Epoxide Cleavage as a Means of Methyl Migration: Model Studies in Cucurbitacin Synthesis: Ring A Aromatic 9β-Methyl Steroids

By J. W. APSIMON* and R. R. KING

(*Department of Chemistry, Carlton University, Ottawa 1, Canada*)

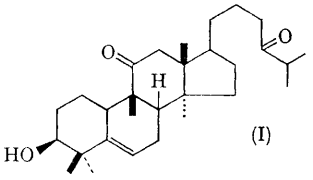
RECENT reports of backbone rearrangements in steroids induced by the creation of a cationic site on epoxide cleavage,[1] prompted us to examine this technique as a means of partial synthesis of triterpenoids with unusual methyl substitution patterns, *e.g.*, cucurbitacins (I).[2] Although extensive acid-catalysed methyl migrations are well known in this series[3] we felt that our approach merited study because of the retention of functionality at both termini of the rearrangement pathway. We reasoned that migration could be induced with methyl groups *trans* and diaxial to one end of the epoxide moiety[4] and therefore chose compound (II) as a model. In this case, further impetus for migration would be expected by ring A aromatisation [arrows in (II)]. Compound (II) was obtained by unexceptional means from adrenosterone.

When BF_3 was bubbled into a benzene solution of (II) and the reaction mixture allowed to stand at room temperature for 10 hr., two main products were obtained,† one phenolic and the other neutral.‡ The phenol (IIIa), m.p. 254·5—256°, $[\alpha]_D$ + 32°, ν_{max} 3550, 3300, 1710, 1610, and 1575 cm.$^{-1}$, λ_{max} 281 mμ, ε 1950 changing to λ_{max} 298 mμ, ε 3160 in base, formed a monomethyl ether with ethereal diazomethane, m.p. 187—189°, ν_{max} 3550, 1720, 1610, and 1575 cm.$^{-1}$, λ_{max} 278 mμ, ε 2140; *M* (mass spectral) 314. Oxidation of (IIIa) with Jones reagent gave the diketone (IIIb), m.p. 278°, $[\alpha]_D$ + 253°, ν_{max} 3400, 1720, 1695, 1610, and 1595 cm.$^{-1}$, λ_{max} 282 mμ, ε 1980 changing to λ_{max} 300 mμ, ε 3010 in base. The n.m.r. spectra of these compounds indicated two *C*-methyl groups and 3 aromatic protons. The C-1 proton signal in (IIIa) appears at τ 1·9 presumably being highly deshielded by the 11-α-hydroxy-group. This signal moves upfield to τ 3·5 in (IIIb). This behaviour is best explained by the stereochemistry indicated (and predicted) for (IIIa).

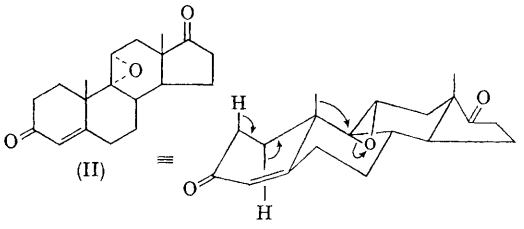
Compound (IVa), m.p. 228—230°, $[\alpha]_D$ + 350°, ν_{max} 3320, 1720, and 1650 cm.$^{-1}$, λ_{max} 245 mμ, ε 15,700 was isolated from the neutral portion of the reaction mixture and possibly indicates the alternate rearrangement pathway for *trans* and diaxial substituents.[5] Oxidation with Jones reagent gave an oily triketone (IVb), ν_{max} 1720, 1700, and 1660 cm.$^{-1}$ which on warming with alcoholic HCl gave the di-α,β-unsaturated ketone (IVc), m.p. 186°, ν_{max} 1720, 1660 cm.$^{-1}$, λ_{max}

† Satisfactory analyses were obtained for all new compounds reported.

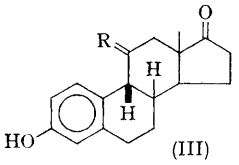
‡ The yields of pure materials so far obtained are 13% for (IIIa) and 23% for (IVa). The remainder of the material appears to be polymeric.



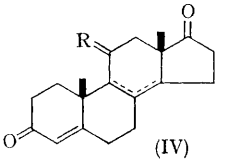
(I)



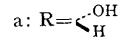
(II) ≡



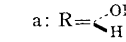
(III)



(IV)

a: R= 

b: R=O

a: R=  , $\Delta^{8,14}$

b: R=O, $\Delta^{8,14}$

c: R=O, $\Delta^{8,9}$

246 mμ, ε 19,700. We are extending this approach to the partial synthesis of cucurbitacins and other triterpenes.

Our observations are in distinct contrast to those of Henbest and Wrigley,[6] who, with similar $\Delta^{9,11}$-α-epoxides, noted only 11-ketone formation. We have been unable to detect any ketone formation in our studies. It is possible that the aromatisation of ring A directs the rearrangement. This however must only be part, if any, of the reason since we observe the alternate mode of rearrangement to (IVa). A similar cleavage of the α-epoxide of $\Delta^{9,11}$-progesterone yielded no C-11 ketone although the main direction of the rearrangement was to give the analogue of (IVa) (Ac at C-17 instead of =O), only 3% ring A aromatisation being observed. Goldsmith[7] has pointed out the importance of solvent in epoxide rearrangements, but in our case gaseous BF_3 was passed into a benzene solution of the epoxide. In our earlier work epoxide (II) was treated with BF_3 etherate in benzene and was found to be unchanged after several days at room temperature. We are continuing our study of the factors relating to the direction of rearrangement on epoxide cleavage.

We thank the National Research Council of Canada for generous financial support.

(*Received September 25th*, 1967; *Com.* 1020.)

[1] J. W. Blunt, J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1967, **23**, 1811; J. C. Jacquesy, J. Levisalles, and J. Wagnon, *Chem. Comm.*, 1967, 25.

[2] G. Ourisson, P. Crabbé, and O. Rodig, "The Tetracyclic Triterpenes", Holden-Day, San Francisco 1964; T. G. Halsall and R. T. Aplin, *Fortschr. Chem. org. Naturstoffe*, 1964, **22**, 153.

[3] J. F. King and P. de Mayo, "Molecular Rearrangements", ed. P. de Mayo, Interscience, New York 1964, p. 813.

[4] N. L. Wendler, ref. 3, p. 1022.

[5] *Cf.*, however, L. A. Lowener, N. L. Wendler, R. P. Graber, C. S. Snoddy, jun., and F. W. Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476.

[6] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1957, 4596.

[7] D. J. Goldsmith, *J. Amer. Chem. Soc.*, 1962, **84**, 3913.