Tetrahedron Letters No.55, pp. 5767-5770, 1968. Pergamon Press. Printed in Great Britain.

A NEW SYNTHESIS OF 2-METHYL-3-HYDROXYPYRIDINE-4,5-DICARBOXALDEHYDE

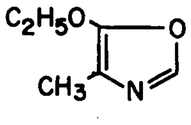
Takeo Naito, Katsujiro Ueno, Mitsuji Sano, Yoshiaki Omura,
Isao Itoh and Fumiyoshi Ishikawa
Central Research Laboratory, Daiichi Seiyaku Co., Ltd.
Tokyo, Japan

(Received in Japan 30 September 1968; received in UK for publication 10 October 1968)

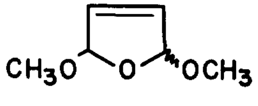
Several synthetic routes to pyridoxine and its derivatives by the Diels-Alder reaction of oxazoles have been described.[1)] We now report a new method of preparing a pyridoxine analog, 2-methyl-3-hydroxypyridine-4,5-dicarboxaldehyde (V) by the Diels-Alder reaction of 4-methyl-5-ethoxyoxazole (I) with 2,5-dimethoxy-2,5-dihydrofuran (II), and the stereochemistry of the compounds obtained is discussed.

Heating oxazole (I)[2)] and excess <u>cis</u>-2,5-dimethoxy-2,5-dihydrofuran (IIa)[3)] at 100° for 20 hours furnished a mixture of two adducts, IIIa, mp. 115° and IIIb, mp. 75° (ratio 2 : 1) in high yield. Treatment of IIIa or IIIb with hot methanolic potassium hydroxide solution for several hours caused the cleavage of the oxygen bridge of the adduct and the loss of a molecule of ethanol, providing quantitatively dimethoxypyridinol (IVa), mp. 165°, which exhibited a positive Gibbs color reaction and a UV absorption maximum at 289 mμ (0.1N HCl) similar to that of pyridoxine.

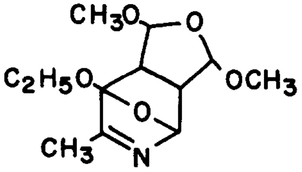
The reaction of I and excess <u>trans</u>-2,5-dimethoxy-2,5-dihydrofuran (IIb)[3)] proceeded about 5 times slower than the <u>cis</u>-isomer (IIa) and gave a mixture of two adducts IIIc and IIId (ratio 2 : 1), which were difficult to isolate in a pure state. Treatment of the mixture with base afforded dimethoxypyridinol (IVb), mp. 134°, which was isomeric to the compound (IVa) obtained above. Hydrolysis of IVa or IVb in hot 10% hydrochloric acid for ten minutes quantitatively gave rise to the same dialdehyde (V). Both the hydrochloride, mp. 158-160° (decomp.), and the free base, mp. 150-160° (partial decomp.), of V in the solid state showed no absorption band characteristic of carbonyl group and its UV absorption maximum (288 mμ in 0.1N HCl) was similar to those of pyridoxine and pyridoxal, which indicated the cyclic monohydrate structure (Va) and/or (Vb). When this work was in progress, synthesis of V by the reaction of 4-methyl-5-alkoxyoxazole and 2,5-dialkoxy-2,5-dihydrofuran followed by the acid hydrolysis of the resultant adduct was reported.4) Other syntheses of V have also been described recently.5,6)



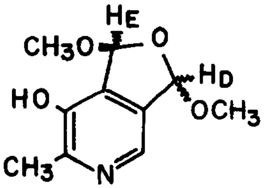
(I)



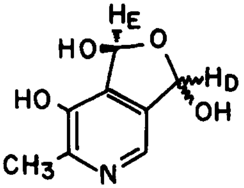
(IIa) = cis
(IIb) = trans



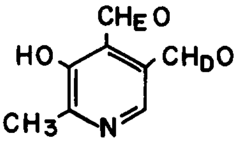
(IIIa-d)



