

um compound was then decomposed with H<sub>2</sub>O (100 ml). The Et<sub>2</sub>O layer was separated, washed with H<sub>2</sub>O, and concentrated. The solid was collected by filtration to give 3.3 g (40% yield) of the desired product, mp 217–220°. Recrystallization from acetone-cyclohexane yielded analytically pure 5f as white crystals, mp 218–220°. *Anal.* (C<sub>22</sub>H<sub>13</sub>F<sub>6</sub>NO) C, H, N.

**3,6-Bis(trifluoromethyl)-9-phenanthryl 4-Pyridyl Ketone (5g).** A solution of 2.1 g (0.005 mol) of 5f in 100 ml of AcOH was treated with a saturated solution of CrO<sub>3</sub> (2.0 g, 0.02 mol) in H<sub>2</sub>O. The reaction mixture was allowed to stand overnight at room temperature, and excess oxidizing agent was then destroyed by the addition of MeOH. The resulting mixture was made basic with aqueous NaOH. The product was isolated by Et<sub>2</sub>O extraction (frequent filtration was required to break up the emulsion). On evaporation of the Et<sub>2</sub>O solution there was obtained 1.26 g (60% yield) of crude 5g, mp 157–159°. An analytical sample was obtained as white needles upon recrystallization from MeOH, mp 162–164°. *Anal.* (C<sub>22</sub>H<sub>11</sub>F<sub>6</sub>NO) C, H, N.

**3,6-Bis(trifluoromethyl)- $\alpha$ -(4-piperidyl)-9-phenanthrene-methanol Hydrochloride (4).** A solution of 1.8 g of 5f in 250 ml of EtOH and 1 ml of HCl was hydrogenated in the presence of Adams catalyst at 5 kg/cm<sup>2</sup> for 4 hr. The reaction mixture was then heated to dissolve the precipitated solid product and filtered to remove the catalyst. The filtrate was evaporated to dryness *in vacuo* and the residue recrystallized from MeOH to give 4 as white crystals, mp 323–325° dec. The combined yield of pure 4 from two similar runs was 2.35 g (60%). This compound could also be prepared by hydrogenation of 3,6-bis(trifluoromethyl)-9-phenanthryl 4-pyridyl ketone (5g) under the same reaction condi-

tions. *Anal.* (C<sub>22</sub>H<sub>19</sub>F<sub>6</sub>NO·HCl) C, H, N.

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## A General Method for Modifying the 2-Methyl Group of Pyridoxol. Synthesis and Biological Activity of 2-Vinyl- and 2-Ethynylpyridoxols and Related Compounds†

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In order to explore the bulk tolerance indicated in the 2 position of vitamin B<sub>6</sub> for enzymes both dependent on the vitamin and metabolizing it, we have developed a general method for modifying the 2 position. To this end, formation of cyclic ketals from acetone and pyridoxol or  $\alpha^2$ -hydroxypyridoxol has been studied, using various amounts of catalyst, principally *p*-toluenesulfonic acid. With a limited amount of catalyst, ketal formation occurs across the  $\alpha^4$ - and  $\alpha^5$ -OH groups, without involving the phenolic OH. When the ratio of acid catalyst to substrate is increased (e.g., to 4:1), acetone condenses with the 3- and  $\alpha^4$ -OH groups in these compounds but not with the 3- and  $\alpha^2$ -OH groups in  $\alpha^2$ -hydroxypyridoxol. By blocking the 3-OH group in  $\alpha^2$ -hydroxypyridoxol with benzyl, and the  $\alpha^4$ - and  $\alpha^5$ -OH groups with acetone, a generally useful intermediate for modifying the 2 position was obtained. An alternative, more efficient method for synthesizing the compound was developed, starting from 3-*O*-benzylpyridoxol, converting it to the  $\alpha^4, \alpha^5$  cyclic ketal, N-oxidizing that, rearranging the N-oxide with trifluoroacetic anhydride, and hydrolyzing the 2-(trifluoroacetyl) group. The 2-CH<sub>2</sub>OH group of this intermediate was oxidized to 2-CHO, which on mild hydrolysis gave 2-formyl-2-norpyridoxol. The 2-CHO groups of the blocked intermediate were converted by Wittig reactions to 2-CH=CH<sub>2</sub> and 2-CH=CHCl groups; dehydrochlorination of the latter gave the 2-C≡CH derivative. The blocking groups in all of these compounds were readily hydrolyzed with acid, and the resulting analogs were tested as inhibitors of the growth of mouse mammary adenocarcinoma (TA-3) cells *in vitro*. 2-Vinyl-2-norpyridoxol, with an ID<sub>50</sub> of  $9 \times 10^{-6}$  M, was the best inhibitor in this series. In contrast to the inhibition caused by the 4-vinyl analog of pyridoxol, readily reversed by pyridoxol, that caused by the 2-vinyl analog of pyridoxol could not be reversed by the vitamin.

