SYNTHESIS OF 4-NORPYRIDOXINE (3-HYDROXY-5-HYDROXYMETHYL-2-METHYLPYRIDINE)

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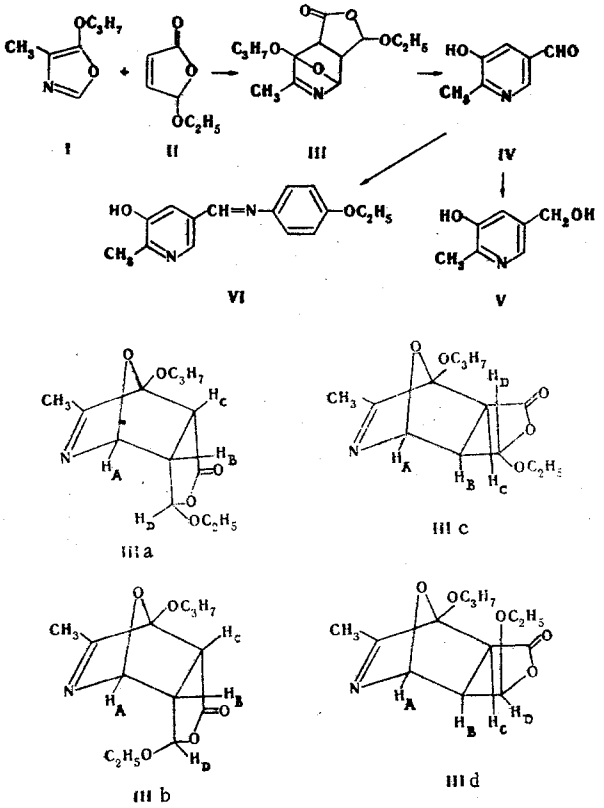
3-Hydroxy-5-hydroxymethyl-2-methylpyridine (4-norpyridoxine) has been synthesized by the heterodiene condensation of 4-methyl-5-propoxyoxazole and 5-ethoxy-2,5-dihydrofuran-2-one through the stage of 3-hydroxy-2-methylpyridine-5-carbaldehyde with reduction of the latter by $NaBH_4$. One of the isomeric adducts has been isolated, and its stereochemistry has been established by PMR spectroscopy.

Recently, interest has increased in 3-hydroxy-2-methylpyridines with various substituents in positions 4 and 5, which are vitamins B_6 and their structural analogs. Great possibilities for the building up of such structures are opened up by the heterodiene condensation reaction of 5-alkoxy-4-methyloxazoles with various dienophiles [1].



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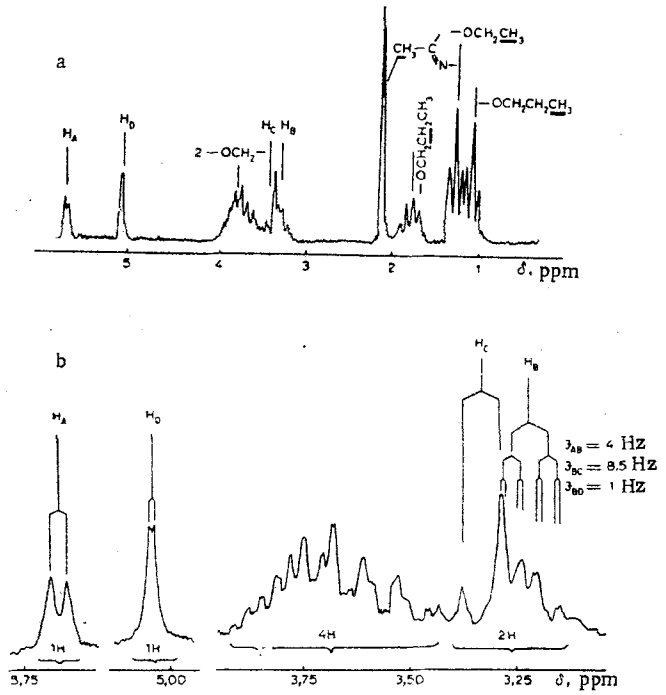


Fig. 1. PMR spectrum of the adduct (IIIa): a) usual form; b) ×1/5.

