Short Communication

On the Formation of Isopropylidenepyridoxines. A Convenient Method for the Preparation of 2,2,8-Trimethyl-4*H*-1,3-dioxino[4,5-*c*]pyridin-5-ylmethanol from Pyridoxine Hydrochloride

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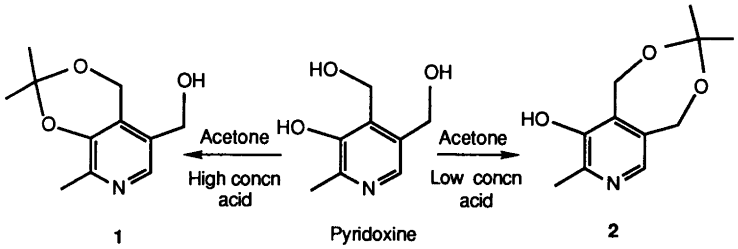
Isopropylidenepyridoxine **1** (2,2,8-trimethyl-4*H*-1,3-dioxino[4,5-*c*]pyridin-5-ylmethanol), an important building block for many biologically interesting pyridoxine derivatives and analogs,[1,2] has previously been prepared from pyridoxine hydrochloride and acetone (Scheme 1) in the presence of a large excess of acid[3–5] (more than 10 equiv.). By using a smaller amount of acid (ca. 6 equiv.), another cyclic ketal (1,5-dihydro-3,3,8-trimethyl[1,3]dioxepino[5,6-*c*]pyridin-9-ol, **2**) was obtained in 74 % yield.[6] Further treatment of compound **2** in acetone with acid at high concentration converted it into **1** in quantitative yield.[6] However, at low acid concentrations compound **1** was not formed[7] even after 24 h. Thus, it seemed that it was the acid concentration, rather than the duration or temperature of the reaction that determined the product, as recently mentioned explicitly by Nelson and Nelson.[7]

In an effort to find out why the conversion of **2** into **1** needed such an unusually large excess of acid, we examined the same reaction in CH_2Cl_2. We found that when **2** (free base) was stirred at room temperature in dry CH_2Cl_2 containing, e.g., 3 equiv. of anhydrous *p*-toluenesulfonic acid, pyridoxine (together with some water, presumably formed from the acid-catalyzed aldol condensation of acetone) was formed within a few minutes. However, subsequent addition of an excess of acetone dimethyl acetal to the reaction system converted the pyridoxine back into **2** within 30 min. Not more than 1 h later, compound **1** was also easily detected by TLC. After a further 5 h of reaction, **1** became the predominant product and was isolated in 83 % yield.

The above results make it clear that in previous experiments the failure to obtain **1** in the absence of a large excess of acid is due to a very slow reaction (even though the amount of the acid used there was already much more than catalytic), rather than an equilibrium in favor of **2**. Compared with CH_2Cl_2, acetone is a much better hydrogen-bond acceptor. Thus, the presence of a large amount of acetone lowers the acidity of the reaction medium and in turn results in a reduced concentration of **3**. Acetone may also raise the activation energies (compared with those in CH_2Cl_2) of conversion of **3** into **5**, because in a more polar solvent **3**, **4** and **5** (with higher charge density, Scheme 2) are stabilized more than the transition states. As a consequence, if compound **1** is to be obtained in an acetone solution within a short time, a high concentration of acid is inevitably needed to compensate the above two unfavorable factors.

The rapid replacement of the isopropylidene moiety in **2** observed in our experiment also gives a reasonable explanation as to why Nelson and Nelson[7] failed to obtain deuteriated **1** from hexadeuteriated **2** (with deuterium atoms at



Scheme 1.

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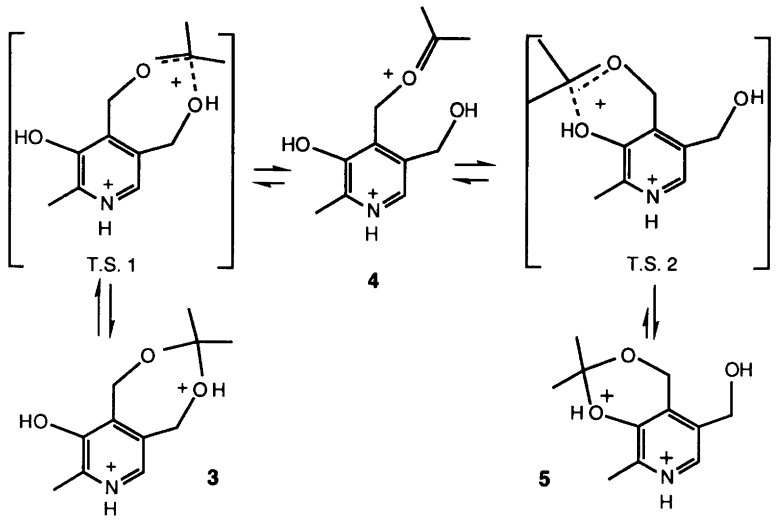

Scheme 2.

the isopropylidene moiety) in non-deuteriated acetone. Before **1** was produced via **5** by ring closure of **4**, a relatively slow step due to the poor nucleophilicity of the phenolic hydroxy group, the hexadeuteriated isopropylidene moiety had already been replaced by its non-deuteriated counterpart from the solvent. Thus, the absence of deuterium in the product (**1**) should not be regarded as evidence[7] that **1** was not formed from **3** via **4**.

