Tetrahedron Letters No.13, pp. 1015-1018, 1969. Pergamon Press. Printed in Great Britain.

CONCERNING THE MECHANISM OF REDUCTION BY DIMETHYL SULPHOXIDE : DEOXYGENATION OF PYRIDINE N-OXIDE

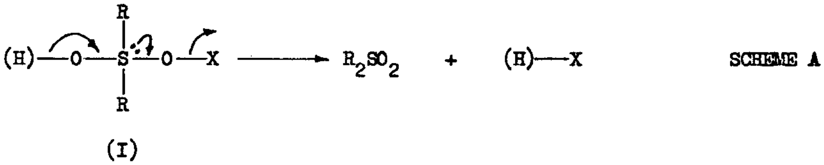
M.E.C. BIFFIN, J. MILLER & D.B. PAUL

Australian Defence Scientific Services, Department of Supply,
Defence Standards Laboratories, P.O. Box 50, Ascot Vale, Victoria, 3032.

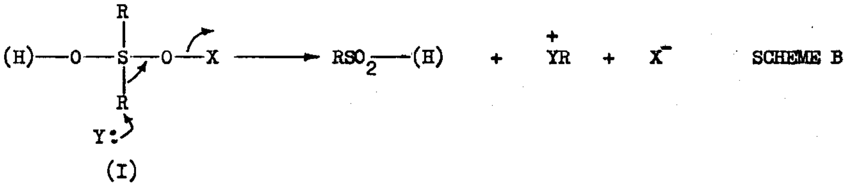
(Received in UK 1 January 1969; accepted for publication 10 February 1969)

The extensive use of dimethyl sulphoxide (DMSO) as both a solvent and reagent is well documented (1). Little attention has been paid to its behaviour as a reducing agent however and the reported examples refer exclusively to reactions with powerful oxidants (2).

Reductions by DMSO may be rationalised as proceeding *via* an initial coordination complex, (I), formed by attack of a nucleophilic oxygen atom in the oxidant on the sulphur atom of DMSO or its conjugate acid. Participation of the sulphur lone pair in the subsequent redox step, with concomitant rupture of the O-X bond, would afford a sulphone and the reduced form of the oxidant (scheme A). Specific proposals for the mechanism of peracid oxidation of DMSO (3,4) are consistent with our general scheme.



An alternative redox step, not previously reported, involves attack of a nucleophile Y on (I), resulting in rupture of the S-R and O-X bonds and formation of a sulphinate (scheme B)



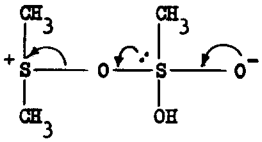
These general schemes have led us to consider the reaction of DMSO with mild oxidants, e.g. heterocyclic N-oxides. These can exist in solution with the conjugate acid of DMSO (5,6) and attack by the nucleophilic N-oxygen atom on the conjugate acid would produce (I; R = CH_3, X = e.g. pyridinium). A subsequent redox step would yield the parent heterocycle and either dimethyl sulphone or products derived from methanesulphinic acid.

Accordingly pyridine N-oxide (0.05 mole) was heated at 195° for 20 hr with DMSO (0.8 mole) containing c. H_2SO_4 (6% v/v). Dilution with water followed by removal of the organic decomposition products of DMSO (7,8) with ether gave a solution of pyridinium salt from which pyridine was isolated as its picrate. The yield was almost quantitative (94%) and these conditions were found to be optimal. The yield did not alter when a control experiment was carried out under nitrogen. Reduction in reaction time, and more critically in temperature, resulted in a lower yield: no deoxygenation was observed below 150°. The catalytic effect of acid was emphasised by comparison with the yield of picrate obtained in the absence of acid (52%). Blank runs for 20 hr at 195° in other dipolar aprotic solvents established that thermal deoxygenation accounted for little of the product (nitrobenzene 2%; hexamethylphosphoramide 5%; acidic sulpholan 2%).

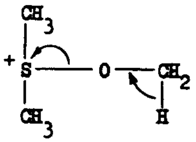
G.l.c. analysis indicated that 2% of dimethyl sulphone was present in the reaction mixture. Prolonged heating of DMSO produces trace quantities of sulphone (7) but analysis of DMSO-acid mixtures showed that only 0.2% of sulphone was produced after 20 hrs at 195°. Reduction by the mechanism as shown in scheme A is therefore relatively insignificant in this case.

On cooling the mixture after reaction in the absence of acid, crystals, m.p. 185°, were isolated and identified as the methanesulphonic acid salt of pyridine by spectroscopic comparison with an authentic sample. Almost equimolar amounts of pyridine and methanesulphonic acid were formed in the reaction. G.l.c. analysis of control reactions established that methanesulphonic acid did not arise from dimethyl sulphone produced as in scheme A, and the sulphone was not consumed under the reaction conditions.

These results may be rationalised by the mechanism in scheme B with subsequent formation of methanesulphonic acid from the methanesulphinic acid thus produced. Formation of methanesulphonic acid was shown to occur in an inert atmosphere and as disproportionation of the sulphinic acid, or its oxidation by the N-oxide, would not give equimolar amounts of pyridine and sulphonic acid as observed, it was concluded that DMSO also effects this oxidation *via* the intermediate (II). The nature of the nucleophile Y involved in the reaction with (I) is equivocal, but it is certain that pyridine *N*-oxide does not act in this capacity since this would result in a pyridine to sulphonic acid ratio of 2:1. An attractive possibility is that nucleophilic attack by DMSO on (I) would produce (III) which could then rearrange to dimethyl sulphide and formaldehyde. Such a sequence, which is analogous to the Kornblum oxidation (6), would explain the large quantities of formaldehyde formed in the reaction whereas only very small amounts are produced when DMSO is refluxed for 3 days (7).



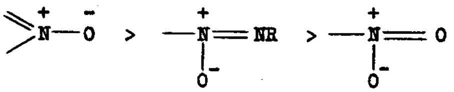
(II)



(III)

Reduction of pyridine *N*-oxide with diphenyl sulphoxide gave equimolar amounts of diphenyl sulphone and pyridine, as in scheme A. The lower yield (34%) would be anticipated on consideration of steric compression in the transition state leading to (I; R = Ph, X = pyridinium). Successful deoxygenation of a number of other *N*-oxides (2-picoline, 48%; 3-picoline, 87%; 4-picoline, 91%; 2,6-lutidine, 40%; 4-phenylpyridine, 92%; quinoline, 80%; quinaldine, 55%; isoquinoline, 95%) confirms the generality of the reaction. The contribution from thermal deoxygenation was < 4% in all cases except quinoline, quinaldine and isoquinoline *N*-oxides which produced 27%, 19% and 7% of the parent bases respectively.

Ortho-substituted *N*-oxides gave lower yields and this is interpreted as a steric rather than an electronic effect as 3- and 4-substituted *N*-oxides show little variation in yield. Only 9% of azobenzene was obtained from azoxybenzene and nitro compounds were inert under the reaction conditions. This implies the reactivity sequence



$$>\overset{+}{N}-\overset{-}{O} \;>\; -\underset{O^-}{\overset{+}{N}}=NR \;>\; -\underset{O^-}{\overset{+}{N}}=O$$

The method appears to be of potential value for deoxygenation of heterocyclic *N*-oxides (and other amine oxides) and should complement existing procedures (5).

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