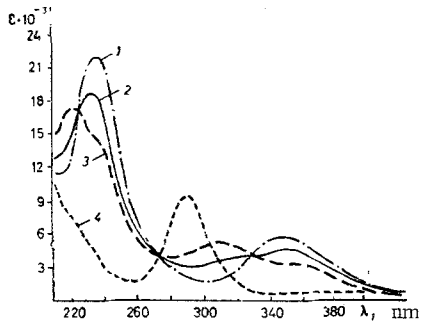


Fig. 2. UV spectrum of 3-hydroxy-2-methylpyridine-5-carbaldehyde (IV); 1) pH 12; 2) pH 8; 3) pH 6; 4) pH 2.

We have investigated the heterodiene condensation of 4-methyl-5-propoxyoxazole (I) and 5-ethoxy-2,5-dihydrofuran-2-one (II), which is readily formed by the photochemical oxidation of furfural [2] and is an active dienophile. Thus, under mild conditions a mixture of equimolecular amounts of (I) and (II) reacts with the formation of the adduct (III).

After purification and crystallization, we isolated with a yield of 32.4% an adduct to which, on the basis of its PMR spectrum (Fig. 1) structure (IIIa) may be assigned [3]. The endo configuration of the adduct (IIIa) is confirmed by the presence in the spectrum of the signal of the proton H_A in the form of a doublet at 5.67 ppm (J_{AB} = 4 Hz). The adducts (IIIa) amounted to more than 60% of the mixture taken for crystallization. The noncrystallizing oil apparently contained a geometric isomer with a different spatial arrangement of H_D (IIIb) and the two exo adducts (IIIc and d), which are formed in smaller amount.

The aromatization of the mixture of adducts takes place in the presence of an acid without heating and is accompanied by the cleavage of the lactone ring and by decarboxylation with the formation of 3-hydroxy-2-methylpyridine-5-carbaldehyde (IV). It is known that the adducts of the heterodiene condensation of oxazoles with maleic anhydride [4] and with diethyl fumarate [5] behave similarly, decarboxylation taking place in position 4 of the pyridine nucleus. The 3-hydroxy-2-methylpyridine-5-carbaldehyde (IV) was characterized in the form of the free base and in the form of the Schiff's base with p-phenetidine (VI). The IR spectrum of the base (IV) has an absorption band at 1690 cm^{-1} due to the carbonyl of the formyl group [6]. A study of the electronic spectra of compound (IV) enabled the mutual transitions of the ionic forms with a change in the pH of the solution to be established (Fig. 2) [7]. To determine the number of ionic forms and to estimate pK_a, we performed spectrophotometric titration at three wavelengths (292, 312, and 354 nm) (Fig. 3). As can be seen from the results given, in the pH range from 1 to 12 there are two one-proton transitions with pK_a 4.5 and 8.0, which corresponds to the existence of three ionic forms:

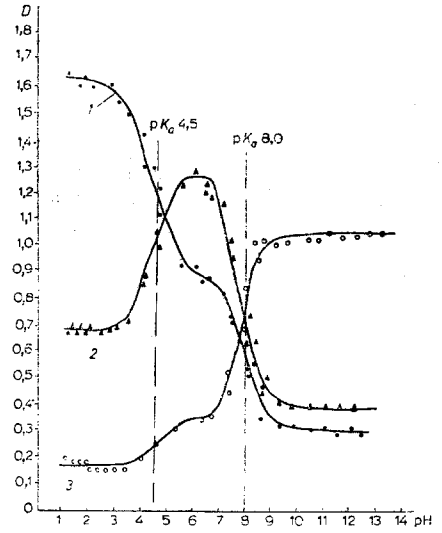
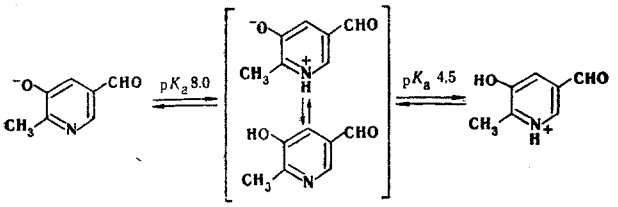


Fig. 3. Curves of the spectrophotometric titration of 3-hydroxy-2-methylpyridine-5-carbaldehyde (IV): 1) at 292 nm; 2) at 312 nm; 3) at 354 nm.



Apparently, at pH 5-7, an equilibrium of the bipolar ion with the uncharged form exists, which permits compound (IV) to be isolated by extraction at these pH values.