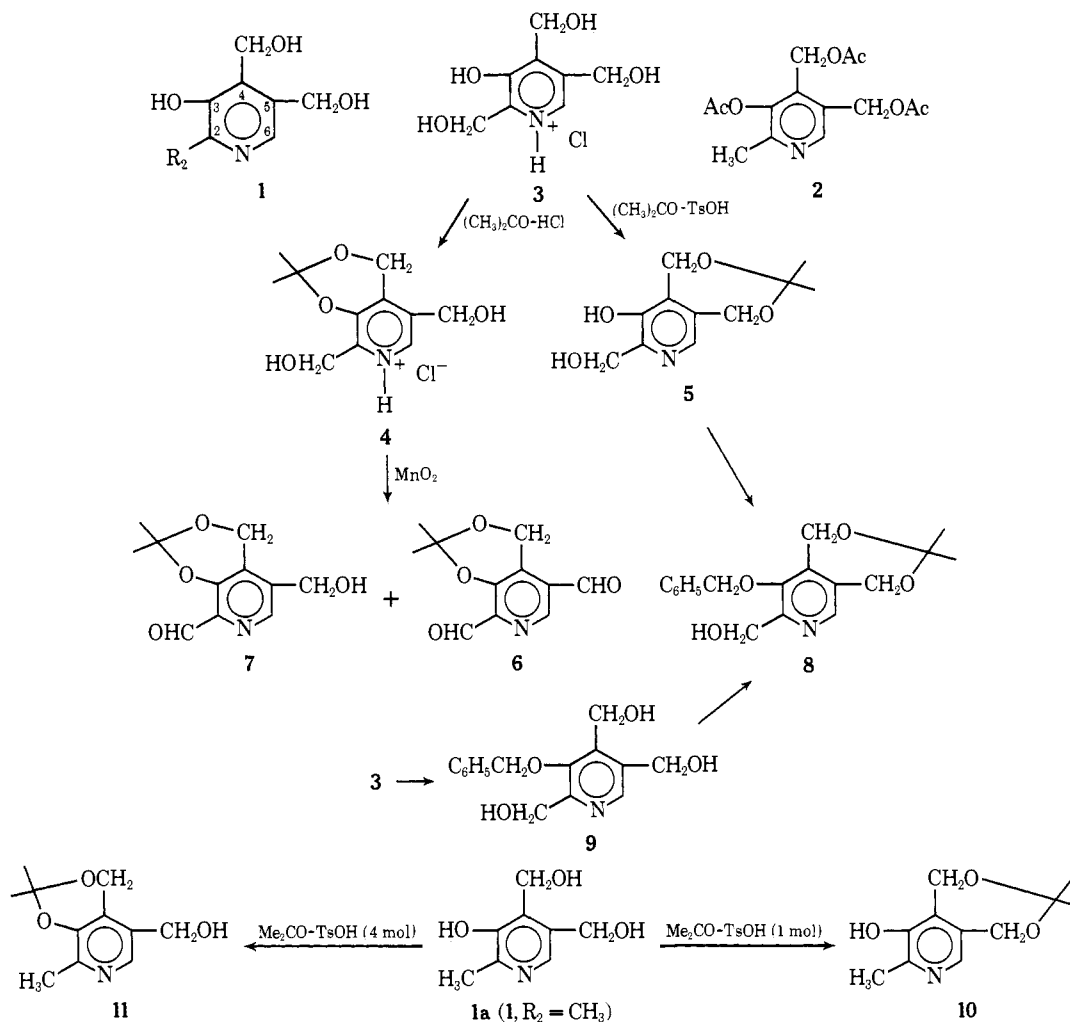
Analogues of vitamin B<sub>6</sub><sup>2</sup> modified in the 2 position, such as  $\alpha^2$ -methylpyridoxol (1, R<sub>2</sub> = Et), have been of considerable biochemical interest in the development of ideas in regard to pyridoxal catalysis<sup>3</sup> and the mode of binding of the cofactor analogs,<sup>4</sup> and in studies of the active sites of enzymes metabolizing vitamin B<sub>6</sub>.<sup>5</sup> Generally, the analogs that were studied had the 2-methyl group replaced either with 2-CH<sub>2</sub>OH (1, R<sub>2</sub> = CH<sub>2</sub>OH) or with various other alkyl groups. The results of these studies indicated that there is a certain bulk tolerance in the 2 position with respect to several enzymes requiring pyridoxal phosphate

