

SYNTHESIS AND CONFORMATIONAL STABILITIES OF 11-OXO-9 α - AND 9 β -ESTRADIOL 3-BENZYL ETHER

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Abstract—11-Oxo-estradiol was prepared from estradiol in five steps with an overall yield of 50%. From an equilibration study, the 9 β epimer was found to be favored over the 9 α by 1.47 kcal/mole. Force field calculations were carried out for these epimers out and compared with the experimental data.

Oxygenated estradiol derivatives are key intermediates in the synthesis of novel 11 β -methyl-19-norsteroids, such as 11 β -methyl-17 α -acetoxy-19-norprogesterone which is useful in the synchronization of estrus in cattle.^{1,2} These substances have been synthesized by a process which begins with the reductive aromatization of 11 β -hydroxy-17-ethylene dioxandrost-1,4-dien-3-one.³ Requirements for the large scale synthesis of 11 β -methyl-19-norsteroids prompted a new investigation into the synthesis of 11-oxygenated estradiol derivatives from estrone.

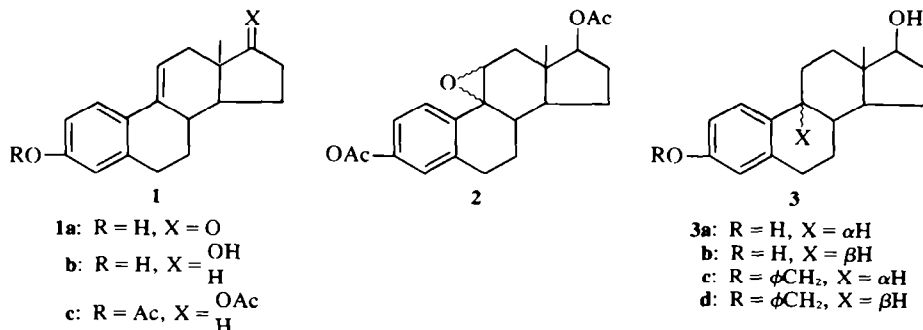
3-Hydroxy-1,3,5(10),9(11)-estratetraen-17-one (1a), which is readily available from estrone,⁴ was reduced with sodium borohydride, and the resulting product 1b was acetylated to give 1c. Epoxidation of 1c gave an 80% yield of 2.⁵ When the epoxide 2 was heated with 5% KOH in methanol, a mixture of epimeric ketones 3a and 3b was obtained in high yield. On recrystallization from methanol, the major component was isolated as prisms, m.p. 255–257°. This compound was assigned the structure of 11-oxo-9 β -estradiol (3b) on the basis of IR and NMR data. The IR spectrum (KBr) showed carbonyl absorption at 1695 cm⁻¹ and the NMR spectrum (100 MHz, CDCl₃) showed that the proton at C-9, δ 3.6, was a doublet with $J_{8,9} = 5.5$ Hz. Since the configuration of the C-8 hydrogen is β (axial), the coupling constant of 5.5 Hz indicated that C-9 hydrogen cannot be α (axial) and, therefore, must be β .

11-Oxo-9 β -estradiol 3-benzyl ether (3d) was obtained from 3b as white needles, m.p. 159–160°, NMR (100 Hz, CHCl₃), H-9, δ 3.64 ($J_{8,9} = 5.5$ Hz). When 3b was refluxed with 5% potassium hydroxide in methanol solution, the product of the reaction contained as its minor component 11-oxo-9 α -estradiol 3-benzyl ether (3c), the thermodynamically less stable epimer. When the 9 β epimer 3d was refluxed with sodium hydride in benzene and the reaction was quenched with acetic acid, 3c was obtained as the major component. Thus 3c is the product of a kinetically controlled reaction. It was obtained from alcohol as white prisms, NMR (100 Hz, CHCl₃), H-9 δ 3.47 ($J_8 = 9.5$ Hz†).

The equilibration mixture of 11-oxo-9 α - and 9 β -estradiol 3-benzyl ether was analyzed by NMR. The 9 β epimer was favored (ΔG 1.47 kcal/mole).

The relative instability of 11-oxo-9 α -estradiol is of interest. These compounds were therefore studied by the molecular mechanics method.⁷ A model shows that when the hydrogen at C-9 is in the normal α -position and ring B has the normal half-chair conformation of a cyclohexene and ring C has a regular chair conformation, there is substantial interference between the carbonyl oxygen at C-11 and the hydrogen attached to C-1. Models show that if ring B goes into a boat conformation in an effort to relieve this interaction, crowding increases. This conformation is not at an energy minimum, but rather spontaneously will revert to the original conformation in the calculations. On the other hand, it is possible to relieve the unfavorable interaction by putting ring C into a boat form, with C-11 the prow of the boat. While this change does alleviate the difficulty between the carbonyl oxygen

†The value 9.5 Hz was also obtained for the analogous coupling constant in the previously known 17,17-ethylenedioxy-11-oxo-estradiol 3-methyl ether.⁶



and hydrogen at C-1, the energy of the boat form costs more than is gained, and this structure has a calculated energy 0.48 kcal/mole above that of the complete chair form.

