Tetrahedron Letters No.6, pp. 441-444, 1970. Pergamon Press. Printed in Great Britain.

A NOVEL REACTION OF THIAMINE ANHYDRIDE

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(Received in Japan 6 November 1969; received in UK for publication 1 January 1970)

Although thiamine anhydride (I) is well known as a product resulting from thiamine and its derivatives by various reactions (1), no reports have yet appeared regarding its reactivity. Reported here (2) is the first example of a reaction of I, ring expansion by the action of hydrogen sulfide to give 1,2-dithiolane derivatives (IV).

In a previous communication (3), it was shown that thiamine sodium salt (II) reacted with carbon disulfide followed by the action of alkyl halide to give dithioalkoxycarbonylthiamine (III). Carbon oxysulfide, instead of carbon disulfide, was allowed to react with III in dimethyl formamide (DMF) and the compound IV was isolated in 22% yield. Compound IV, mp 144-147°, has the molecular formula $C_{12}H_{18}ON_4S_2$, i.e., H_2S more than I. Therefore, I was allowed to react with hydrogen sulfide in DMF for 5 days at room temperature and the same product, IV, was obtained in 91% yield. This reaction period could be shortened by the addition of piperidine, but with the addition of p-toluenesulfonic acid no reaction occurred and I was recovered.

The UV spectrum of IV in EtOH gives absorption bands at 237, 278, and 330 mμ (log ε 3.94, 3.72, 2.60). The NMR spectrum (4) of IV suggests the presence of a CH_3-CH< system (τ 8.63, 3H-doublet, J = 6.5 Hz) and a 1,2-dithiolane ring, showing a similar pattern to lipoic acid; in addition to 2-methyl-4-amino-pyrimidinomethyl group (pyrimidine 2-CH_3, 7.53, 3H-singlet; bridged methylene, 5.17, 5.42, 5.70, 5.95, AB quartet; amino, 3.90, deuterium exchangeable 2H-broad singlet; N-CHO, pyrimidine C_6-H, 1.90, 1.70, 1H-singlets).

The mass spectrum (5) of IV exhibits significant peaks at m/e values of 105, 122, 133, and 193 in addition to the molecular ion peak (298). $NaBH_4$ reduction of IV followed by the action of benzyl chloride afforded S,S'-dibenzylsulfide (V) as an oil (NMR: 2 x ϕCH_2: 6.42, 6.35 2H-singlets; $C_{26}H_{32}ON_4S_2$; m/e (M^+) 480).

The above observations suggest the structure 2-methyl-4-amino-5-{N-formyl-N-[1-(1,2-dithiolan-3-yl)ethyl]aminomethyl}pyrimidine for the compound IV. In an attempt to clarify the reaction mechanism, reaction of deuterium sulfide, instead of hydrogen sulfide, with I in DMF was carried out. The compound VI, mp 138-139°, was obtained in a good yield and a comparison of the NMR spectra of IV and VI indicates the following differences: the 3H-doublet at τ 8.63 changed into a 3H-singlet at τ 8.67, indicating a CH_3-CD<