and also with respect to enzymes involved in metabolic interconversions of different forms of vitamin B<sub>6</sub>. In order to exploit this bulk tolerance in the design of potential antagonists of vitamin B<sub>6</sub>, we had to develop a method for modifying the 2-methyl group of pyridoxol in such a way that the method would also be suitable for the introduction of reactive groups. The present paper describes the synthesis of a blocked intermediate that satisfies these requirements. The utility of this intermediate parallels that of  $\alpha^4, 3$ -*O*-isopropylidenepyridoxol for modifying the 5-CH<sub>2</sub>OH group<sup>6</sup> and that of 3,  $\alpha^5$ -*O*-dibenzylpyridoxol for modifying the 4-CH<sub>2</sub>OH group.<sup>1a, 7</sup>

Initially, we investigated the acetonation of  $\alpha^2$ -hydroxypyridoxol (Scheme I). The latter compound was prepared from tri-*O*-acetylpyridoxol by a simplified version of the

†Chemistry and Biology of Vitamin B<sub>6</sub>. 33. Previous paper in this series, ref 1a. A brief report of part of the present study has appeared.<sup>1b</sup> Part of the present study was submitted by P. G. G. Potti in partial fulfillment of requirements for the Ph.D. degree.

Scheme I



procedure described by Bedford, *et al.*,<sup>8</sup> in which the intermediates were not isolated. Using HCl as the catalyst, we did not obtain the expected (from our previous experience<sup>9</sup>) cyclic ketal **5**, but its isomer **4**, irrespective of the reaction temperature or the concentration of HCl. The structure of **4** was indicated partly by its spectral properties and partly by oxidation experiments. The uv spectrum of **4** at pH 7.0 has a maximum at 283 nm, which is not shifted in basic (pH 9) solution; a red shift would be expected if the phenolic OH were unsubstituted.<sup>7</sup> The nmr spectrum of **4** in DMSO-*d*<sub>6</sub> shows a splitting of the methylene protons by the hydroxyl protons. It was demonstrated earlier that whenever the phenolic OH is free, such splitting is not observable, and all of the exchangeable protons appear as one single peak ("mobile" protons).<sup>10</sup>

These data, however, were not sufficient to distinguish **4** from its isomer  $\alpha^2,3$ -*O*-isopropylidene- $\alpha^2$ -hydroxypyridoxol. Hence, we decided to conduct oxidations of the remaining two hydroxymethyl groups. Previous experience indicated that if these groups occupy positions ortho to each other, as in pyridoxol, the resulting product of oxidation will be a hemiacetal or, if further oxidized, an acid or a lactone.<sup>11</sup> Oxidation of **4** with MnO<sub>2</sub> gave rise to two compounds. The nmr spectrum of one compound showed clearly two aldehyde peaks at  $\delta$  10.38 and 10.58, and hence that compound was assigned the structure **6**. The other compound had a single aldehyde peak at  $\delta$  10.50 and hence was assigned the structure **7**. The position of the aldehyde group in **7** has been established unequivocally by removing the isopropylidene and demonstrating the iden-

tity of the resulting compound with the product of the hydrolysis of **15**.

