The Mechanism of the "Abnormal" Beckmann Rearrangement of Triterpenoid Oximes†

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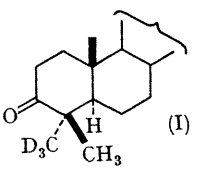
Summary The "abnormal" Beckmann rearrangement of [4α-CD_3]-4,4-dimethyl-5α-cholestan-3-one oxime gives predominantly the dideuterio-seco-nitrile *via* a seven-membered ring tosyloxy-imine.

UNDER basic conditions 3-oxo-triterpenoid oximes are converted[1] into a seco-nitrile rather than the normal ε-lactam product of a Beckmann rearrangement.[2] This reaction has been termed the "abnormal" Beckmann rearrangement.[1] If this reaction is stereospecific with a known specificity it might be suitable for distinguishing between the two methyl groups at C-4 of triterpenoids to examine their biosynthetic origin.[3]

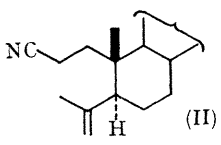
In this report we show that the rearrangement is largely stereospecific. We examined the rearrangement with a stereospecifically labelled model compound, [4α-CD_3]-4,4-dimethyl-5α-cholestan-3-one (I). Preparation of this compound used the reductive alkylation[4] of 4-methylcholest-4-en-3-one. This method should be more stereospecific than base-catalysed alkylation, followed by reduction of the 4,4-dimethylcholest-5-en-3-one. Both preparations were shown to give the same product, although the latter method gave on reduction the 5β-isomer as well. Probably about 80% of the methyl group is introduced from the α-side with base-catalysed alkylation.[5] The intermediate dienolate ion which controls the stereochemistry is less affected by the 10β-methyl than the comparable enolate ion involved in reductive alkylation.[4] Hence the model compound should be better than 80% labelled in the 4α-methyl position.

Examination of the n.m.r. spectrum of the deuteriated and unlabelled 4,4-dimethyl-5α-cholestan-3-one in chloroform and benzene permits the identification of the 4α- and 4β-methyl signals.[6] The spectrum of the deuteriated compound in benzene shows the absence of the 4α-methyl signal at τ 8·83 and no detectable effect on the 4β-methyl signal at τ 9·00. However, the methylene envelope prevents accurate quantitative estimation of the stereoselectivity of the alkylation reaction.

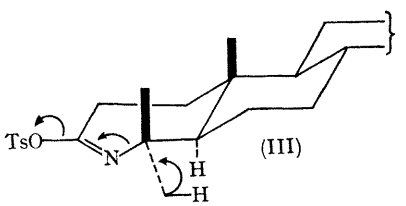
[4α-CD_3]-4,4-Dimethyl-5α-cholestan-3-one (I) was converted into its oxime, m.p. 205°, and rearranged in the presence of tosyl chloride in pyridine to the seco-nitrile (II), m.p. 65°. Examination of the n.m.r. of this compound showed that the vinyl protons were practically absent at τ 5·08 (integration indicates *ca.* 30% remains but the signal cannot be detected), and the methyl group attached to a double bond at τ 8·22 was unchanged. This could not be confirmed by mass spectrometry due to the non-reproducible nature of the $M - 1$, M, and $M + 1$ peaks.[7]



(I)



(II)



(III)

Even neglecting any deuterium isotope effect it is concluded that the "abnormal" Beckmann rearrangement is largely stereospecific, with elimination of a hydrogen atom from the 4α-methyl group. Two mechanisms may be postulated for the rearrangement. One[1] involves the direct rearrangement of the oxime tosylate to the seco-nitrile, and the other mechanism proceeds *via* the tosyloxy-imine, (III). The latter suggestion is strongly supported by the isolation of only the normal Beckmann rearrangement product on work-up after a short reaction time, with little starting material left. After longer reaction times up to 72% of the seconitrile is isolated. Furthermore the ε-lactam from the normal Beckmann rearrangement is not converted into the seco-nitrile under these conditions.[8] These results may be explained by the rapid formation of the tosyloxy-imine, (III) which on hydrolysis gives the

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ε-lactam, but it will further react to give the seco-nitrile (II). (See arrows).

The related rearrangement of the ε-lactone[9] was shown to be non-stereoselective. However, with the added restriction of the imine double bond in the seven-membered ring A, the conformations are more limited. For a concerted rearrangement only the 4α-methyl group can assume the necessary conformation for a *trans*-elimination mechanism.[10] Even with a non-concerted rearrangement the 4α-methyl group is more available for removal of a proton through shielding of the 4β-methyl group by C-19.

The application of this rearrangement to lanosterol biosynthesised from [2-^{14}C]mevalonic acid is described in the communication accompanying.[3] These results confirm the above conclusions and show that there is no appreciable deuterium isotope effect.

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