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.

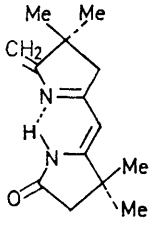
WE have previously described the first application of Cornforth's original idea[2] of the synthesis of the corrin nucleus by reductive cleavage of a polyisoxazole ring system.

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).

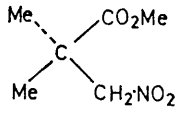
Cycloaddition of the nitrile oxide prepared *in situ* from phenyl isocyanate[5] and the nitro-ester (II) (obtained by esterification with diazomethane of 2,2-dimethyl-3-nitropropanoic acid[6]) and the acetylenic acetal (III)[7] affords the isoxazole (IV) (85%), b.p. 114—115°/0·01 mmHg, which was reduced 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°.

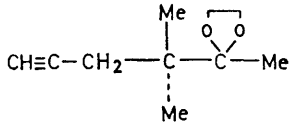
Similar treatment of the keto-acid (XI),[3] as we observed, gives mainly over-reduced products, owing to the presence of several functions sensitive to reduction.



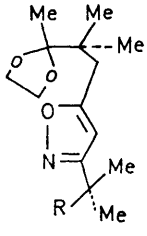
(I)

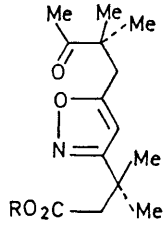


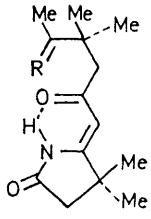
(II)



(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.

We thank the Consiglio Nazionale delle Ricerche, Rome, for financial support.

(*Received, May 17th*, 1971; *Com.* 783.)

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[8] Unpublished results.