The preference for the formation of **4** vs. the other isomer with a six-membered ring, the one that would be formed by joining the 2 and 3 positions with isopropylidene, may be related to the bulk of the anion (Cl<sup>-</sup> or *p*-toluenesulfonate), which would hinder the approach of acetone to form a hemiacetal with the  $\alpha^2$ -OH group, the reaction considered to be the first step in the formation of cyclic ketals.<sup>12,†</sup> The cyclic ketal **5**, with a seven-membered ring, was obtained by acetonation of **3** with *p*-toluenesulfonic acid in an equimolar ratio to substrate. The presence of the free phenolic OH group in this compound is indicated by its uv spectrum (maxima at 253 and 315 nm at pH 6.8, which shifted to 244 and 305 nm in 0.1 *N* NaOH). The desired intermediate **8** was obtained either by direct benzylation of **5** with dimethylphenylbenzylammonium chloride,<sup>7</sup> or by first benzylating  $\alpha^2$ -hydroxypyridoxol to give **9**, and then subjecting the latter to acetonation.

Our experience with the acetonation of **3** with *p*-toluenesulfonic acid and dimethoxypropane led us to reinvestigate the acetonation of pyridoxol with these reagents. When HCl was used as the catalyst as originally described,<sup>9</sup> the yield of **10** was variable, since it was not al-

†The following experiments support this idea. 3-Hydroxy-2-hydroxymethylpyridine does not form an acetonide under any of various conditions (HCl and *p*-toluenesulfonic acid were used as catalysts); similarly, a second isopropylidene group could not be introduced into **5**. An alternative mechanism preventing the formation of the acetonide across  $\alpha^2$ -OH and 3-OH groups would be intramolecular hydrogen bond formation between the  $\alpha^2$ -OH and N<sup>+</sup>-H of the pyridine ring.

ways possible to reproduce the original reaction conditions for the synthesis of this key intermediate. When *p*-toluenesulfonic acid was used as the catalyst, however, either 10 or 11 or both would be formed, depending on the molar ratio of catalyst to pyridoxol hydrochloride. If that ratio was equimolar, 10 was obtained exclusively, in excellent yield. If the proportion of the catalyst was increased, mixtures of 10 and 11 were obtained, the yield of 11 increasing with the catalyst concentration. Finally, at a 4:1 ratio of catalyst to substrate, 11 was the only product. For practical purposes, the *p*-toluenesulfonic acid method is superior for the synthesis of 10, but the HCl method<sup>13</sup> is still the method of choice for the synthesis of 11, since it gives a better yield and a cleaner product.

The possibility was considered that 10 was the initial product even when a large proportion of the catalyst was used and that the formation of 10 is followed by isomerization to 11. Apparent isomerization of 10 to 11 has been reported to occur in acetone with HCl.<sup>9</sup> To test this hypothesis, we prepared  $\alpha^4, \alpha^5$ -*O*-isopropylidene-*d*<sub>6</sub>-pyridoxol by reacting 1a (1, R<sub>2</sub> = CH<sub>3</sub>) with acetone-*d*<sub>6</sub>. We subjected this labeled material to the "isomerization procedure" using *p*-toluenesulfonic acid in acetone, and we isolated 11 lacking the label. This finding indicates that the "isomerization procedure" first causes the isopropylidene group in 10 to be completely hydrolyzed off, and then the cyclic ketal 11, with a six-membered ring, is formed directly. It also makes it likely that ketal formation is under kinetic control; *i.e.*, the outcome of the reaction is not dependent on the relative stabilities of the cyclic ketals formed but on the relative rates of their formation. § Thus, acid media increase the rate of formation of ketals involving the phenolic OH group relative to those involving only the alcoholic OH groups.