If C-9 is epimerized to the 9β epimer, the interaction between the carbonyl oxygen and hydrogen at C-1 is completely relieved. The best conformation here has the C-9 hydrogen axial, ring B in a half-chair form, and ring C in a chair form. This conformation has an energy which is 0.48 kcal/mole below that of the best of the 9α forms, in a medium of dielectric constant 1. A second conformation for the 9β isomer bends the carbonyl oxygen down, keeps ring B in a half-chair form, but puts ring C into a twist form. This conformation, as might be anticipated, has quite a high energy, 5.2 kcal/mole above the better conformation.

These seem to be the only reasonable and stable conformations for this molecule. Computer drawings of the preferred conformation for each isomer are shown in the figure. Hence the calculations indicate that the 9β form will be more stable than the 9α by 0.48 kcal/mole in a medium of dielectric constant 1. As the dielectric constant increases, the 9α is stabilized more than the 9β . In the limit at infinite dielectric constant, the 9α form becomes more stable than the β by 0.12 kcal/mole.

The available experimental measurements were made in methanol solution, which corresponds to an effective dielectric constant at some intermediate point. The calculations would therefore indicate that the 9α and 9β isomers should be very similar in stability, with the 9α perhaps slightly less stable. While the qualitative prediction is born out, the difference in stability found experimentally is substantially larger than the calculated difference. It is not clear why this is the case. This may result from an inadequate treatment of the electrostatics of the situation, or perhaps from the van der Waals characteristics of the oxygen atom, for which little critical

test data is available. This is an important example for molecular mechanics, because it is one of the few cases so far found where the calculated results are not adequate and no simple "fix" is apparent. On the positive side, we believe that the structures calculated are quite accurate, and would probably be as good as could be determined by X-ray crystallography.

EXPERIMENTAL

M.ps were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60 or XL-100 high resolution spectrometer. IR spectra were recorded with a Beckman IR-5 spectrophotometer.

Epoxy - $9\xi,11\xi$ - *estra* - 1,3,5(10) - *triene* - 3,17 β - *diol* 3,17 - *diacetate* (2). *m*-Chloroperbenzoic acid (0.38 g, 85% pure, 1.8 mmol) in CHCl_3 (3 ml) was added dropwise with stirring to a soln of $\Delta^{9,11}$ -estradiol* (0.55 g, 1.55 mmol) in CHCl_3 (7 ml) at 0°. The stirring was continued for 2 hr at 0°. Sat NaHCO_3 aq was added to the mixture and the organic layer was separated and washed with water until neutral. The CHCl_3 soln was dried and evaporated to dryness. The residue was recrystallized from MeOH, and gave epoxy - $9\xi,11\xi$ - *estra* - 1,3,5(10) - *triene* - 3,17 β - *diol* 3,17 - *diacetate* (0.45 g, 80% yield); m.p. 129–130°, IR (CHCl_3), $\nu_{\text{C=O}}$ 1730 cm^{-1} , 1750 cm^{-1} (broad); NMR δ 3.0 (m, 2 protons), 84.08 (m, 1 proton), 84.7 (m, 1 proton). (Found: C, 71.41; H, 7.21. Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_5$: C, 71.33; H, 7.24%).

11 - *Oxo* - 9β - *estradiol* (3b). Compound 2 (0.45 g, 1.2 mmol) was dissolved in MeOH (45 ml) and then mixed with 5% KOH in MeOH (45 ml). The soln was refluxed for 30 min and cooled. The solvent was evaporated and the organic material was taken up in CHCl_3 . The organic layer was washed until neutral and the residue after removal of the solvent was recrystallized from MeOH and 3b was obtained as prisms: (300 mg, 66%), m.p. 255–257°, ir (KBr), $\nu_{\text{C=O}}$ 1695 cm^{-1} . (Found: C, 75.47; H, 7.84. Calc. for $\text{C}_{18}\text{H}_{22}\text{O}_3$: C, 75.49; H, 7.74%).

11 - *oxo* - 9β - *estradiol* 3 - *benzyl ether* (3d). A mixture of 3b (5 g, 174. mmol), benzyl chloride (2.4 g, 19 mmol), K_2CO_3 (4.8 g, 35 mmol) in EtOH was refluxed for 24 hr. EtOH was removed, and the organic material was taken up in CHCl_3 . The organic layer was washed with water until neutral. It was dried, and the residue obtained after removal of the solvent was recrystallized from MeOH and 3d was obtained as needles, m.p. 159–160° (5.2 g, 90%), NMR δ 3.64 (d, $J = 5.5$ Hz proton at C-9), 85.3 (S, 2 protons). (Found: C, 79.74; H, 7.54. Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_3$: C, 79.75; H, 7.50%).

