Studies on Substituted γ-Butyrolactams: Synthesis of a Semicorrin

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Summary A synthesis of the semicorrin (I) through isoxazole intermediates is described.

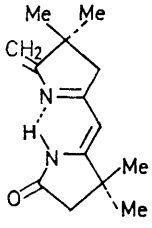
WE have previously described the first application of Cornforth's original idea[2] of the synthesis of the corrin nucleus by reductive cleavage of a polyisoxazole ring system.

A recent communication[3] on the use of isoxazoles as intermediates in the synthesis of semicorrins led us to report this new synthesis of the known[4] semicorrin (I).

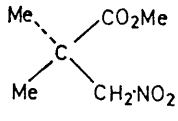
Cycloaddition of the nitrile oxide prepared *in situ* from phenyl isocyanate[5] and the nitro-ester (II) (obtained by esterification with diazomethane of 2,2-dimethyl-3-nitropropanoic acid[6]) and the acetylenic acetal (III)[7] affords the isoxazole (IV) (85%), b.p. 114—115°/0·01 mmHg, which was reduced with $LiAlH_4$ to the alcohol (V), m.p. 76—77°. Esterification with toluene-*p*-sulphonyl chloride–pyridine gives quantitatively the tosylate (VI), m.p. 72—73°, which was converted into the nitrile (VII) (90%), m.p. 75—76°, under forcing conditions (a ten-fold excess of NaCN in Me_2SO at 150—170°) necessary to effect the nucleophilic displacement at the neopentyl carbon atom.[8]

Hydrolysis with alkaline hydrogen peroxide of the nitrile (VII) quantitatively gives the amide (VIII), m.p. 86—87°, which after saponification with NaOH in ethylenic glycol–ethanol–water (2:1·5:2), followed by dilution and careful acidification at 0° with dilute phosphoric acid, affords the acetal-acid (IX) (85%), m.p. 85°, characterized as the methyl ester (X), a thick oil, b.p. 120°/0·01 mmHg. Acidification with hydrochloric acid produces the liquid keto-acid (XI) [methyl ester (XII), b.p. 107°/0·01 mmHg], identical to material obtained by Stevens's procedure.[3] Hydrogenolysis at atmospheric pressure of the protected isoxazole-acid (IX) in the presence of "active" Raney nickel gives with satisfactory yield the mono-oxo-butyrolactam (XIII), m.p. 92—93°, which, after hydrolysis by treatment with dilute acetic acid,[1,7] produces a high yield of the known[4] dioxo-butyrolactam (XIV), m.p. 110°.

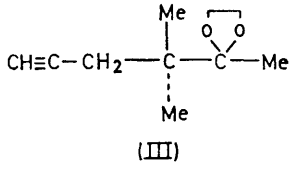
Similar treatment of the keto-acid (XI),[3] as we observed, gives mainly over-reduced products, owing to the presence of several functions sensitive to reduction.



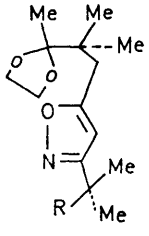
(I)

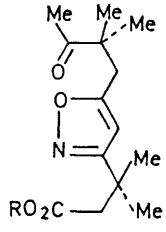


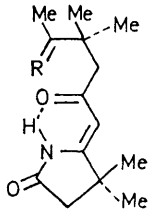
(II)



(III)







(IV) R = CO_2Me
(V) R = CH_2OH
(VI) R = $CH_2{\cdot}OTs$
(VII) R = $CH_2{\cdot}CN$
(VIII) R = $CH_2{\cdot}CO{\cdot}NH_2$
(IX) R = $CH_2{\cdot}CO_2H$
(X) R = $CH_2{\cdot}CO_2Me$

(XI) R = H
(XII) R = Me

(XIII) R = $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$
(XIV) R = O

Treatment of (XIV) as described by Eschenmoser *et al.*[4] affords the semicorrin (I).

Satisfactory elemental analyses and spectra consistent with the suggested structure were obtained for all new compounds described.

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[8] Unpublished results.