(IVa) = cis
(IVb) = trans



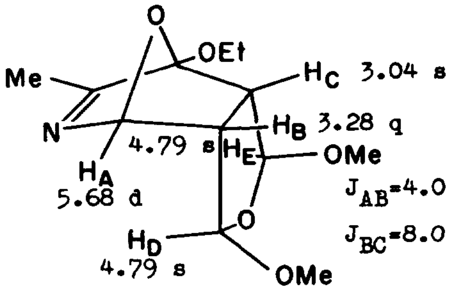
(Va) = cis
(Vb) = trans



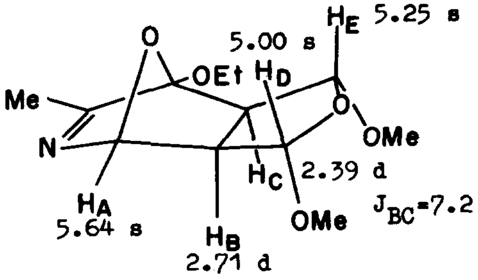
(Vc)

The stereochemistry of the compounds III, IV and V was studied by NMR spectroscopy. The coupling (4.0 cps) between the H_A and H_B protons of IIIa and IIIc indicated them to be endo adducts, whereas no split was observed in the signals of the H_A protons of IIIb and IIId showing them exo adducts.

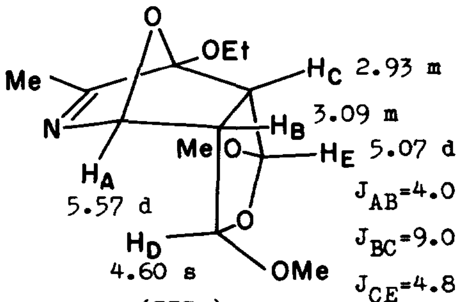
The orientation of the methoxy group on the tetrahydrofuran ring was determined based on the observation whether the coupling was present between the vicinal protons H_B and H_D or H_C and H_E. Since all the protons H_D and H_E of IIIa and IIIb appeared as singlets, the methoxy groups were found to be all in the cis to the vicinal protons H_B or H_C. Instead, the appearance of coupling (4.8 cps) in the H_E proton signal of IIIc clearly showed that the H_C and its vicinal methoxy group were in the trans-configuration. The split was again observed in the H_D proton signal of IIId. In this manner the structures of all the adducts were determined as shown in the following formulae.



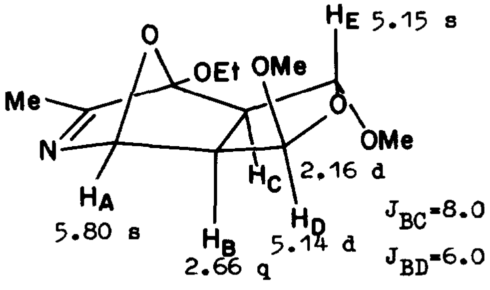
(IIIa)



(IIIb)



(IIIc)



(IIId)

(Chemical shifts are indicated by ppm from TMS.)

The cis-trans isomerism of the dimethoxypyridinols (IVa) and (IVb) was confirmed by the assignment of the methine protons H_D and H_E on the dihydrofuran ring of the molecules, because the signals of the methine protons of the trans-configuration should be expected to appear at a lower magnetic field than the cis-configuration as a result of dispersion force.[7,8)

NMR spectrum of the hydrochloride of V indicated that the compound exists almost entirely as a mixture of cis- (Va) and trans-isomer (Vb) in D_2O, for reasons of appearance of two pairs of the protons in methine region, but the aldehyde form (Vc) was present along with the isomeric mixture of Va and Vb in DMSO-d_6. The equilibrium position among Va, Vb and Vc appeared to be dependent on the concentration of water in solvent, temperature and pH, as well as solvent and concentration. Those observations were also supported by the investigation of UV absorption of V in various media.

Small spin couplings were found between the methin protons H_D and H_E of trans-isomer of IV and V, and the similar coupling constant between two methine protons of trans-isomer of II was reported by C. Barbier et al.[9] after this work had been finished. These results are summarized in Table I.

Table I

Chemical Shifts and Coupling Constants of Methine Protons of IV and V in DMSO-d_6 (60°) at 100 MHz.

	H_D	H_E	J_{DE}
IVa	6.005 s	6.072 s	0
IVb	6.320 d	6.341 d	2.1
Va	6.252 s	6.410 s	0
Vb	6.533 d	6.658 d	1.8
Vc	10.218 s	10.629 s	0

Chemical shifts are indicated by ppm from TMS, and coupling constants by cps.

The authors would like to express their gratitude to Dr. T. Ishiguro, President, Dr. K. Miyatake, General Manager of Research and Development Division and Dr. M. Shimizu, Director of this laboratory for their unfailing encouragement.

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