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A NEW SYNTHESIS OF VITAMIN B_6 GROUP

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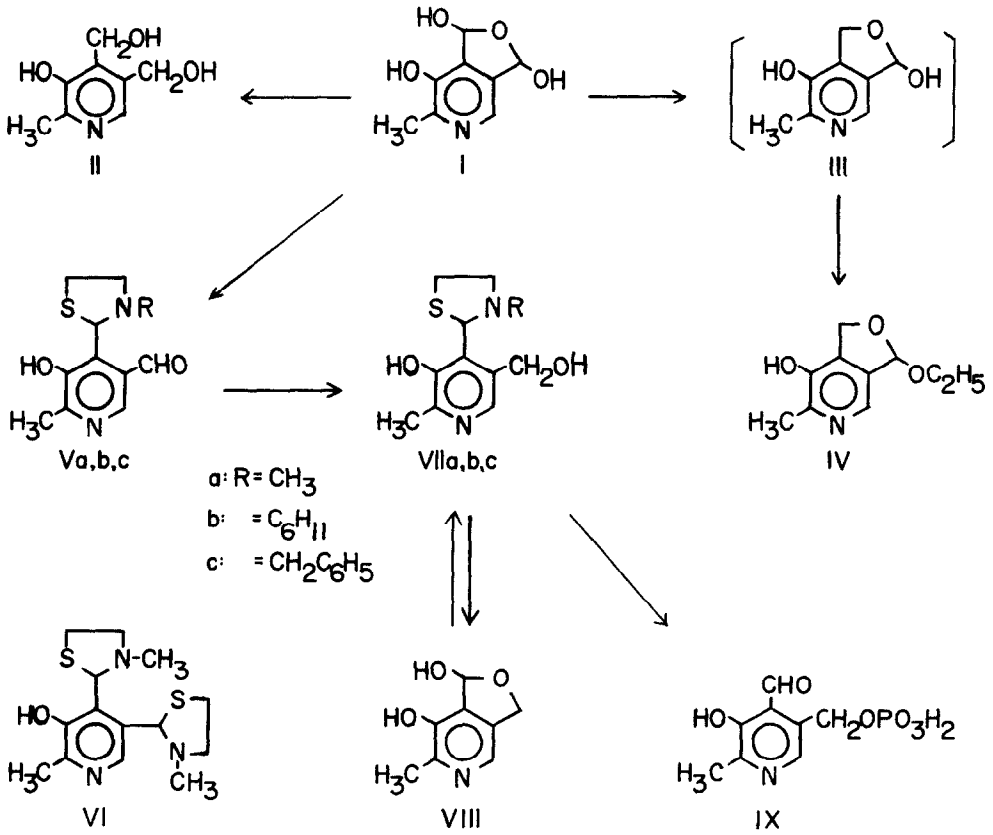
In the preceding paper[1] a new method of preparing 2-methyl-3-hydroxypyridine-4,5-dicarboxaldehyde (I)[2] by the Diels-Alder reaction of 4-methyl-5-ethoxyoxazole and 2,5-dimethoxy-2,5-dihydrofuran was described. We now report a novel synthesis of several members of the vitamin B_6 group by transformation of the two neighboring formyl groups involved in the compound (I).

Reduction of I with sodium borohydride or with zinc in aqueous acetic acid and usual work-up almost quantitatively gave pyridoxine (II) hydrochloride, m.p. 205° (decomp.). Meerwein-Ponndorf reduction of I, however, using excess aluminum isopropoxide in refluxing isopropanol and subsequent treatment of the reaction mixture with ethanolic hydrochloric acid unexpectedly afforded in more than 90% yield isopyridoxal ethyl hemiacetal (IV) hydrochloride, which was identical in all respects with a sample of IV prepared by a standard method.[3] In this reaction neither pyridoxine (II) nor pyridoxal (VIII) was formed as indicated by paper chromatography. This fact shows that aluminum isopropoxide exclusively attacks the 4-formyl group of I to form aluminum isopropoxide complex which in turn exerts a steric hindrance upon the other 5-formyl group. The specific difference in reactivity between the two formyl groups shoud be ascribed to activation of the 4-formyl, more electrophilic in itself than the 5-formyl, by the vicinal phenolic hydroxyl group. The analogous vicinal effect has been observed in the reaction of 5-methoxy-6-hydroxyisophthalaldehyde with nucleophiles.[4]

