Selective Hydrogenation of 4,5-Dihydro-1,3-oxazin-6-ones to Carboxaldehyde Derivatives; Chemical Differentiation Between Acylazetidin-2-ones and the Corresponding Isomeric Oxazin-6-ones

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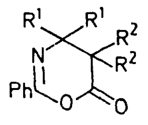
Summary The structural ambiguity between a substituted acylazetidin-2-one and the isomeric dihydro-oxazin-6-one has been resolved by chemical studies; catalytic hydrogenation of the latter leads, unexpectedly, to preferential reduction of the carbonyl group to carboxaldehyde.

1,3-Oxazin-6-ones are useful intermediates for the preparation of hindered β-peptides.[1] The dihydro-oxazinone[2]† (**1a**) was first synthesised by cyclisation‡ of 3-benzoylamino-3-methylbutyric acid (**2a**) with acetic anhydride, but under similar conditions 3,3-diarylbenzoylamino-acids have been reported[3] to yield the isomeric acylazetidin-2-ones. Zeifman *et al.*[4] subsequently concluded that the latter were probably oxazinones. It is now evident[5] that chemical precedence and physical parameters are insufficient criteria for the designation of structure.

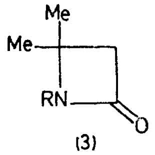
The oxazinone (**1a**) and the azetidinone[6] (**3a**) have quite different properties. Electrolytic cleavage[7] of the benzoyl group from (**3a**) gave (**3b**), whereas the oxazinone (**1a**) was degraded. Catalytic hydrogenation of (**3a**) over Pd–C in benzene did not effect any change; similar treatment of (**1a**) afforded a crystalline compound whose molecular weight (205) was in accordance with the expected structure (**4**). However, hydrolysis of this hydrogenated product did not give benzaldehyde, which would be expected to be formed from (**4**). Instead the pure hydrogenated product gave two derivatives (**2b**) and (**5**) on reaction with 2,4-dinitrophenylhydrazine. The hydrazone (**2c**) may be converted into (**5**) through β-elimination.[8]

The hydrogenated product of (**1a**) gave positive Schiff's and Tollen's tests and its n.m.r. spectrum showed a low-field aldehydic triplet supporting the designation of the hydrogenated product as (**2b**) rather than (**4**). It can be concluded therefore that the formulation of (**1a**) as the 4,5-dihydro-1,3-oxazin-6-one shown rather than the isomeric azetidinone is correct.



(1)

a; $R^1 = Me$, $R^2 = H$
b; $R^1R^1 = [CH_2]_5$, $R^2 = H$
c; $R^1 = R^2 = Me$
d; $R^1 = H$, $R^2 = Me$



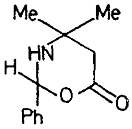
(3)

a; R = PhCO
b; R = H

$PhCONH \cdot CMe_2 \cdot CH_2 \cdot R$

(2)

a; $R = CO_2H$
b; $R = CHO$
c; $R = CH{:}N \cdot NH\ Dnp$



(4)

$Me_2C{=}CH \cdot CH{=}N \cdot NH\ Dnp$

(5)

Dnp = 2,4-dinitrophenyl

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† Previously reported (ref. 1) as an oil, m.p. 34·5—36·5 °C; all new compounds gave satisfactory elemental analyses.

‡ Isobutyl chloroformate, *NN'*-dicyclohexylcarbodi-imide and thionyl chloride have also been used in this conversion.

It is noteworthy that Cavallito and Haskell[9] have reported that 2-pyridinylbenzoates were subject to hydrogenolytic cleavage between the carbon–oxygen bond of the ester linkage.

Preliminary hydrogenation studies on (**1b**—**d**) include positive Schiff's tests and the appearance of aldehydic proton resonances in the n.m.r. spectra, supporting their designation as oxazinone derivatives.

In view of the selective and unexpected site of hydrogenation of 4,5-dihydro-1,3-oxazin-6-ones, this route provides a means for the converison of the readily accessible 3-acylaminopropionic acids[10] into 3-acylaminopropionals.

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