After the preceding investigation was completed, we eventually developed a new method for the synthesis of 8 (Scheme II). In this new method, the least satisfactory step is the benzylation of pyridoxol to 12, which is obtained in only 53% yield. Other steps gave almost quantitative yields, and it was not necessary to isolate the product in every case. The crucial step in the synthesis is the rearrangement of the *N*-oxide 14 with trifluoroacetic anhydride and the subsequent hydrolysis of the  $\alpha^2$ -*O*-trifluoroacetyl group. These steps were carried out under very mild conditions, without any concomitant hydrolysis of the acid-sensitive blocking groups. The 2-aldehyde 15 was the key intermediate in this method and was obtained by MnO<sub>2</sub> oxidation of 8. The blocking groups could be removed by mild acid hydrolysis (typically, heating with 1 *N* HCl on a steam bath for 1 hr). Such treatment of 15 gave 2-formyl-2-norpyridoxol [1b (1, R<sub>2</sub> = CHO)], which was identical with the product of the hydrolysis of 7, thus indicating the structure of 7. =

With the ready availability of 15, it is now possible to introduce various groups into the 2 position of pyridoxol. Initially we have chosen to introduce 2-vinyl, 2-ethynyl, and related groups, since pyridoxol analogs with these groups in the 4 position have been shown to be very potent reversible inhibitors of vitamin B<sub>6</sub><sup>1a, 15</sup> or irreversible

§ This was also supported by the following experiment. 5-Deoxypyridoxol was acetonated in the presence of a 1 *M* proportion of *p*-toluenesulfonic acid. Thus it is not necessary to have a larger proportion of the catalyst for the formation of a cyclic ketal with a six-membered ring in the absence of vicinal hydroxymethyl groups competing for the formation of a cyclic ketal with a seven-membered ring. Since the proportions of *p*-toluenesulfonic acid used are large, a reviewer has suggested describing it as a "reaction carrier" instead of a "catalyst." Since the proportions of *p*-toluenesulfonic acid used are large, a reviewer has suggested describing it as a "reaction carrier" instead of a "catalyst."

A preliminary report has been published by Sartorelli, *et al.*,<sup>14</sup> on the synthesis of the thiosemicarbazone of 2-formyl-2-norpyridoxol, as well as that of ketal 5.

inhibitors directed to cofactor sites of apoenzymes dependent on pyridoxal phosphate.<sup>16</sup>

The aldehyde group in 15 was converted into vinyl, as in 11, by means of a Wittig reaction in which the required ylide was generated from triphenylphosphonium bromide, using both *n*-butyllithium and potassium *tert*-butoxide as the base, as has been described earlier for the synthesis of the 4-vinyl analog.<sup>1a</sup> Mild acid hydrolysis gave 2-vinyl-2-norpyridoxol [1c (1, R<sub>2</sub> = CH=CH<sub>2</sub>)], which on hydrogenation (Pd/C) gave the known  $\alpha^2$ -methylpyridoxol.<sup>5, 17</sup> Further hydrogenolysis occurred very readily, giving 2-ethyl-3-hydroxy-4,5-dimethylpyridine. The blocked  $\beta$ -chlorovinyl analog 17 was similarly prepared from 15 by a Wittig reaction (chloromethyltriphenylphosphonium chloride was used), giving 17 as a mixture of *cis* and *trans* isomers. The two isomers were not separated but were subjected to hydrolysis, giving 1c (1, R<sub>2</sub> = CH=CHCl), and to dehydrochlorination (NaNH<sub>2</sub> in liquid ammonia), giving in good yield the blocked ethynyl compound 18, which was similarly hydrolyzed to 1d (1, R<sub>2</sub> = C≡CH).

