VITAMIN B_6 ANALOGS

IX.* SYNTHESIS OF 5'-DEOXY- AND 5'-O-METHYL ANALOGS

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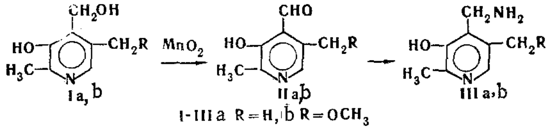
A method has been developed for the synthesis of 5'-deoxy- and 5'-O-methylpyridoxal by oxidation of the 4-hydroxymethyl group of the corresponding diols. Reduction of the oximes of the aldehydes obtained leads to 5'-substituted analogs of pyridoxamine.

Pyridoxal (P) and pyridoxamine (PA) analogs in which the free hydroxyl group in the 5-position of the pyridine ring is absent are of substantial interest both for the study of paths for the biosynthesis of pyridoxal-5'-phosphate and for elucidation of the mechanism of catalytic transformations of amino acids in model systems. There are several publications in which the synthesis of one of these analogs, viz., 5'-deoxy P, is reported [1-3]. All of these methods are based on the oxidation of 5'-deoxypyridoxine. The low yield of the aldehyde is apparently explained by the unfortunate conditions selected for the oxidation and by difficulties arising during its isolation in pure form.

In this communication we describe a convenient method for the synthesis and isolation of 5'-deoxy P (IIa), 5'-O-methyl P (IIb), and the corresponding amines (IIIa-b):



I-IIIa R=H, b R=OCH_3

For the synthesis of the P analog we used the method of oxidation of the diols with manganese dioxide previously worked out in [4]. The aldehydes obtained (II) were isolated from the reaction mixture either as Schiff bases with p-phenetidine or as bisulfite derivatives. Chromatography of the Schiff bases on a sulfo resin and elution with 1 N hydrochloric acid give hydrochlorides IIa and b in good yields (Table 1). Acid hydrolysis of the bisulfite derivatives also leads to hydrochlorides of the aldehydes. The yields of final reaction products, which are somewhat less than those obtained by the first method, are compensated for by the extreme simplicity of the experiment and the small time expenditure.

The PMR spectra of the aldehydes obtained are as follows (δ, ppm): 5'-deoxy P (base in $CDCl_3$), 2-CH_3, 2.50; 6-H, 7.90; 5-CH_3, 2.44; 4'-H, 10.33; 3-OH, 11.27; Schiff base of 5'-O-methyl P with p-phenetidine (in deuteropyridine), 2-CH_3, 2.56; 6-H, 8.31; 5-CH_2, 5.01; 5-OCH_3, 3.21; 4'-H, 9.43; C_6H_4, 6.91 and 7.25; OC_2H_5, 1.15 and 3.83.

To obtain the pyridoxamine analogs (III), the aldehydes were converted to the oximes, the catalytic hydrogenation of which proceeds with almost quantitative yields.

The synthesized compounds were characterized by their UV spectra, the data of which are presented in Table 2.

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*See [4] for communication VIII.

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TABLE 1. 5-Substituted Analogs of Pyridoxal and Pyridoxamine

Compound	Name	Prep. method	mp	mp of oximes	Empirical formula	Found, %		Calc., %		Yield, % (for diol)
						C	H	C	H	
IIa	5'-Deoxypyridoxal, hydrochloride	A* B	108—110†	237—240 (decomp)						64 54
IIb	5'-Deoxypyridoxamine, dihydrochloride	C	259—261‡ (decomp)							62
IIIa	5'-O-Methylpyridoxal, hydrochloride	A B	144—145 (decomp)	197—199 (decomp)	$C_9H_{12}ClNO_3$	49,91	5,27	49,66	5,56	50 39
IIIb	5'-O-Methylpyridoxamine, dihydrochloride	C	233—235 (decomp)		$C_9H_{18}Cl_2N_2O_2$	44,75	6,91	44,61	6,74	57

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*See Experimental section.

†Base (mp 111.5-113° [3]).

‡mp 262-263° (decomp.) [8].

TABLE 2. UV Spectra of 5-Substituted Analogs of P and PA

Compound	λ_{max} ($\varepsilon \cdot 10^{-3}$)		
	0,1 *N* HCl	pH 7	0,1 *N* KOH
5'-Deoxy P	295 (6,4) 342 (1,9)	309 (2,9) 381 (4,3)	390 (6,2)
5'-O-Methyl P	297 (7,7) 341 (1,95)	305 (3,95) 388 (2,35)	302 (2,1) 393 (7,05)
5'-Deoxy PA	294 (8,4)	253 (3,9) 331 (7,6)	248 (6,4) 312 (6,1)
5'-O-Methyl PA	297 (8,2)	254 (3,6) 333 (7,7)	249 (6,5) 314 (6,3)

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EXPERIMENTAL

The UV spectra were obtained with a JOAN spectrometer (France), while the PMR spectra were obtained with a JEOL JNM-H-100 spectrometer (Japan). 5'-Deoxypyridoxine (Ia) and 5-O-methylpyridoxine (Ib) were obtained by the methods described in [5, 6], respectively.

Pyridoxal Analogs. "B" grade MnO_2 [7] was added to a solution of 3 mmoles of the hydrochloride of diol Ia or Ib in 10 ml of 0.3 M H_2SO_4, and the mixture was stirred at room temperature for 4 h. The aldehydes were isolated by the following methods.

A. The aldehydes were isolated as Schiff bases with p-phenetidine and hydrolysis of the latter via the method we described in [4].

B. A stream of SO_2 was bubbled for 20 min into the mixture obtained after oxidation of the diols. The mass was held for 1 h in a refrigerator, and the resulting crystals were filtered, washed with water, and dried. A suspension of 0.23 g of the bisulfite derivative in 20 ml of 2 N HCl was heated for 1 h at 80°, and the mixture was evaporated to dryness in vacuo. The residue was stirred with dry acetone and filtered.

Pyridoxamine Analogs. C. A total of 150 mg of 5% Pd/C was added to a solution of 1 mmole of the oxime in 20 ml of water and 0.5 ml of concentrated HCl, and the compound was hydrogenated at atmospheric pressure and room temperature. The theoretical volume of hydrogen was absorbed in 35-40 min. The catalyst was removed by filtration and washed with water. The filtrates were evaporated to dryness in vacuo. The products were recrystallized from alcohol−ether.

LITERATURE CITED

1. D. Heyl, S. A. Harris, and K. Folkers, J. Am. Chem. Soc., 75, 653 (1953).
2. T. Kuroda, Vitamin, 29, 116 (1964).
3. P. F. Muhlradt and E. E. Snell, J. Med. Chem., 10, 129 (1967).
4. N. A. Drobinskaya, L. V. Ionova, M. Ya. Karpeiskii, and V. L. Florent'ev, Khim. Geterotsikl. Soedin., 356 (1971).
5. W. Korytnyk, B. Paul, A. Bloch, and C. A. Nichol, J. Med. Chem., 10, 345 (1967).
6. U. Schmidt and G. Giesselmann, Ann. Chemie, 657, 162 (1962).
7. M. Harnfest, A. Bavely, and W. A. Lazier, J. Org. Chem., 19, 1608 (1954).
8. T. Naito and K. Ueno, Yakugaku Zasshi, 79, 1277 (1959).