11 - *Oxo* - 9α - *estradiol* 3 - *benzyl ether* (3c). Compound 3d (4 g, 10.6 mmol) was dissolved in benzene (200 ml) and NaH (1 g, 57% oil suspension, 24 mmol) was added. The mixture was refluxed for 5 hr, then AcOH (10 ml) was added dropwise to the mixture. Water was added and the organic layer was washed with water until neutral and dried over MgSO_4 . The solvent was removed. Residue was recrystallized from EtOH, and 3c was obtained: (2.4 g, 60% yield), m.p. 188–190°, NMR δ 3.47 (d, $J = 9.5$ Hz proton at C-9), IR (CHCl_3), $\nu_{\text{C=O}}$ 1720 cm^{-1} . (Found: C, 79.42; H, 7.82. Calc. for $\text{C}_{22}\text{H}_{28}\text{O}_3$: C, 79.75; H, 7.50%).

11 - *Oxo* - *estradiol* (3a). 11 - *Oxo* - *estradiol* 3 - *benzyl ether* (0.15 g) in EtOH was hydrogenated over 5% Pd/C at atmospheric pressure. The solvent was removed by distillation and the residue was recrystallized from benzene to yield 3a (90 mg, 80% yield); m.p. 219–223° (dec). (Found: C, 75.32; H, 7.56. Calc. for $\text{C}_{18}\text{H}_{22}\text{O}_3$: C, 75.49; H, 7.74%).

Equilibration of 11 - *oxo* - *estradiol* 3 - *benzyl ether*. 11 - *Oxo* - 9α - and 9β - *estradiol* 3 - *benzyl ether* were refluxed separately in 5% KOH–MeOH solns for 2 hr. The mixtures were quenched with water and extracted with chloroform. The equilibrated mixtures were analyzed by NMR. Studies of the Me proton signal region both with and without added Eu(FOD), shift reagent indicated the presence of 10% of 9α isomer starting either from the pure 9α or 9β epimer. This corresponds to ΔG of 1.47 kcal/mole, in favor of the 9β epimer.

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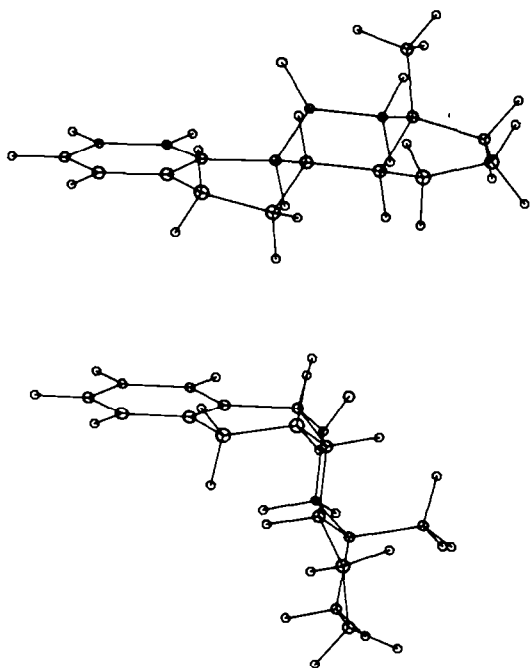


Fig. 1. 9α - (1,3,5(10) - Estratriene - 11 - one (top), and 9β - 1,3,5(10) - Estratriene - 11 - one (O-up), as calculated by molecular mechanics.

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REFERENCES

- ¹J. S. Baran, H. D. Lennon, S. E. Mares and E. F. Nutting, *Experientia* **26**, 762 (1970).
- ²D. F. Wishart and I. M. Young, *Verterinary Record* **95**, 503 (1974).
- ³J. S. Baran, *J. Med. Chem.* **10**, 1188 (1967).
- ⁴W. H. Lunn and E. Farkas, *Tetrahedron* **24**, 6773 (1968).
- ⁵K. Tsuda, S. Nozoe and Y. Orada, *Chem. Pharm. Bull.* **11**, (8), 1022 (1963).
- ⁶J. S. Baran, *J. Med. Chem.* **10**, 1188 (1967).
- ⁷A 1973 force field was used. See D. H. Wertz and N. L. Allinger, *Tetrahedron* **30**, 1579 (1974); N. L. Allinger, J. T. Sprague and T. Liljefors, *J. Am. Chem. Soc.* **96**, 5100 (1974); N. L. Allinger, M. T. Tribble and M. A. Miller, *Tetrahedron* **28**, 1173 (1972).