ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 8, pp. 1266–1268. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © N.V. Shtyrlin, A.D. Strel'nik, L.P. Sysoeva, O.A. Lodochnikova, E.N. Klimovitskii, Yu.G. Shtyrlin, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 8, pp. 1274–1275.

SHORT COMMUNICATIONS

New Synthetic Method for 2,3,4-Tris(hydroxymethyl)- 6-methylpyridin-5-ol

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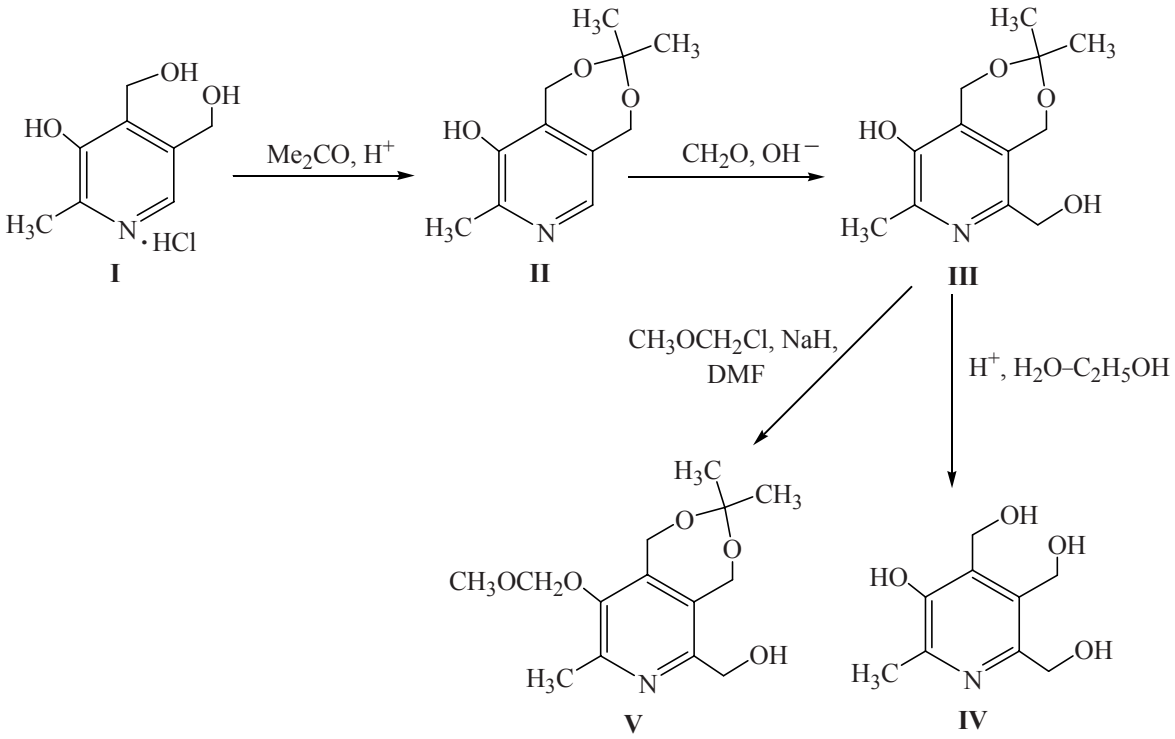
Received October 16, 2008

DOI: 10.1134/S1070428009080314

Vitamin B_6 and its derivatives are included into the composition of over fifty enzymes taking part in the biosynthesis of amino acids, in the metabolism of carbohydrates, fatty acids, and membrane unsaturated lipids. The pyridoxine, pyridoxal, and pyridoxamine derivatives also attract close attention because of their pharmacological and biological action [1–3]. In this study we developed a new method of the synthesis of pyridoxine **IV** hydroxymethylated in the position *6*.

The previously reported five-stage synthesis of compound **IV** [4, 5] involving preliminary formation of the pyridine ring with its subsequent functionalization is relatively labor-consuming and is not sufficiently effective (the yield of the target product does not exceed 18%). The newly developed preparation procedure includes three stages: the acetonide protection of hydroxymethyl groups in the positions *4*, *5* of pyridoxine, the hydroxymethylation of the seven-membered cyclic pyridoxine



ketal **II** in alkaline medium, and the subsequent removal of the protection in the acid medium. In contrast to the former method our procedure contains less stages, they are simple, the substrate and reagents are available, and the target product **IV** is obtained in an overall yield 47%.

Acetonide **V** alkylated with the methyl chloromethyl ether at the phenol hydroxy group was subjected to XRD analysis that demonstrate the twist form of the seven-membered ring. The bond distances, bond and torsion angles were virtually identical to the corresponding values in the pyridoxine acetonide [6].

