Regioselective Base-catalysed Rearrangement of Steroidal αβ-Unsaturated Epoxides

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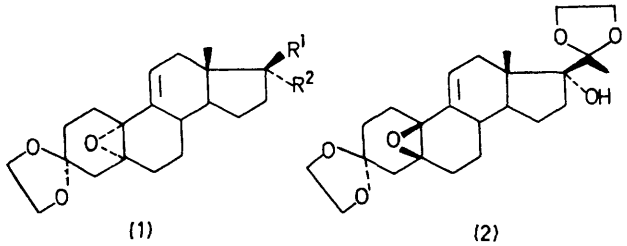
Summary Rearrangement of 5,10-epoxy-$\Delta^{9(11)}$-steroids in the presence of potassium t-butoxide or lithium dialkylamides occurs by proton abstraction at C-4 or C-12 depending on the nature of the base and the configuration of the epoxide.

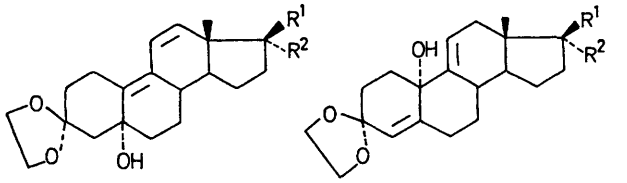
BASE-CATALYSED rearrangement of epoxides to allylic alcohols has been known for a long time[1] and is now well documented, especially by the work of Crandall[2] and Rickborn.[3] These studies were mainly concerned with non-allylic epoxides (for αβ-unsaturated epoxides, see

refs. 1 and 2c); the bases were generally lithium dialkylamides[4]. It became clear that epoxide opening with lithium dialkylamides occurs via a *syn* pathway,[3a,d] but the reason for this has not been fully clarified.



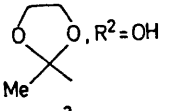
(1)

(2)



(3)

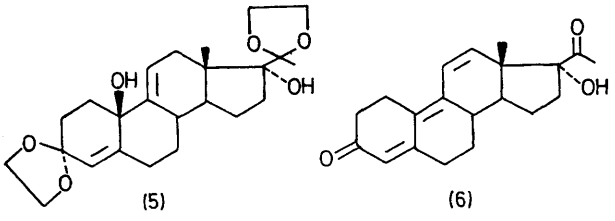
(4)

a; R^1 =  , R^2=OH

b, R^1=OH, R^2=H

c; R =OH, R^2=Me

d; R^1, R^2= 



(5)

(6)

Our investigations on 10β-substituted corticoids,[5] showed that 9,11-unsaturated steroidal 5,10-epoxides rearrange in basic medium leading to two different dienols, depending on the reaction conditions. The α-epoxides of type (**1**), when treated with Bu^{t}OK in refluxing tetrahydrofuran, yield dienols (**3**) by proton abstraction at C-12. Changes in the size of the C-17 side chains and stereochemical considerations suggest that it is the 12α(axial) proton which is lost.† Indeed, the nature of the 17β side chain does not affect the yield of the dienol very much [80—100% by t.l.c. and u.v. for (**1a**) and (**1b**)], whereas increase of the bulk of the α-side chain [(**1c**) *vs.* (**1b**)] dramatically decreases this yield‡ (except for the replacement of H by OH). The β-epoxide (**2**), when treated under identical conditions, yields exclusively the dienol (**5**) by proton abstraction at C-4. These results are readily rationalized by assuming an antiperiplanar type opening (resulting in abstraction of the *syn* proton in the 1-4 vinylogous system),§ and we have investigated the action of lithium dialkylamides on the epoxides (**1a**) and (**2**). As expected for a *syn* opening, the α-epoxide (**1a**) yielded the dienol (**4a**) upon treatment with lithium diethylamide or lithium di-isopropylamide (LDA) at room temperature for 10 min. The β-epoxide (**2**) however, upon reaction with LDA, gave exclusively the dienol (**5**) by proton abstraction at C-4, although the 12α-proton is in suitable orientation for a *syn* opening. This experiment suggests that *syn*-epoxide opening by lithium dialkylamides is the result of a proximity effect in the transition state, the amide being poorly dissociated, and the lithium co-ordinating with the epoxide oxygen. This assumption is supported by the fact that treatment of (**1a**) with $NaNH_2$ in ethylenediamine gave exclusively the dienol (**3a**) by proton abstraction at C-12. In this case the nature of the base and of the solvent favour charge dissociation, leading therefore to the *anti* opening.

Our results may be satisfactorily rationalized in terms of orbital symmetry by the 'parity' concept of Mathieu.[6] Two cases have to be considered: (i) with dissociated bases (*e.g.* Bu^{t}OK or $NaNH_2$) the 1,2 opening is predicted to be *antarafacial* (2 electron pairs involved), and the 1,4 opening *suprafacial* (3 electron pairs); (ii) with poorly dissociated bases (*e.g.* lithium dialkylamides) a cyclic concerted pathway is most likely and the 1,2 opening is predicted to be *suprafacial* (3 electron pairs).

Finally, from a synthetic point of view, concomitant deacetalization and dehydration of (**3a**) (for instance by a sulphonic resin) leads quantitatively to the trienone (**6**).

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† The departing proton must have axial stereochemistry.

‡ 15% of (**3c**) and traces of (**3d**) were isolated.

§ The terms *syn* and *anti* are given with reference to a 1,2-opening. In the vinylogous system the *syn* opening results in the abstraction of the *trans*-proton and *vice-versa* (orbital symmetry).

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