The notable difference in reactivity found between the two formyl groups

of I prompted us to prepare the active form of vitamin B_6, pyridoxal 5-phosphate, by a new method which comprises protecting the 4-formyl group of I, reducing the 5-formyl to a hydroxymethyl group, phosphorylating the hydroxymethyl and cleaving the protecting group at the 4-position. For the selective protection of 4-formyl group, a thiazolidine ring formation by reaction of I with 2-aminoethanethiol and its N-substituted derivatives in equimolar amounts was examined.



Reaction of I and 2-aminoethanethiol gave a resinous product. 2-Methylaminoethanethiol, however, when warmed with I in aqueous methanol, gave monothiazolidine (Va), m.p. 134-135°, and bisthiazolidine (VI), m.p. 143-144°, in 55 and 10% yields, respectively. Sodium borohydride reduction of Va afforded a hydroxymethyl compound, m.p. 163-165°, which was identical with pyridoxal N-methylthiazolidine (VIIa) prepared by reaction of pyridoxal (VIII)

and 2-methylaminoethanethiol. This result suggested us to employ a 2-aminoethanethiol derivative possessing a bulky substituent on the nitrogen atom, since such a derivative would provide at the 4-position of I a thiazolidine so voluminous as to keep the 5-formyl group intact owing to the steric hindrance.

2-Cyclohexylaminoethanethiol, when reacted with I in aqueous methanol, afforded in high yield only a monothiazolidine (Vb), m.p. 108-109°, which was quantitatively converted with sodium borohydride to pyridoxal N-cyclohexylthiazolidine (VIIb), m.p. 199-200°, identical with a sample prepared from pyridoxal and 2-cyclohexylaminoethanethiol. This clearly shows that the aminoethanethiol derivative selectively attacked the 4-formyl group of I. The same result was also obtained with 2-benzylaminoethanethiol.

Pyridoxal thiazolidines VIIb and VIIc were phosphorylated without difficulty on gentle heating with polyphosphoric acid. Treatment of the phosphorylation mixture with hot water hydrolyzed polyphosphoric ester group, subsequent treatment of the mixture with excess sodium hydroxide solution at room temperature caused the cleavage of the thiazolidine ring, and then purification on Amberlite CG-50 gave pyridoxal 5-phosphate (IX) in more than 60% yield.

Pyridoxal thiazolidine (VIIb) also underwent ring cleavage on treatment with dilute sodium hydroxide solution and purification on Amberlite CG-50 provided pyridoxal (VIII) in 95% yield.

As can be seen from the results presented above, protection of the 4-formyl group of I by a thiazolidine ring formation has proved to be a useful tool in transforming I into pyridoxal (VIII) and its 5-phosphate (IX), since the ring is stable in the reduction and phosphorylation reactions and is easily hydrolyzable to regenerate the 4-formyl group.[5)]

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Reference

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2. The compound (I) in general has a cyclic monohydrate structure shown in the Chart.
3. W. Korytnyk, E. J. Kris and R. P. Singh, J. Org. Chem., 29, 574 (1964).
4. E. Profft and K. Stuehmer, Arch. Pharm., 300, 1 (1967).
5. For thiazolidine derivatives of vitamin B_6, Heyl, Harris and Folkers (J. Am. Chem. Soc., 70, 3429 (1948)) prepared them by the reaction of pyridoxal with cysteine and penicillamine, and Buell and Hansen (J. Am. Chem. Soc., 82, 6042 (1960)) studied spectroscopically thiazolidine ring formation in aqueous solution containing pyridoxal 5-phosphate and several N-unsubstituted 2-aminoethanethiol derivatives.