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THE STEREOCHEMISTRY OF 12-HYDROXY-12-METHYL-TIGOGENIN DERIVATIVES

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Two groups of workers have examined 12-hydroxy-12-methyl derivatives of tigogenin. In each report the stereochemical assignments were made on the basis of "the well-known propensity of steroids to rear attack particularly in the region of ring C", this generalisation being applied both to the 12-ketone of hecogenin (reaction with lithium methyl[1] and methyl magnesium bromide[2]) and to the epoxidation of the exocyclic methylene group of the 12-methylene tigogenin.

In connection with other work[3] we had occasion to repeat these reactions, and we wish to report our results and stereochemical assignments which are at variance with those previously given.

Reaction of hecogenin acetate with MeMgBr gave two 12-hydroxy-12-methyl derivatives in the ratio 4:1. The configurations of these products were revealed by their dehydration reactions with thionyl chloride-pyridine, which, in our hands, each gave distinct olefins and not mixtures[2].

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Thus the major alcohol (as 3-monoacetate, m.p. 222-223° $[\alpha]_D$ -35°) to which we assign the 12α-hydroxy-12β-methyl configuration, gave the Δ^{11}-olefin (80% yield) resulting from the favourable[4] trans-diaxial elimination. The minor 12β-hydroxy-12α-methyl isomer (3-monoacetate, m.p. 226-227° $[\alpha]_D$ -50°) underwent the expected[4] smooth dehydration to give 12-methylene-tigogenin acetate in high yield. (77% yield).

Epoxidation of 12-methylene-tigogenin acetate with monoperphthalic acid gave the two 12,12'-epoxides (α-epoxide, m.p. 242-243°, $[\alpha]_D$ -10°; β-epoxide, m.p. 172-173°, $[\alpha]_D$ -62° : α:β ratio 2:1). Each isomer afforded the corresponding 12-hydroxy-12-methyl compound on reduction with $LiAlH_4$, thereby establishing the stereochemistry of the epoxides. Bladon and McMeekin[1] characterised only one of the 12,12'-epoxides (m.p. 240-242°, $[\alpha]_D$ -24°), which presumably corresponds to our major product, the α-epoxide. Their assignment of the β-configuration to this epoxide followed from its reduction to give their supposed 12β-alcohol.

The apparently abnormal β-attack of the Grignard reagent on hecogenin may be rationalised from a consideration of Dreiding models of the two transition states. In brief, approach of the bulky nucleophilic species $\overset{\delta-}{CH_3}\text{-}\overset{\delta+}{Mg}\text{-Br}$ towards the 12α-position brings in three "skew-butane" interactions involving the 9α, 14α, and 17α-hydrogen atoms. The resulting destabilisation out-weighs the single such interaction from the C-18 angular methyl group in the transition state for β-attack. The C-21 methyl group, which blocks 12α-approach in cholanes and similar compounds where the side chain is free to assume

its stable conformation, is constrained in a position well clear of C-12 in hecogenin[5]. These factors would be much less important in the reduction of hecogenin with complex hydrides, where the entering species is H^- rather than CH_3^-, and the 12β-alcohol is the major product. The epoxidation process, probably involving attack by incipient OH^+ at the 12'- carbon as the rate-determining step, should be relatively insensitive to steric factors affecting C-12.

A full account of this and related work will be published elsewhere[3].

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