By reduction with sodium tetrahydroborate, the pyridine (IV) was converted into the 5-hydroxymethyl derivative (V), the synthesis of which has been effected previously by different methods [5, 8]. The compound (V) obtained can be considered an analog of pyridoxine lacking the hydroxymethyl group in position 4 of the pyridine nucleus – 4-norpyridoxine – which is phosphorylated by pyridoxal phosphokinase in the same way as pyridoxal [9].

EXPERIMENTAL

The UV spectra were taken on a Hitachi EPS-3T instrument at a concentration of $5 \cdot 10^{-5}$ M. The spectrophotometric titration in the pH range from 1 to 12 was performed at a concentration of (IV) of $2.2 \cdot 10^{-4}$ M in 0.1 N $HClO_4$ with 4.0 N NaOH using a pH-meter (glass electrode) on a SF-4A spectrophotometer. The PMR spectrum was measured on a JNM-4H-100 instrument in CCl_4 solution with tetramethylsilane as internal standard, and the chemical shifts are given in the δ scale. The IR spectra were taken on a Perkin–Elmer 257 instrument (in paraffin oil). Thin-layer chromatography was performed on Silufol UV-254 in the ethyl acetate–acetone–25% ammonia (10 : 5 : 0.75) system.

Adduct of 4-Methyl-5-propoxyoxazole with 5-Ethoxy-2,5-dihydrofuran-2-one (III). A mixture of 4.78 g (0.034 mole) of 4-methyl-5-propoxyoxazole (I), 4.34 g (0.034 mole) of 5-ethoxy-2,5-dihydrofuran-2-one (II), and 50 ml of hydroquinone was kept at 18-20°C for 12 h. Then it was dissolved in 10 ml of dry benzene and was deposited on a column filled with 180 g of alumina of activity grade IV. The substance was eluted with dry benzene. After elimination of the solvent, 4.88 g (53.6%) of an oily substance which crystallized on standing was obtained. The yield of the adduct (IIIa) was 2.95 g (32.4%), mp 69-70°C (from hexane). Found %: C 58.1; H 6.9; N 4.9. $C_{13}H_{19}NO_5$. Calculated %: C 58.0; H 7.1; N 5.2. IR spectrum, cm^{-1}: 1780 (C=O); 1630 (C=N).

3-Hydroxy-2-methylpyridine-5-carbaldehyde (IV). A mixture of 1.6 g (12.3 mmoles) of (I), 1.45 g (12.3 mmoles) of (II), and 50 mg of hydroquinone was kept at 18-20°C for 12 h. Then it was dissolved in 30 ml of ether, and the solution was cooled to 0°C and was extracted with 150 ml of 5% hydrochloric acid. The aqueous solution was treated with sodium acetate to pH 6 and extracted with ether. The ether and the acetic acid were driven off and the residue was dried. Yield 0.55 g (35%), mp 245-249°C (from ethanol). R_f 0.5. Found %: C 61.2; H 5.1; N 10.3. $C_7H_7NO_2$. Calculated %: C 61.3; H 5.1; N 10.2. Schiff's base with p-phenetidine (VI): mp 226-230°C (from ethanol). Found %: C 70.0; H 6.3; N 10.9. $C_{15}H_{16}N_2O_2$. Calculated %: C 70.3; H 6.1; N 10.9. UV spectrum in ethanol, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 228 (22.6), 341 (18.0). IR spectrum, cm^{-1}: 1625 (C=N); 1610, 1580, 1510 (C=C, nucleus).

3-Hydroxy-5-hydroxymethyl-2-methylpyridine Hydrochloride (V). With stirring, 0.25 g (6.6 mmoles) of sodium tetrahydroborate in 3 ml of water was added to a solution of 0.5 g (3.6 mmoles) of (IV) in 25 ml of methanol. The reaction mixture was stirred for 30 min and was evaporated, the residue was treated with 12 ml of methanol, the solution was filtered, and the filtrate was evaporated. The residue was dissolved in ether, and the solution was saturated with hydrogen chloride. The precipitate was separated off. The yield of the hydrochloride (V) was 0.51 g (78%), mp 169-170°C (from a mixture of ethanol and ether) [7]. R_f 0.21. UV spectrum in 0.1 N HCl, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 226 (3.5), 291 (9.9); in 0.1 N NaOH, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$): 243 (7.35), 304 (6.0) [10]. IR spectrum, cm^{-1}: 3340-3330 (OH), 1630, 1530-1520.

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