Epimerization and Rearrangement of Des-A-steroid Hydroxy-ketones *via* Quinonoid Intermediates

Alan B. Turner

Chemistry Department, University of Aberdeen, Aberdeen AB9 2UE, Scotland

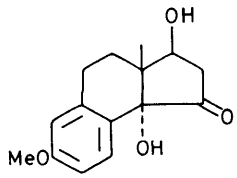
In aqueous or alcoholic hydrochloric acid the 14α-hydroxy-ketone (**1**) undergoes epimerization and dehydration to give the 14β-hydroxy-ketone (**2**) and the 14β-alkoxy-15-ketones (**3**)—(**5**), together with the rearranged 17-alkoxy-16-en-15-ones (**8**) and (**9**).

Acid-catalysed epimerizations of alkaloid hydroxy-ketones having the epimerization centre adjacent to an electron-rich aromatic ring have been reported by Shamma *et al.*[1] Quinonoid cations are thought to be intermediates in these reactions. We have investigated the behaviour of steroidal 14α-hydroxy-ketones in which enolization of the 15-oxo-group allows the formation of quinonoid zwitterions.

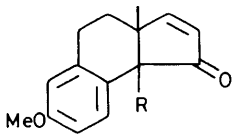
A 0.2 M solution of the 14α-hydroxy-ketone (**1**)[2] in ethanol saturated with hydrogen chloride showed two main products after 2 h at 20 °C. These were isolated by reversed-phase h.p.l.c. and identified as the unsaturated 14β-hydroxy-ketone (**2**)[2] and the 14β-ethoxy-derivative (**3**), m.p. 142—145 °C,† in 34 and 40% yield, respectively. The configuration of the alkoxy group at C-14 in the less polar product was clear from the ^{1}H n.m.r. chemical shifts of the C-7 aromatic proton (δ 7.68) and the angular methyl protons (δ 1.32).

When the reaction was repeated using more dilute ethanolic hydrogen chloride (acetyl chloride : ethanol, 1 : 10) the product consisted of three main components by h.p.l.c., but on storage the most polar compound was seen to decrease and the other two to increase. On work-up as before, the major products were (**2**) and the 14β-ethoxy-16-en-15-one (**3**) in yields of 27 and 35%, respectively. Preparative h.p.l.c. using the reversed-phase system with aqueous ethanol as eluent failed to yield the polar intermediate, which reverted to the products (**2**) and (**3**) during the work-up procedures. Attempts to determine the ^{1}H n.m.r. spectrum of the intermediate by

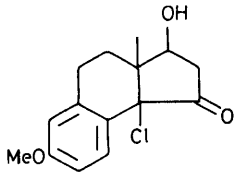
† Satisfactory analytical and spectral data have been obtained for all new compounds.



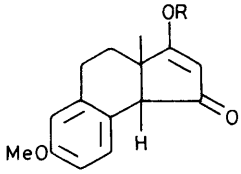
(1)



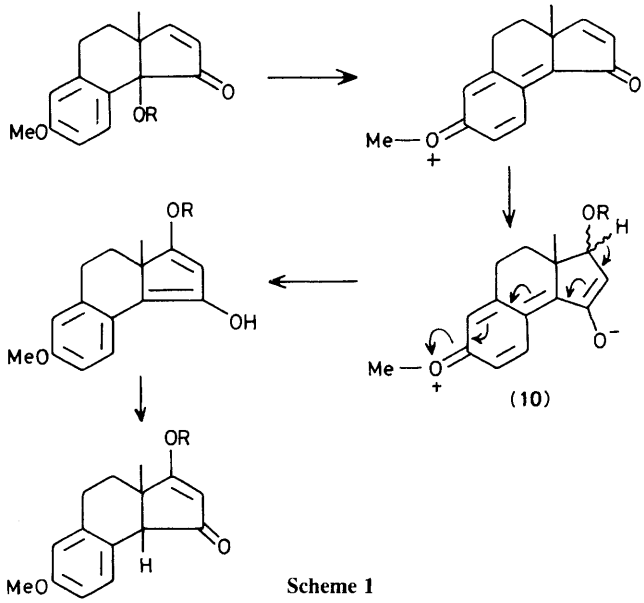
(2) R = OH
(3) R = OEt
(4) R = OCD_3
(5) R = OMe
(7) R = Cl



(6)



(8) R = Et
(9) R = Me



Scheme 1

dissolving the crude product (obtained after brief contact with acid) in deuteriomethanol were inconclusive, but did result in the incorporation of deuterium. The main product isolated was the 14β-deuteriomethoxy derivative (**4**); together with compound (**2**). When unlabelled methanol was used, the corresponding methoxy-ketone (**5**), m.p. 101—103 °C, was obtained as the major product in 36% yield. Another product was isolated in 10—12% yield from the epimerizations in ethanol. This was an isomer of the ketone (**3**), possessing characteristic non-exchangeable single proton singlets in its ^{1}H n.m.r. spectrum at δ 3.26 and 5.27, consistent with the rearranged structure (**8**). The analogous compound (**9**) was isolated in 15% yield from the HCl-catalysed reaction of (**1**) in methanol. The 14β-methoxy-15-ketone (**5**) gave the rearranged ketone in 70% yield after 2h at 20°C in 3 M methanolic HCl under nitrogen.

It is clear that a relatively stable intermediate is involved in these transformations, and the most likely structure for this polar intermediate is the 14β-chloro-compound (**6**). Mass spectral evidence for the presence of this compound (*m/z* 282 and 280) and its dehydration product [(**7**), *m/z* 264 and 262] in the freshly-isolated crude product from (**1**) has been obtained. Dehydration at C-16,17 is facilitated in steroids of the C/D-*cis* series owing to the favourable geometry which can be achieved with the flexible *cis* ring junction.

To test whether the rearrangement was intramolecular, the methoxy-ketone (**5**) was treated with ethanolic HCl for 2 h at 20 °C under nitrogen to give as major product (73% yield) the 17-ethoxy-16-en-15-one (**8**). Thus no evidence for a concerted process was obtained, and an intermolecular mechanism involving the quinonoid zwitterion (**10**) is suggested (Scheme 1). The involvement of the zwitterion (**10**), which undergoes proton loss from C-17, explains the addition of alcohol to the 16-en-15-one system followed by regeneration of the Δ^{16}-bond by a non-oxidative pathway.

Received, 24th February 1984; Com. 247

References

1 N. Murugesan, G. Blasko, R. D. Minard, and M. Shamma, *Tetrahedron Lett.*, 1981, **22**, 3131.
2 P. J. Cox, R. A. Howie, A. W. Nowicki, and A. B. Turner, *J. Chem. Soc., Perkin Trans. 1*, 1982, 657.