Configuration of the *C/D* Ring Junction in Equilenin and Other Steroids

THE configuration of the *C/D* ring fusion in equilenin has been the subject of a number of communications[1-3]. We consider that the arguments advanced for a *trans* ring junction leave much to be desired. Shoppee's[1] conclusion that the dehydrogenation of equilin to equilenin under mild conditions proves the steric identity of the *C/D* union in these two substances can no longer be accepted, since *iso*equilin, which is now known[4,5] to be also *trans*, gives *iso*-equilenin (which has the opposite *C/D* configuration to equilenin) under the same conditions[6].

It is evident that the same uncertainty is present in any correlation based on the formation of equilenin (or *iso*equilenin) by reactions involving a centre adjacent to C_{14} [2]. One would anticipate epimerization at C_{14} in some of these experiments because of the possibility offered of relieving the strain associated with the *trans* *C/D* hydrindane system.

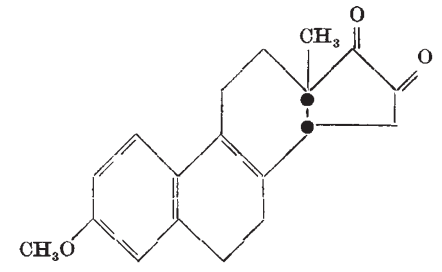
Another attempt to correlate the *C/D* configuration of equilenin with that of other natural steroids through a determination of the configuration at C_{14} was based on the use of the method of molecular rotation differences[3]. Since this centre is adjacent to an unsaturated system which might give rise to considerable 'vicinal effect'[7], the validity of this conclusion is questionable.

An unambiguous proof of the configuration of equilenin follows from the fact that Bachmann's[8] α-7-methoxy-2-methyl-2-carboxy-1,2,3,4 tetrahydrophenanthrene-1-acetic acid (III) (which was converted to *iso*equilenin) is obtained[5] by hydrogen peroxide cleavage of the α-diketone (I) to the diacid (II), followed by dehydrogenation. The diketone I is one of the products of the Diels–Alder reaction between 1-vinyl-6-methoxy-3,4-dihydronaphthalene and 3-methyl-*cyclo*pentene-1,2-dione[9,5], and must therefore be *cis*.

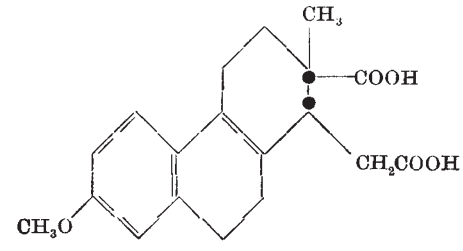
Dehydrogenation of II would not be expected to invert C_1 (C_{14} sterol numbering), since the strain associated with a *trans* hydrindane system is no longer present. Dehydrogenation experiments in the doisynolic acid series confirm this view[10]. The *C/D* ring junction is therefore *cis* in *iso*equilenin and *trans* in equilenin.

Compound II proved identical with a diacid prepared by Miescher *et al.*[2]. This diacid, which is therefore unambiguously *cis*, gave after homologation and ring closure a substance which was *not dl-iso*equilin. *Iso*equilin is therefore *trans*, and its formation from equilin by acid isomerization cannot involve epimerization at C_{14} (which would have produced a *cis* compound). This means that the *C/D* junction in œstrone must then also be *trans*, since it follows from the work of Pearlman and Wintersteiner[11] that this junction is the same as that of equilin.

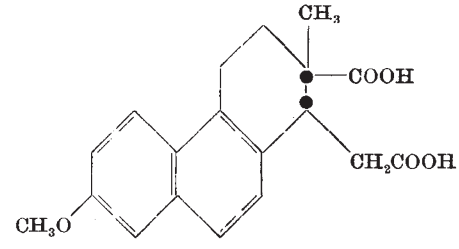
This derivation of the *trans* *C/D* junction in œstrone can be used as chemical evidence for the *trans* *C/D* union in the non-aromatic steroids, since cholesterol can be degraded to œstrone by a reaction which, although a pyrolysis, cannot involve C_{14} [12,13]. This evidence is more convincing than that of Wieland and Dane[14], which is open to serious criticism[15], or that of Dimroth and Jonsson[16], which logically demonstrates only the fact that vitamin D_2 has a *C/D* *trans* union, because the identity of the *C/D* junction in vitamin D_2 and ergosterol has not been convincingly demonstrated. It was possible that the *trans* *C/D* vitamin D_2 had resulted from the irradiation of a *cis* *C/D* ergosterol. Such a change to the less stable configuration is known[17] to take place when *iso*dehydrocholesterol, which is a C_5 α-compound, is transformed during irradiation to the C_5 β-configuration, which contains the less stable *cis*-decalin system.



I



II



III

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