Synthesis of Oximino-macrolides

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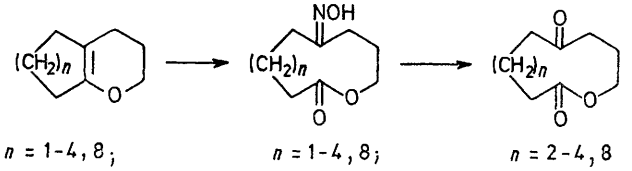
Summary A number of oximino-macrolides have been prepared by the action of n-butyl nitrite on the corresponding enol ethers in the presence of aqueous acetic or hydrochloric acid.

WE report a simple synthesis of oximino-macrolides which can be hydrolysed to the corresponding keto-macrolides. Several 10- to 12-membered keto-macrolides have previously been prepared by Borowitz *et al.*[1]

A solution of the cyclic enol ether (1 equiv.)† and n-butyl nitrite (1 equiv.)‡ in 50% ethanol was treated with acetic acid or 10% hydrochloric acid. The oximino-macrolide was extracted with ether in almost quantitative yield.§ With the exception of 5-oximino-octanolide, these oximes are smoothly converted into the corresponding semicarbazones and 2,4-dinitrophenylhydrazones, under usual conditions, and are hydrolysed to the corresponding keto-macrolides according to the procedure described by Pines *et al.* (Scheme).[2]



SCHEME

The reaction proceeds very vigorously with dihydropyran, affording a number of products which are under investigation. However, the reaction is comparatively slow and incomplete with the enol ether derived from cholestan-3-one.

Although both nitrosyl chloride and alkyl nitrites react with acyclic enol ethers, under anhydrous conditions, to afford the corresponding nitroso-adducts,[3] the present hydrolytic nitrosation of the cyclic enol ethers with the subsequent fission of the C–C bond represents a novel reaction of possible general applicability.

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† Enol ethers were prepared by slight modifications of the enamine + acrylate/reduction sequence used by Borowitz *et al.*[1a]

‡ Any alkyl nitrite or even sodium nitrite may be used.

§ All the compounds described here gave satisfactory elemental analyses and expected n.m.r. and i.r. spectra.

[1] (a) I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, *J. Org. Chem.*, 1972, **37**, 581; I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *ibid.*, 1968, **33**, 2013; (b) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *ibid.*, 1966, **31**, 3062.

[2] S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, 1966, **31**, 3446.

[3] S. Tchelitcheff, U.S.P. 267425-6/1954; *Chem. Abs.*, 1955, **49**, 6301h.