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PHOTOEXCITED NITROBENZENE FOR BENZYLIC HYDROXYLATION: THE SYNTHESIS OF 17β-ACETOXY-9α-HYDROXY-3-METHOXY-ESTRA-1,3,5(10)-TRIENE

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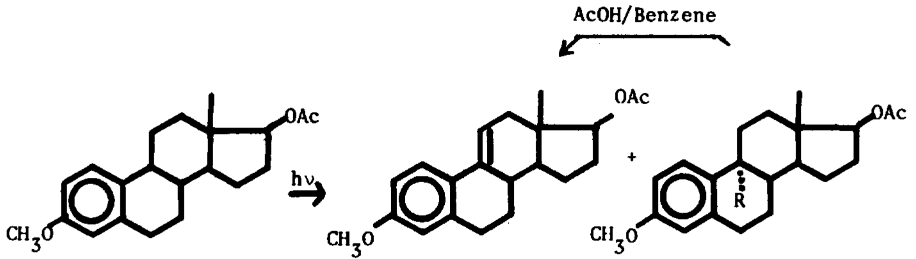
Abstract: A novel method for benzylic hydroxylation is introduced based on the use of photoexcited nitrobenzene. Applying this method 17β-acetoxy-3-methoxy-estra-1,3,5(10)-triene (I) is efficiently converted to 17β-acetoxy-9α-hydroxy-3-methoxy-estra-1,3,5(10)-triene (IIIa).

Benzylic oxidation of estrane derivatives has been attempted by various methods, including the use of dehydrogenating agents like DDQ[1] or Pd/C[2], of oxidizing agents like CrO_3[3] or RuO_4[4] and of molecular oxygen in the presence of $(Ph_3P)_3RhCl$[5]. Yet, most of these processes led to complex reaction mixtures the 9-hydroxy derivative being obtained in small amounts only, if at all.

We found that irradiation of 17β-acetoxy-3-methoxy-estra-1,3,5(10)-triene (I) in the presence of nitrobenzene yields 17β-acetoxy-9-hydroxy-3-methoxy-estra-1,3,5(10)-triene (III) in high chemical yield.

Photolysis of 2.64 g steroid I and 1.96 g nitrobenzene in 40 ml acetonitrile with a medium pressure mercury lamp through Pyrex filter for 2 days at 15°C gave, after evaporation of the solvent in vacuo and chromatography of the oily residue through silica gel, 528 mg of 17β-acetoxy-3-methoxy-estra-3,5(10),9(11)-tetraene (II), mp 116-118°C, and 1.053 g of 9-hydroxy-estra-1,3,5(10)-trienes, IIIa and IIIb, in a 4:1 ratio. Crystallization of the alcohol fraction from methylene chloride-petrol ether afforded pure IIIa. Heating either pure alcohol IIIa or a 1:1 mixture of alcohols IIIa and IIIb with 10% acetic acid in benzene under reflux afforded quantitatively estratetraene II, indicating that IIIa and IIIb are stereoisomers.

Alcohol IIIa exhibits: mp 158-162°C; uv max (ethanol) 284 (ε 1395) and 276 nm (ε 1415); ir (KBr) ν 3520, 2930, 1720, 1610, 1580, 1250 and 1025 cm^{-1}; nmr ($CDCl_3$) δ 0.82 (s, 3, $C^{18}\underline{H}_3$). 2.03 (s, 3, $OCOC\underline{H}_3$), 3.78 (s, 3, $OC\underline{H}_3$), 4.78 (t, 1, $C\underline{H}OAc$). 6.54-6.9 (m, 2, $Ar\underline{H}$) and 7.46 ppm (d, J=9Hz, 1, $Ar\underline{H}$). Mass spectrum molecular ion m/e 344.2004.



I $C_6H_5NO_2$ II

R = 9αOH, IIIa

R = 9βOH, IIIb

These data are compatible with an estratriene derivative bearing a tertiary hydroxy group. Structure IIIa for the isolated alcohol was confirmed by ^{13}C nmr analysis.

Complete self-consistent assignments[6] for the estratriene I and its hydroxy derivative IIIa were made and found to be in good agreement with those reported[7] for related steroidal compounds. The signal at 43.90 ppm (doublet) for C-9 in the hydrocarbon I was shifted to 69.90 ppm (singlet)[8] in the alcohol IIIa. Moreover, the observed shifts effects $\Delta\delta$ (defined as $\delta^{III}a - \delta^{I}$) for the carbons at α,β and γ positions to the alcohol bearing carbon were close to those found in analogous systems[9] (standard deviation ca 0.6 ppm), and the negative shift effect for C-18 ($\Delta\delta$=-0.75 ppm) was compatible with the presence of a 9α hydroxy group in IIIa.

The use of nitrobenzene for the light induced benzylic hydroxylation of aromatic derivatives thus represents a new, mild and efficient functionalization method whose scope and limitations are under present investigation, as are its mechanistic implications.

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References

1. A. Bodenberger and H. Dannenberg, Chem. Ber., 104, 2389 (1971).
2. S.W. Pelletier, Y. Ichinohe and D.L. Herald Jr., Tetrahedron Letters, 4179 (1971).
3. R.C. Cambie, V.F. Carlisle, C.J. LeQuesne and T.D.R. Manning, J. Chem. Soc. C, 1234 and 1240 (1969); R.C. Cambie and V.F. Carlisle, ibid., 1706 (1970).
4. D.M. Piatek, G. Herbst, J. Wicha and E. Caspi, J. Org. Chem., 34, 116 (1969).
5. A.J. Birch and G.S.R. Subba Rao, Tetrahedron Letters, 2917 (1968).
6. The spectra were measured on a Bruker-WH 90 Spectrometer in $CDCl_3$ solution (0.1 M). The assignments are based on single frequency off resonance decoupling and lanthanide induced shift experiments as well as the analysis of partially relaxed spectra. Shifts given are relative to internal TMS.
7. G. Engelhardt, G. Schneider, I. Weisz-Vincze and A. Vass, J. Prakt. Chem., 316, 391 (1974); G. Engelhardt, D. Zeigan, B. Schoenecker and K. Ponsold, Z. Chem., 15, 60 (1975).
8. J.B. Stothers "Carbon-13 NMR Spectroscopy", Academic Press, 1972.
9. The shift effects for cholestan-5α-ol versus cholestane (reference 10), and for cholestan-3β,14α-diol versus cholestan-3β-ol (unpublished results) were employed as reference values.
10. H. Eggert, C.L. Van Antwerd, N.S. Bhacca and C. Djerassi, J. Org. Chem., 41, 71 (1976).