The ethynyl proton in 18 is shifted in 1d (1, R<sub>2</sub> = C≡CH) by 1.07 ppm downfield, indicating an intramolecular H bonding between the OH and ethynyl groups. An analogous intramolecular H bonding has been postulated for *o*-hydroxyphenylacetylene.<sup>18</sup> Like the 4-vinyl analog of pyridoxol, the 2-vinyl and 2-ethynyl analogs are less reactive than the corresponding unsubstituted pyridine compounds, since the phenolic OH ortho to these groups has a deactivating influence. The relative ease with which the blocked intermediate 15 can now be synthesized and the ease of removal of the blocking groups make it feasible to introduce other, more reactive groups into the 2 position. The present method extends and supplements the procedures applied earlier to modification of the 2-methyl group in vitamin B<sub>6</sub>. Such procedures were based on methods for synthesizing the vitamin itself,<sup>17</sup> and their scope is limited.

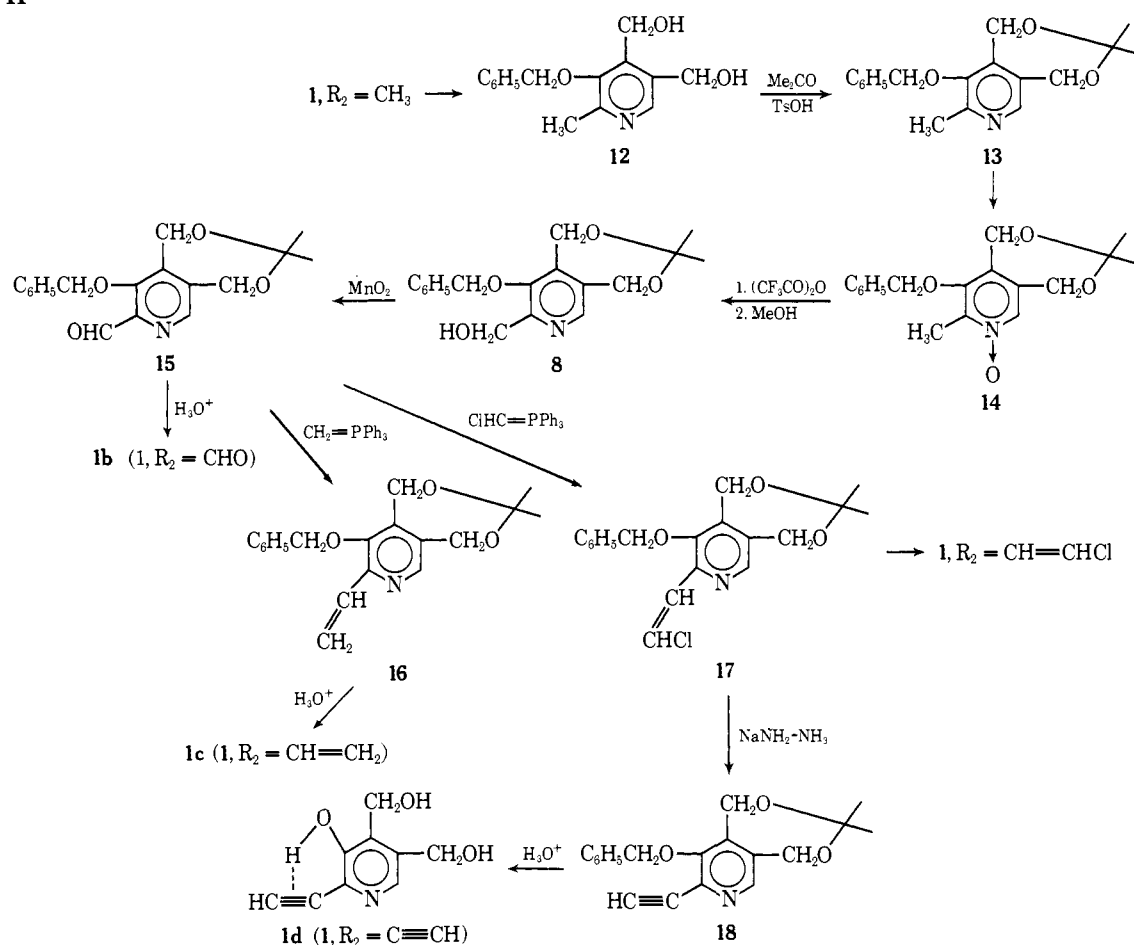
**Biological Activity.** Compounds synthesized in this study were tested as inhibitors of the growth of mouse mammary adenocarcinoma (TA-3) cells grown in tissue culture in Eagle's medium containing a minimal amount of pyridoxal (1 × 10<sup>-7</sup> *M*) to sustain optimal growth.<sup>15</sup> 2-Vinyl-2-norpyridoxol was the most active inhibitor in the series, with an ID<sub>50</sub> of 9.4 × 10<sup>-6</sup> *M*. Although it was less active than the 4-vinyl analog of pyridoxal (ID<sub>50</sub> 1 × 10<sup>-7</sup> *M* under the same conditions), it was not reversed by pyridoxal at approximately 10<sup>-5</sup> *M*. As in the case of the 4-vinyl analog, saturation of the double bond almost abolished its inhibitory activity; the ID<sub>50</sub> for  $\alpha^2$ -methylpyridoxol was approximately 3 × 10<sup>-4</sup> *M*. 2-( $\beta$ -Chloro)vinyl, 2-ethynyl, 2-formyl, and 2-(hydroxymethyl) analogs inhibited the half-maximal growth of these cells at 1 × 10<sup>-4</sup>, 1.7 × 10<sup>-4</sup>, 1.7 × 10<sup>-4</sup>, and 1 × 10<sup>-4</sup> *M*, respectively. The substantial activity of the 2-vinyl analog and the apparently irreversible nature of the inhibition make it attractive to design other vitamin B<sub>6</sub> analogs incorporating the 2-vinyl group.