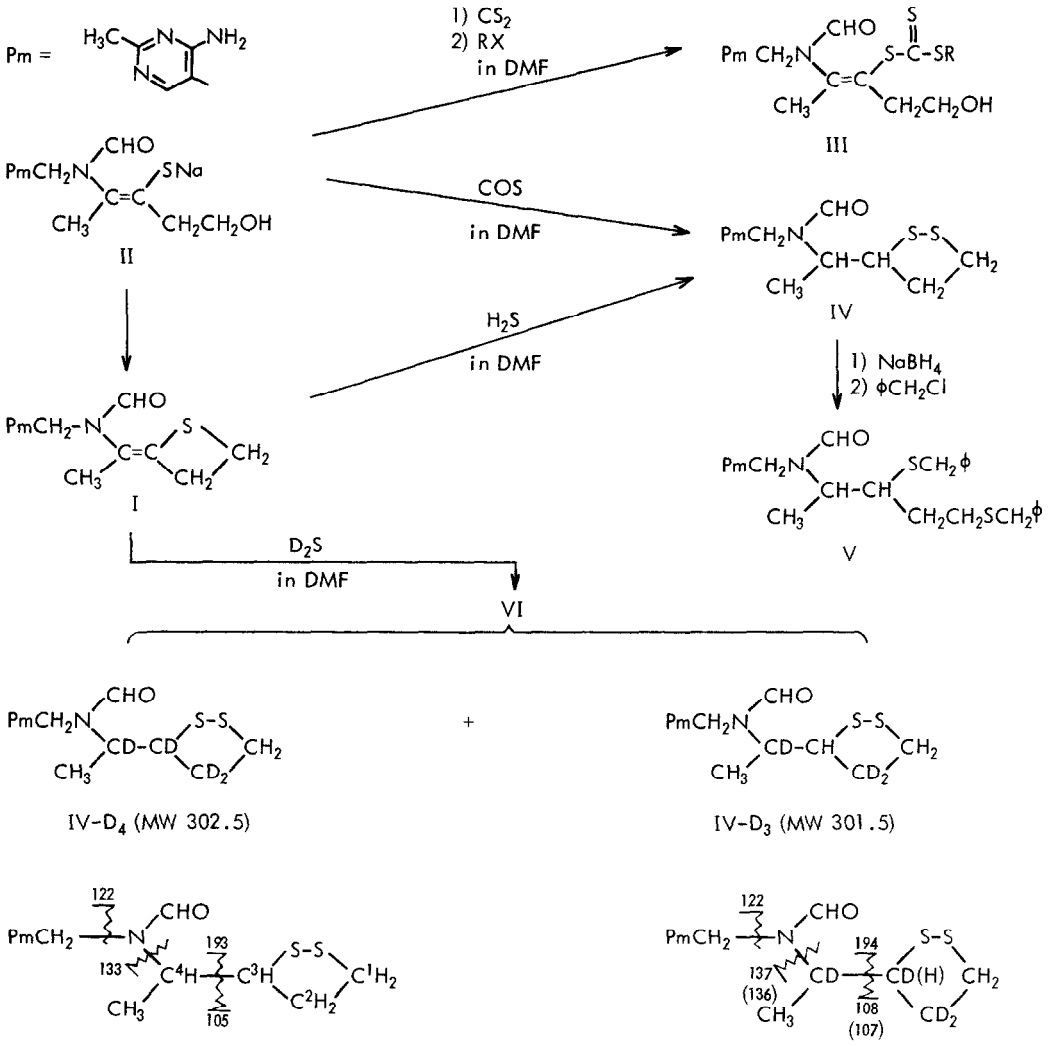


Chart 1

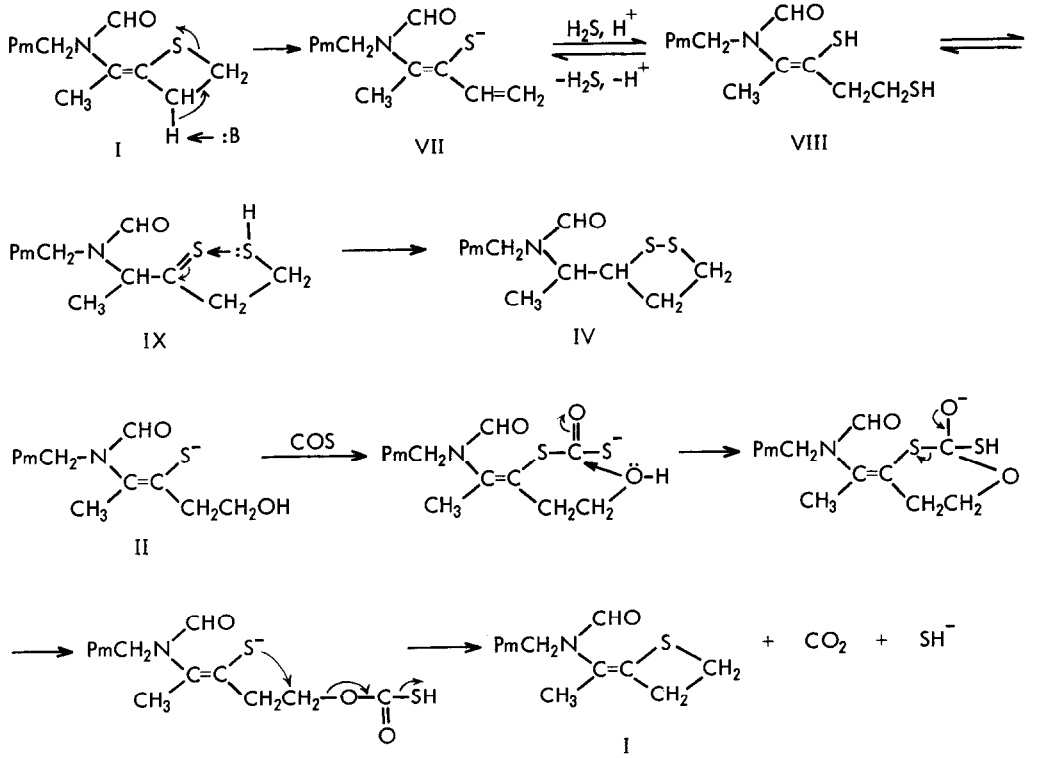
system; the 2H-multiplet around τ8.0, due to C-2 methylene, disappeared; the 2H-multiplet centered at τ 6.82, due to C-1 methylene, changed into a broad 2H-singlet at τ 6.87; and the 2H-multiplet centered at τ 6.35, due to C-3 and C-4 methines, changed into a broad 0.5H-singlet at τ 6.35.

These facts suggest that the hydrogens at C-2 and C-4 positions were exchanged by deuteriums and that the hydrogen at C-3 position was half deuterated.

Thus, compound VI was found to be a 1 : 1 mixture of IV-D_3 (three deuteriums incorporated) and IV-D_4 (four deuteriums incorporated).

The mass spectrum of VI strongly supports the structure. The molecular ion peaks appeared at m/e values of 301 and 302 corresponding to IV-D_3 and IV-D_4 in about 1 : 1 ratio. Formation of other fragments at m/e values of 194, 135, 122, 108, and 107 can be rationalized as indicated at the bottom of Chart 1.

A reasonable mechanism that accounts for all the above data proposed in Chart 2 (6).



I VII VIII IX IV II I

Chart 2

Base-induced elimination-addition reaction gives the ene-thiol (VIII) and the attack of thiol to the tautomeric thioketone (IX) affords the ring expanded product IV. The course from II also proceeds through I as shown in Chart 2.

Acknowledgement. The authors are grateful to Dr. K. Takeda, Director of this laboratory, for his encouragement and also to Dr. K. Tori for NMR spectra and to Dr. Y. Nakagawa for mass spectra measurements.

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2. C, H, N, S-Analyses of all new compounds are consistent with their proposed formulations.
3. A. Takamizawa, K. Hirai, and T. Ishiba, Chem. Pharm. Bull. (Tokyo), 17, 2299 (1969).
4. NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ containing TMS as an internal reference. Chemical shifts are given as τ values.
5. Mass spectra were taken with a Hitachi RMU-6E mass spectrometer using direct inlet system with the ionizing energy at 70 eV and the ionizing current at 80 μA.
6. Half deuteration of C-3-H might be due to half hydrogen exchange at the acidic C-3 position on H_2O treatment after the deuteration reaction.