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BECKMANN REARRANGEMENTS IN THE BICYCLO[2.2.1]HEPTAN-2-ONE SERIES

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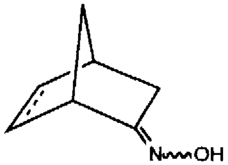
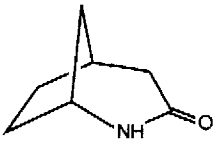
Summary: In contrast to norcamphor oxime (2), the E-oxime (6), derived from the acetonide of 5,6-dihydroxybicyclo[2.2.1]heptan-2-one, undergoes regiospecific Beckmann rearrangement to give the lactam (7).

The recent publication describing Beckmann fragmentations and Beckmann rearrangements in the oximes (1) and (6) derived from dehydronorcamphor,[1] prompts us to report our own results in this area, which both confirm and complement those of Pappalardo and co-workers.

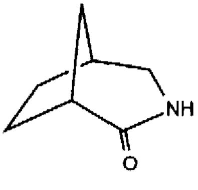
Stimulated by our interest in the Beckmann rearrangement in general,[2] we were intrigued by the conflicting accounts, summarised in a comprehensive review on nitrogen insertion reactions of bridged bicyclic ketones,[3] concerning the oxime (2) derived from norcamphor. This is reported to give varying ratios of the two possible lactam products (3) and (4), with the alternative fragmentation products being formed in some instances. Of particular interest was the report that the use of boron trifluoride etherate in tetrachloroethane gave *regiospecifically* the 2-azalactam (3) in 91% yield.[4] However, no experimental details of these rather unusual conditions were recorded, and therefore we decided to re-investigate the Beckmann rearrangement of norcamphor oxime (2). Although we could obtain mixtures of the lactams (3) and (4) in modest yield using either 85% sulphuric acid or tosyl chloride/sodium hydroxide to effect the Beckmann rearrangement,[3] we were unable to reproduce the reported result using boron trifluoride etherate in tetrachloroethane.[4]



(1) with 5,6-double bond
(2) without 5,6-double bond

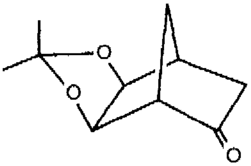


(3)

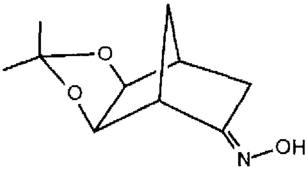


(4)

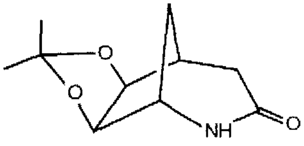
Since conformational and torsional effects are thought to be important in nitrogen insertion reactions of bridged bicyclic ketones,[3] we thought that the problems encountered with norcamphor oxime (2) compared with, say, the successful Beckmann rearrangements in the bicyclo[2.2.2]octanone series, might be conformation related. Therefore we decided, like Pappalardo and co-workers who arrived at the same conclusion for different reasons,[1] to investigate the Beckmann rearrangement of the oxime (6) in which the additional dioxolane ring alters the conformation of the bicyclo[2.2.1]heptane system.[5] The required ketone (**5**) was prepared from commercially available 5-norbornen-2-ol using a literature procedure.[6] Reaction of the ketone with hydroxylamine under standard conditions gave the oxime, initially as a mixture of E- and Z-isomers, but subsequent recrystallisation from cyclohexane gave the pure E-oxime (**6**), m.p. 143-144°C, the structure of which was confirmed by *X*-ray crystallography.[7] The Z-oxime was obtained from the mother liquors as a crystalline solid, m.p. 113-115°C, which readily converted into the E-isomer above its melting point. Treatment of the E-oxime (**6**) with mesyl chloride and triethylamine in acetonitrile gave the 2-azabicyclo[3.2.1]octan-3-one (**7**), m.p. 164-166°C, in 73% yield. The exclusive formation of the 2-aza bicycle (**7**) was expected on the basis of preferred *anti* migrations in the Beckmann rearrangement, but the structure was confirmed by 2-D ^{1}H n.m.r. and by *X*-ray crystallography.[7] Treatment of the Z-oxime, or the E/Z mixture of oximes, under similar conditions gave the same lactam product, although in lower yield, perhaps indicating that the oximes pre-equilibrate.



(**5**)



(**6**)



(**7**)

Therefore we conclude that the Beckmann rearrangement of oximes derived from bicyclo[2.2.1]heptan-2-ones is even more complicated than was thought, and subtle differences in conformation, as well as the presence of the 5,6-double bond which is responsible for the alternative fragmentation pathway,[1] may play an important role.

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5 Our initial computer modelling studies using Macromodel®(Version 2.5) indicate that the dioxolane ring does indeed change the conformation of the bicyclo[2.2.1]heptane system; further modelling studies are in progress.
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7 Carried out by Dr D. J. Williams and Ms A. M. Z. Slawin of this Department.

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