## Experimental Section

Where analyses are indicated only by symbols of elements, analytical results obtained for these elements were within  $\pm 0.4\%$  of the theoretical values. Tlc (silica gel) was used routinely as described earlier.<sup>19</sup> Ir spectra were determined with a Perkin-Elmer 457 spectrophotometer, and nmr spectra with a Varian A-60A instrument, using 8-15% solutions in CDCl<sub>3</sub>, DMSO, or D<sub>2</sub>O; positions of peaks are expressed in parts per million from TMS, or from dioxane ( $\delta$  3.70), as an internal standard. Peaks are assigned on the basis of previous work.<sup>20</sup>

**Tri-*O*-acetylpyridoxol (2).** To a suspension of pyridoxol hydrochloride (7.5 g, 36 mmol) in pyridine (dry, 50 ml), Ac<sub>2</sub>O (30 ml) was added, and the mixture was heated on a steam bath for 1 hr.

## Scheme II



The clear solution thus obtained was stirred at room temperature for 15 hr, and the solvent was evaporated. Next, EtOH was added to the residue and was then evaporated. The residue was taken up in EtOAc, and the solution was washed with H<sub>2</sub>O (three times) and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was completely removed, yielding 9.5 g (85%) of oily product.

**$\alpha^2$ -Hydroxypyridoxol (3, 3-Hydroxy-2,4,5-tris(hydroxymethyl)pyridine Hydrochloride).** Tri-*O*-acetylpyridoxol (2, 10.0 g, 32.5 mmol) in CHCl<sub>3</sub> (200 ml) was treated with *m*-chloroperbenzoic acid (12.0 g, 69.5 mmol) for 12 hr in the dark. The mixture was washed with NaHSO<sub>3</sub> solution (10% in H<sub>2</sub>O), followed by NaHCO<sub>3</sub> solution and H<sub>2</sub>O. Evaporation of CHCl<sub>3</sub> gave an oil (10 g), which was heated with Ac<sub>2</sub>O (100 ml) at 100° for 1 hr. The residue from evaporation of the reagent was dissolved in EtOH, and the solution was again evaporated. The residue was heated on a steam bath with 2.5 N HCl (100 ml) and was then stirred at room temperature for 12 hr. At this stage, benzoic acid crystallized. It was filtered off and was washed with a little 2.5 N HCl. The combined filtrates were concentrated, when the desired compound crystallized. It was suspended in Et<sub>2</sub>O, filtered, and washed with Et<sub>2</sub>O. Recrystallization from MeOH-Et<sub>2</sub>O gave 4.0 g (64%) of the product, mp 171-173°.