The results of the reaction in CH_2Cl_2 not only provide a better understanding of the formation of two isopropylidenepyridoxines but also suggest a convenient way to prepare compound **1**. As an immediate extension of the transformation of **2** into **1**, we tested pyridoxine hydrochloride under similar conditions. In spite of the poor solubility of pyridoxine hydrochloride in CH_2Cl_2, compound **2** began to form immediately. Shortly afterwards, compound **1** was detected by TLC as well. After 24 h of reaction at room temperature, most of the suspended pyridoxine was transformed into **1**. At reflux temperature, substantial conversion into **1** was effected within a few hours.

The simplification using concentrated H_2SO_4 to replace anhydrous *p*-toluenesulfonic acid made our procedure even more practical for preparative purposes. Acetone dimethyl acetal was used in large excess, because under the reaction conditions, acetone was generated from the ketals continuously and consumed by the subsequent aldol condensation. Reflux of the crude residue (after removal of CH_2Cl_2) in diethyl ether/pentane followed by washing of the crystals of **1** with cold pentane proved to be an effective way of getting rid of the colored aldol products without any significant loss of yield. After such a simple work-up, compound **1** was obtained in good yield with high purity as judged from its m.p., GLC, and NMR spectroscopy.

This procedure works equally well on large scale (e.g., 20 g).

Experimental

Pyridoxine hydrochloride (98 %) was purchased from Aldrich Chemie GmbH & Co. KG. Acetone dimethyl acetal (98 %) was purchased from Fluka AG. CH_2Cl_2 was dried over $CaCl_2$ before use. ^1H and ^{13}C NMR spectra were determined on a Varian XL 400 NMR spectrometer (operating at 400 MHz for ^1H) using [$^2H_6$]DMSO as the solvent and TMS as the reference. Melting points were taken on a Reichert KIFA micromelting point apparatus and are uncorrected. Gas chromatography was performed on a Varian 3400 gas chromatograph using a 30-meter DB-17 megabore capillary column (0.53 mm ID, coated with 50 % of phenylmethylsilicone with a film thickness of 1 μm, manufactured by J & W Scientific, Inc.) with a temperature program operating from 150 to 220 °C min^{-1} and keeping 220 °C henceforth. A Varian DS 654 Data System was connected to the gas chromatograph to process the GC data. Helium was used as the carrier gas with a flow rate of ca. 6 ml min^{-1}.

2,2,8-Trimethyl-4H-1,3-dioxino[4,5-c]pyridin-5-ylmethanol (**1**). Concentrated H_2SO_4 (96 %, *d* 1.835, 0.3 ml, 5.4 mmol) was added to a stirred mixture of pyridoxine hydrochloride (1.011 g, 4.8 mmol) and acetone dimethyl acetal (5 ml, ca. 40 mmol) in dry CH_2Cl_2 (20 ml). The resulting mixture was heated to reflux under N_2 with stirring for 6 h. The dark red solution was diluted with more CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (15 ml). The layers were separated and the aqueous phase was extracted once more with CH_2Cl_2. The CH_2Cl_2 phases were combined (75 ml), dried (Na_2SO_4), and evaporated (rotary evaporator, under aspirator vaccum) to dryness. Diethyl ether/pentane (2:1, ca. 30 ml) was added to the yellow residual solid, and the resulting mixture was refluxed for 30 min with occasional

swirling, during which the initial solids gradually changed into fine needles. After being allowed to stand at room temperature for 15 min and at −20 °C for 2 h, the first crop was collected by suction filtration, washed with cold pentane (chilled to −20 °C before use), and dried in a 50 °C oven. The off-white needles weighed 856 mg (85 %); m.p. 108.5–109 °C (lit. 108–109 °C,[3] 113–115 °C,[4] 111–112 °C,[5] and 109–111 °C[7]); GLC: a single peak at 12.7 min with purity higher than 99.76 %. The same yield and purity was obtained on larger scale.

The last trace of yellow color was removed by treating the first crop with charcoal (ca. 75 mg) in refluxing diethyl ether/ethyl acetate (10:1, ca. 35 ml) for 10 min. About two thirds of the solvent were removed on a rotary evaporator and the residue was cooled to −20 °C for 1 h. Suction filtration and washing with cold pentane afforded pure white needles (787 mg, 92 %); m.p. 110 °C (very sharp); ^{1}H NMR: δ 7.92 (1 H, s), 5.16 (1 H, t, *J* 5.4 Hz), 4.88 (2 H, s), 4.41 (2 H, d, *J* 5.4 Hz), 2.28 (3 H, s), 1.49 (6 H, s). ^{13}C NMR: δ 145.26, 144.90, 138.26, 130.44, 125.04, 99.24, 58.09, 57.73, 24.40, 18.17.

The mother liqour of the first crop was concentrated and allowed to stand at −20 °C for 1.5 h. After filtration and washing as above, the second crop was obtained as off-white crystals (49 mg, m.p. 102–104 °C) containing 58 % of **1** and 41 % of **2** as shown by GLC (t_R 12.6 min for **1** and 14.0 min for **2**).

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