SOLVOLYTIC OXIDATION OF *O*-TOSYL-4-HYDROXYPROLINES IN DIMETHYL SULPHOXIDE*

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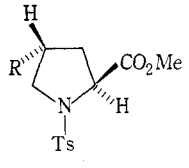
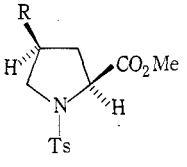
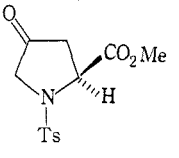
Dimethyl sulphoxide has been used widely as a solvent in nucleophilic substitution reactions,[1] because of its high polarity and low solvating power for anions.[2] Complications may arise due to side reactions such as elimination and oxidation. Elimination reactions of sulphonic esters to olefins in dimethyl sulphoxide have received considerable attention in recent years.[3–5] Very easy solvolytic oxidation of primary alkyl sulphonates, activated alkyl halides such as phenacyl halides, and α-halo esters has been reported.[6,7] Little elimination to olefin was observed with primary alkyl halides and sulphonic esters.[8] Sulphonic esters of secondary cyclic alcohols, however, have been reported to give mainly olefins, with ketones and alcohols as minor products.[3] The mechanism of oxidation involves S_N2 displacement of the sulphonate group by a solvent molecule, followed by collapse of the intermediate to ketone and dimethyl sulphide. Presence of base should then promote the formation of ketone at the expense of olefin by neutralization of liberated sulphonic acid, and this is observed.[3]



(I) R = TsO
(III) R = Cl



(II) R = TsO
(IV) R = Cl



(V)

We wish to report solvolytic oxidation of proline sulphonates and to emphasize the importance of steric factors in this reaction.

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Treatment of the *trans*-4-hydroxyproline derivative (I) with hot dimethyl sulphoxide alone gave the 4-keto derivative (V) in 43% yield, and in 49% yield when collidine was present. The *cis* epimer (II) yielded the same product in 61% yield in dimethyl sulphoxide alone. The lower relative yield for the *trans* compound as compared with the *cis* compound is a result of greater steric hindrance to the development of an S_N2 transition state by attack of nucleophile from the same face of the heterocyclic ring as the carbomethoxyl group. This effect has been noted in S_N2 displacements of other 4-substituted prolines.[9]

N.m.r. examination of the crude reaction products from which (V) crystallized revealed no evidence of an olefinic product. In contrast, therefore, to previous reports that the predominant reaction of sulphonate esters of secondary cyclic alcohols in dimethyl sulphoxide is elimination,[3,10] solvolytic oxidation can be the major pathway. On the other hand, for reasons not yet clear, the 4-hydroxyproline series may be a special case. Drs J. E. Francis and B. Witkop (unpublished results cited by Robertson and Witkop[11]) failed to obtain dehydroproline compounds by any usual elimination procedure on 4-hydroxyproline derivatives. Yet Kenner and co-workers have recently dehydrated a 3-hydroxyproline derivative without difficulty.[12]

The 4-chloroproline epimers (III) and (IV)[9] were inert to hot dimethyl sulphoxide.

Experimental

Dimethyl sulphoxide was dried and distilled from calcium hydride. Product analyses were carried out by nuclear magnetic resonance spectroscopy in $CDCl_3$ with a Varian Associates A60 instrument.

Dimethyl Sulphoxide Oxidation of N,O-*Ditosyl*-trans-*4-hydroxy*-L-*proline Methyl Ester*

(i) The *trans*-ditosyl ester (I)[9,13] (0·5 g) in dimethyl sulphoxide (25 ml) was heated at 105° for 5 hr. The reaction mixture became light brown and the odour of dimethyl sulphide was noted. After being cooled, the mixture was poured into brine and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with brine and dried ($MgSO_4$). Removal of solvent and trituration of the brown residual oil with ethyl acetate/ether gave *N*-tosyl-4-oxo-L-proline methyl ester[9] (V) as colourless prisms (0·075 g), m.p. 101–102°, undepressed on admixture with an authentic sample. N.m.r. spectra of both specimens were superposable, and details will be included in an n.m.r. survey of proline derivatives.[14] More keto ester crystallized upon concentration of the mother liquor (total yield 0·14 g).

(ii) Repetition exactly as in (i) except for the initial addition of collidine (0·3 ml) gave a total yield of colourless crystalline (V) of 0·16 g.

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Dimethyl Sulphoxide Oxidation of N,O-*Ditosyl*-cis-*4-hydroxy*-L-*proline Methyl Ester*

Solvolysis of the *cis*-ditosyl ester (II)[9,13] (0·5 g) as in (i) above gave a total yield of 0·20 g of keto ester (V).

Acknowledgment

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