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A NOVEL ACETYL MIGRATION REACTION FROM OXYGEN TO OXYGEN IN A PYRIDOXINE DERIVATIVE PROMOTED BY METAL IONS

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2'-Acetoxy-3-acetyl-4',5'-O-isopropylidenepyridoxine (I) was specifically converted to 2'-acetoxy-4'-acetylpyridoxine (III) in acetone in the presence of metal ions such as zinc, copper(II), iron(III), and aluminium in varying degree. Of these catalysts ferric ion was the most effective to complete the migration reaction. In the other pyridoxine analogues, no migration reaction was induced by these catalysts.

The investigations concerning the weak interaction of organic compounds with metal ions in relation to understanding biological reactions have increasingly received much attention.$^{1)}$ Our recent findings with respect to new reactions catalyzed by cupric ion$^{2,3)}$ prompted further studies along the same line. One of such attempts was applied to pyridoxine derivatives with particular expectation of the conversion of 2'-acetoxy-3-acetyl-4',5'-O-isopropylidenepyridoxine (I), which was synthesized in three steps from pyridoxine hydrochloride for the purpose of modification of C_2 and C_5 substituents of pyridoxine, to the corresponding 3,4'-O-isopropylidene isomer (II) by copper(II) catalyst in acetone.$^{4)}$ Unexpectedly, however, a novel acetyl migration reaction was found in which I was converted to 2'-acetoxy-4'-acetylpyridoxine (III). Thus we briefly describe here the characteristics of the new reaction.

When 3.34 mmol of I was stirred with 1.5 equivalent mole of cupric chloride dihydrate in 30 ml of dry acetone at room temperature for 70 hr, III was obtained in a 23% yield after usual workup followed by column-chromatographic separation using silica gel (solvent: $CHCl_3$-MeOH, 9 : 1 v/v). The structure of III was supported by its spectral data [a pale brown liquid; MS, m/e 269(parent); ir(neat), 1735cm^{-1}; nmr($CDCl_3$), δ 2.10(s, $-CO\underline{CH_3}$), 2.15(s, $-CO\underline{CH_3}$), 4.78(s, $C_5-\underline{CH_2}$), 5.27(s, $C_4-\underline{CH_2}$), 5.33(s, $C_2-\underline{CH_2}$), and 8.20(s, C_6-H)] and was further chemically confirmed by converting III into 2'-hydroxy-2',3-O-isopropylidenepyridoxine (IV); namely, when 0.85 g of III in 20 ml of dry acetone was stirred with 1.22 g of p-toluenesulfonic acid monohydrate at room temperature for two days, 0.16 g of IV was obtained after usual workup [mp 101-3°C(colorless crystals); MS, m/e 225(parent); nmr($CDCl_3$), 1.53(s, $C(\underline{CH_3})_2$), 3.28(s, $-CH_2\underline{OH}$), 4.93(s, $C_2-\underline{CH_2}$), 4.65 and 4.59(s, C_4- and $C_5-\underline{CH_2}$), and 7.96(s, C_6-H)]. Since 2'-hydroxy-3,4'-O-isopropylidenepyridoxine or 2'-acetoxy-5'-acetyl-3,4'-O-isopropylidenepyridoxine would be predominantly produced over the other acetonides under these conditions if the hydroxyl groups at C_3 and $C_{4'}$ were free,$^{5)}$ the formation of IV supported that the migrated acetyl group resided at $C_{4'}$ but not at $C_{5'}$.

The acetyl migration reaction of I was also induced by metal ions such as zinc(yield, 10%, reaction time, 30 hr), zinc-copper(II)(1 : 1)(37%, 42 hr), aluminium(15%, 51 hr), and iron(III)(80%, 22 hr) which were selected in consideration of the Irving-Williams order or in comparison with the Fries rearrangement catalyst. On the other hand, in order to examine the generality of the reaction, the structurally similar compounds to I such as II and V through VIII were synthesized from pyridoxine hydrochloride,$^{6)}$ and treated with each of those metal ions under similar conditions to those of I. However, no acetyl migration occurred and the starting materials were recovered. Thus it seems reasonable to consider that the deacetalization accompanying the intramolecular acetyl migration is characteristic for the compound I.

Although little attempts to elucidate the reaction mechanism of this acetyl migration have been done, some speculation about it is possible on the basis of the results obtained. The fact that the reaction was not induced when the compound was lacking in an acetoxyl group at $C_{2'}$ and/or in phenolic acetate suggests that metal ion crucially participates in the catalytic mechanism by forming a transient metal complex with $C_{2'}$-acetoxyl group and/or phenolic oxygen. Additionally, there is likely to exist the best fit site of metal ion suitable for catalysis because the reaction yield depends on kinds of metal ions.

The newly found acetyl migration reaction from phenolic oxygen to primary alcoholic oxygen is of interest in the following points of view; (a) the products III and IV which are unlikely to be accessible by usual means are to become new synthetic intermediates to modify pyridoxine, (b) in relation to biological reactions, the reaction assisted by metal ion might provide a clue to elucidate the role of metal ion in the catalytic mechanism of hydrolytic enzymes, and (c) the compound I would function as an acetyl-carrier if there coexists a suitable acceptor in the reaction system. Related works to those are in progress.

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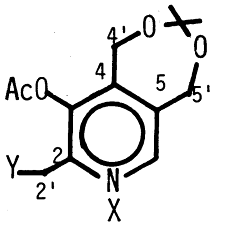

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V X = none Y = H
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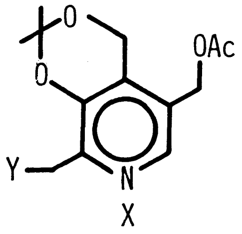

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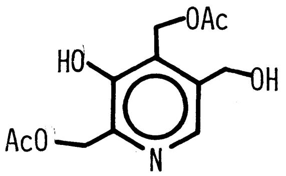
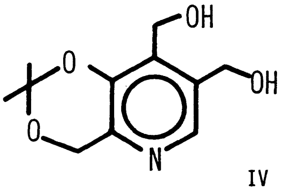
VIII X = O Y = H



III



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References and Notes

1) See, for example; "Inorganic Biochemistry," Vol. 1, ed. by G. L. Eichhorn, Elsevier, Amsterdam, (1973), part IV.
2) M. Iwata and S. Emoto, Chem. Lett., 1974, 759.
3) M. Iwata and S. Emoto, ibid., 1974, 959.
4) The possibility of this conversion was suggested by the equilibrium between six and seven membered acetonides under dry acidic conditions; W. Korytnyk, J. Org. Chem., 27, 3724 (1962).
5) The mp of 2'-hydroxy-3,4'-O-isopropylidenepyridoxine was 119-22°C in our unpublished data and 110°C in the report; W. Korytnyk, S. C. Srivastava, N. Angelino, P. G. G. Potti, and B. Paul, J. Med.Chem., 16, 1096 (1973), where the mp of the corresponding 4',5'-O-isopropylidene isomer has been also shown to be 149-151°C.
6) All the synthesized compounds were characterized by their physical data which will be detailed elsewhere, and see also; W. Korytnyk and W. Wiedeman, J. Chem. Soc., 1962, 2531.

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