3,3,8-Trimethyl-1,5-dihydro[1,3]dioxepino-[5,6-*c*]pyridin-9-ol (II). Through a suspension in 300 ml of acetone of 20 g (96 mmol) of commercial pyridoxine hydrochloride (**I**) dried in a vacuum of a water-jet pump at cooling to 3–5°C while stirring was passed 22 g (603 mmol) of hydrogen chloride. The reaction mixture was stirred for 5 h, maintained for 20 h at room temperature, then the precipitate was filtered off, washed with ether, and neutralized with 25% water solution of K_2CO_3. The precipitate was filtered off, dried in air, and recrystallized from ethanol. Yield 17.9 g (87%), mp 184.5–186°C (184–185°C [7]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.44 s (6H, $2CH_3$), 2.38 s (3H, CH_3), 4.74 s (2H, CH_2), 4.86 s (2H, CH_2), 7.75 s (1H, CH)

6-Hydroxymethyl-3,3,8-trimethyl-1,5-dihydro-[1,3]dioxepino[5,6-*c*]pyridin-9-ol (III). A mixture of 7 g (33 mmol) of compound **II**, 2.15 g (54 mmol) of NaOH, and 4.7 g (58 mmol) 37% water solution of formaldehyde in 50 ml of water was heated for 60 h at 70°C. On cooling the reaction mixture was neutralized with concn. HCl, the tarry precipitate was separated, water was distilled off in a vacuum. The reaction product was extracted from the precipitate with ethanol, the solvent was distilled off in a vacuum, the residue was washed with acetone. Yield 6.4 g (80%), light-yellow crystals, mp 161–163°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.41 s (6H, $2CH_3$), 2.32 s (3H, CH_3), 4.41 s (2H, CH_2), 4.80 s (2H, CH_2), 4.82 s (2H, CH_2). Found, %: C 60.15; H 7.10; N 5.90. $C_{12}H_{17}NO_4$. Calculated, %: C 60.24; H 7.16; N 5.85.

2,3,4-Tris(hydroxymethyl)-6-methylpyridin-5-ol (IV). In a mixture of 40 ml of ethanol and 2.5 ml (24.7 mmol) of concn. HCl was dissolved 1 g (4.8 mmol) of compound **III**, and the solution was stirred for 10 h and afterwards it was neutralized with 25% aqueous K_2CO_2, the solvent was removed in a vacuum, the residue was treated with ethanol. The precipitate insoluble in ethanol was filtered off, the solvent was removed in a vacuum, and the oily residue was crystallized from a mixture of acetone with ethanol, 5:1. Yield 0.56 g (68%), colorless crystals, mp 140–141°C (140°C [5]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.33 s (3H, CH_3), 4.52 s (2H, CH_2), 4.54 s (2H, CH_2), 4.78 s (2H, CH_2).

3,3,8-Trimethyl-9-(methoxymethoxy)-1,5-dihydro[1,3]dioxepino[5,6-*c*]pyridine (V). To a solution of 1 g (4.2 mmol) of alcohol **III** in 20 ml of DMF was added at room temperature while stirring 0.18 g (4.5 mmol) of 60% dispersion of NaH in mineral oil, then was added dropwise 0.35 g (4.3 mmol) of methyl chloromethyl ether. After 6 h the separated precipitate of NaCl was filtered off, and the solvent was removed in a vacuum. The oily dark precipitate was treated with chloroform, the insoluble part was separated, and the filtrate was purified by column chromatography on silica gel, eluent chloroform. Yield 0.89 g (71%), colorless crystals, mp 85°C (from petroleum ether). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (6H, $2CH_3$), 2.48 s (3H, CH_3), 3.58 s (3H, CH_3), 4.54 s (2H, CH_2), 4.71 s (2H, CH_2), 4.92 s (2H, CH_2), 4.95 s (2H, CH_2). Found, %: C 59.72; H 7.36; N 4.95. $C_{14}H_{21}NO_5$. Calculated, %: C 59.35; H 7.47; N 4.94.

^{1}H NMR spectra were registered on a spectrometer Varian Unity-300 (300 MHz), internal reference HMDS. Elemental analysis was performed on a Perkin Elmer 2400 Series II instrument. The reaction progress was monitored and the purity of compounds was checked by TLC on Silufol UV-254 plates, eluent ethanol–chloroform, 4:1. The preparative chromatography was carried out on silica gel KSKG (Ecofarm), fraction 0.10–0.16 μm.

XRD analysis of crystals of compound (V) was performed at 20°C on a diffractometer Smart Apex II (MoK_α radiation, CCD-detector, graphite monochromator). Crystals monoclinic, $C_{14}H_{21}N_1O_5$. M 283.32; a 15.094(5), b 11.947(5), c 8.143(5) Å; β 97.558(5)°; V 1455.7(12) Å^3, d_{calc} 1.293 g/cm^3, Z 4, space group $P2_1/c$, final divergence factors: R_1 0.0786 for 1866 reflexions with $I > 2\sigma(I)$, wR_2 0.1914 for 3375 reflexions. The structure was solved by the direct method using SIR program. All calculations were carried out applying WinGX software.

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