Acid Catalyzed Reduction of Dihydrothiamine in Aqueous Dimethylsulfoxide

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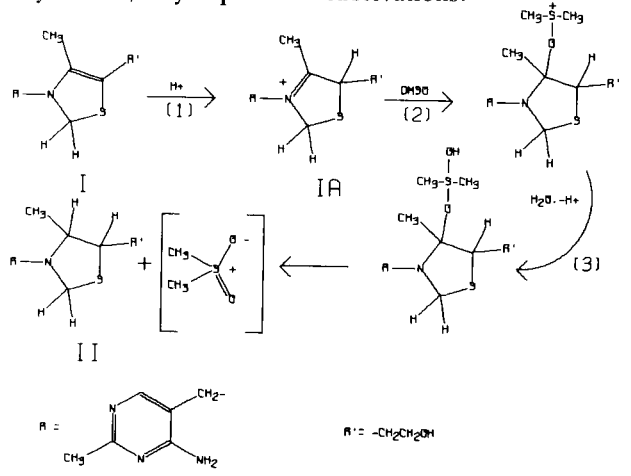
We have found that dihydrothiamine (I) is reduced to tetrahydrothiamine (II) in a medium of dimethylsulfoxide with a trace of mineral acid. Tetrahydrothiamine (88% conversion) was identified by its nuclear magnetic resonance spectrum and by isolation of the product and examination of its infrared spectrum and melting behavior.

The reaction rate is dependent on both dihydrothiamine and acid. We propose that the acid protonates carbon 5 of the thiazoline ring. This is supported by nuclear megnetic resonance studies of dihydrothiamine in tricloroacetic acid which show that carbon 5 can be readily protonated. This protonation is probably facilitated by the thiazoline nitrogen assuming a positive charge (Ia). The hydrogens from DMSO apparently do not become involved in any way in this reaction, which is as expected.

That we have observed the reduction of dihydrothiamine to tetrahydrothiamine seems clear. The logical question in this context is what is the nature of the reducing agent? Since much greater than 50% conversion is observed, disproportionation of dihydrothiamine to thiamine and tetrahydrothiamine is not possible. Therefore, the DMSO, aqueous hydrochloric acid components must be supplying the reducing power.

If DMSO is the reducing agent, some oxidized product of DMSO must be produced in the reaction mixture. It seems reasonable that dimethylsulfone would be the oxidation product, but since none is found, it must be further oxidized if produced or, perhaps more likely, an alternative oxidation product formed.

We suggest that the following mechanism, or something very similar, may explain our observations:



Nucleophilic attack on the protonated specie by DMSO could be followed by Step 3 which is reminiscent of DMSO disproportionation. The final intermediate might cleave with a concerted rearrangement of the dimethyl sulfone fragment to yield a methyl methylsulfinic ester. Under the conditions of reaction a sulfinic ester would probably be cleaved to yield the unstable sulfinic acid. This could account for the failure to identify directly an oxidation product.

Although it is not possible here to unequivocally assign a mechanism to this reaction, it seems clear that DMSO is serving as a reducing agent. Although DMSO is oxidized by several strong oxidizing agents, this is the first evidence of DMSO serving as a reducing agent in a simple organic reaction, *i.e.* DMSO smoothly converts dihydrothiamine, a 4-thiazoline, to a thiazolidine.

EXPERIMENTAL

Dihydro- and Tetrahydrothiamine.

Dihydrothiamine was prepared by the method of Karrer and Krishna (2) and found to have an infrared spectrum identical to that previously reported (3). The nmr spectrum of dihydrothiamine was consistent with the proposed structure (I) and was readily differentiated from the spectra of tetrahydrothiamine by the presence of a singlet at 1.58 δ (4) attributed to the 4-methyl of the thiazoline ring. Tetrahydrothiamine (3) has a characteristic doublet at 0.95 δ attributed to the methyl of the thiazolidine ring.

Reduction of Dihydrothiamine.

In a typical experiment 0.01 ml. aqueous 6 *N* hydrochloric acid was added to a solution of 21.7 mg. of dihydrothiamine in 0.50 ml. of DMSO at 39°. The production of tetrahydrothiamine was monitored *via* nuclear magnetic resonance of the reaction mixture or, alternatively, the disappearance of dihydrothiamine was measured by nuclear magnetic resonance or gas chromatography. The half life of dihydrothiamine was found to be 6.8 minutes. The nmr and infrared spectra of the product were identical to those obtained from authentic tetrahydrothiamine. Melting points and mixed m.p. 144° (uncorrected), reported, 145°.

Protons in the Reduction.

That the protons incorporated are from the aqueous hydrochloric acid has been demonstrated by showing that when the reaction is carried out in fully deuterated DMSO, no deuterons appear in the product, tetrahydrothiamine.

When the nuclear magnetic resonance of dihydrothiamine in trifluoroacetic acid is measured, a triplet is observed at 4.69 δ. This is probably due to the protonated 4-thiazoline ring (Ia). This

interpretation is supported by the absence of such a resonance in deuteriotrifluoroacetic acid. Such a protonation is roughly analogous to that observed with indole.

REFERENCES

(1) The instructions for the figure were generated on an IBM 7044 computer for the CalComp 750 plotter using subroutines CYCMOL and LINMOL. The routines CYCMOL and LINMOL were developed by H. Sorensen to allow rapid construction of molecular figures. Inquiries may be addressed to the authors. This work was supported by USPHS GM 8285 while H. Sorensen was an USPHS trainee.

(2) P. Karrer, H. Krishna, *Helv. Chim. Acta*, 33, 555 (1950).

(3) E. E. Bonvicino, D. J. Hennessy, *J. Am. Chem. Soc.*, 79, 6325 (1957).

(4) All nmr spectra were 60 Mc with tetramethylsilane as internal standard. The deuterated solvents were 99.5% isotopically pure.

(5) T. J. Wallace, J. J. Mahon, *Nature*, 201, 817 (1964).

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