Cl). After the usual workup we isolated 0.19 g (95%) of diol (XI) with mp 142-143° (from ether). Ultraviolet spectrum: λ_{max} 278 nm (log ε 3.60). Infrared spectrum (ν, cm^{-1}): 3490, 3465 (OH), 1610, 1587, 1500 (aromatic); (CCl_4, C $1.36 \cdot 10^{-3}$) 3631 and 3613 (OH). Mass spectrum, m/e: 302 (M^+), 284 (M^+-H_2O), 266 (M^+-2H_2O), 172, 161. NMR spectrum (δ, ppm): 0.96 (18-CH_3), 3.78 (OCH_3), 4.28 m (17α-H). The oxidation of the mixture from the reduction of diol (VII), with subsequent GLC analysis, gave only one peak, which corresponded to ketol (IV).

CONCLUSIONS

1. The reduction of the 17-keto group in ketol (II) with $LiAlH_4$ gives predominantly the 17α-diol (VI), whereas the similar reduction with $NaBH_4$ leads to a mixture of the 17β- and 17α-diols (VII) and (VI) in a 5:4 ratio.

2. The catalytic hydrogenation of diols (VI) and (VII) proceeds stereospecifically to give the corresponding 3-methyl ethers of the 8α,9α-estra-3,14β,17-triols (VIII) and (X).

3. The reduction of the $\Delta^{9(11)}$ double bond in diols (VI) and (VII) with sodium in liquid NH_3 proceeds in a strictly stereospecific manner to give the corresponding 3-methyl ethers of the 8α,9β-estra-3,14β,17-triols (IX) and (XI).

4. The formation of an intramolecular hydrogen bond in the series of 14β,17β-cis-diols (X) and (XI) depends on the configuration of the hydrogen at C-9.

LITERATURE CITED

1. A. V. Zakharychev, I. Gora, É. Abu-Mustafa, S. N. Ananchenko, and I. V. Torgov, Izv. Akad. Nauk SSSR, Ser. Khim., 1351 (1970).
2. A. V. Zakharychev, S. K. Kasymov, S. N. Anachenko, and I. V. Torgov, Izv. Akad. Nauk SSSR, Ser. Khim., 96 (1973).
3. N. S. Wulfson, V. J. Zaretskii, V. L. Sadovskaya, A. V. Zakharychev, S. N. Anachenko, and I. V. Torgov, Tetrahedron, 23, 3667 (1967).
4. A. Weissberger (editor), Establishing the Structure of Organic Compounds by Physical and Chemical Methods [Russian translation], Vol. 1, "Khimiya" (1967), p. 172.
5. S. N. Ananchenko and I. V. Torgov, Tetrahedron Lett., 23, 1553 (1963).
6. A. V. Zakharychev, J. Hora, S. N. Ananchenko, and I. V. Torgov, Tetrahedron Lett., 30, 3585 (1966).