**Acetonation of  $\alpha^2$ -Hydroxypyridoxol Hydrochloride.  $\alpha^4,3$ -*O*-Isopropylidene- $\alpha^2$ -hydroxypyridoxol Hydrochloride (4) by HCl Catalysis.**  $\alpha^2$ -Hydroxypyridoxol (200 mg, 0.90 mmol) was suspended in acetone (10 ml, freshly distilled over K<sub>2</sub>CO<sub>3</sub>). The suspension was cooled to -10° (ice-salt bath) and saturated with HCl. The flask, well stoppered, was stirred for 30 min at room temperature. The product was poured into Et<sub>2</sub>O (400 ml, anhydrous), kept at -15° overnight, filtered, and washed with Et<sub>2</sub>O: yield 162 mg (69%); mp 166-168.5° dec from EtOH. *Anal.* (C<sub>11</sub>H<sub>16</sub>ClNO<sub>4</sub>) C, H, N. The free base was obtained by neutralization of the hydrochloride with 10% K<sub>2</sub>CO<sub>3</sub> and extraction with EtOAc: mp 110° (from MeOH-Et<sub>2</sub>O).

**$\alpha^4, \alpha^5$ -*O*-Isopropylidene- $\alpha^2$ -hydroxypyridoxol (5).**  $\alpha^2$ -Hydroxypyridoxol hydrochloride (3, 960 mg, 4.33 mmol) was suspended in acetone (dried, 15 ml) to which *p*-toluenesulfonic acid (823 mg, 4.33 mmol) and 2,2-dimethoxypropane (10 ml) had been added, and the reaction mixture was stirred for 3-5 days. The

precipitate was filtered, dissolved in 5% NaHCO<sub>3</sub> (ca. 50 ml, final pH about 8), and extracted continuously with EtOAc. After drying (Na<sub>2</sub>SO<sub>4</sub>), the EtOAc solution was evaporated, and the residue was crystallized from EtOH, yielding 630 mg (65%) of product, mp 149-151°. *Anal.* (C<sub>11</sub>H<sub>15</sub>NO<sub>4</sub>) C, H, N.

**Acetonation of  $\alpha^2$ -Hydroxypyridoxol Hydrochloride, Catalyzed by Increasing Proportions of *p*-Toluenesulfonic Acid.** The preceding experiment was repeated, using *p*-toluenesulfonic acid and  $\alpha^2$ -hydroxypyridoxol hydrochloride in a molar ratio of 6:1. The experimental procedures were the same, except that after neutralization (10% Na<sub>2</sub>CO<sub>3</sub>), the product was extracted with petroleum ether to remove the acetone condensation products. The cyclic ketal with a six-membered ring predominated over the one with a seven-membered ring, in a ratio of 6:1, as estimated by the ratio of the isopropylidene peaks in the nmr spectrum of the mixture. The former was isolated from the reaction mixture and amounted to 205 mg (21%) of pure product.

When the ratio of *p*-toluenesulfonic acid to  $\alpha^2$ -hydroxypyridoxol hydrochloride was 4:1, the ratio of the cyclic ketal with a six-membered ring to the one with a seven-membered ring was 5:3.

**Oxidation of  $\alpha^4,3$ -*O*-Isopropylidene- $\alpha^2$ -hydroxypyridoxol. Experiment A.** Compound 4 (free base, 50 mg, 0.22 mmol) was dissolved in a mixture of CHCl<sub>3</sub> (5 ml) and EtOH (2 ml), and the solution was stirred with MnO<sub>2</sub> (500 mg) for 70 hr. The major spot had an *R*<sub>f</sub> of 0.78 (EtOAc, red spot with phenylhydrazine). The reaction mixture was heated for 5 min on a steam bath with a solution of NaOAc (200 mg) and NH<sub>2</sub>OH·HCl (100 ml) in H<sub>2</sub>O (5 ml), when the dioxime of 6 separated out in a yield of 40 mg (72%), mp 230° dec (shrinks at 210°, from MeOH). *Anal.* (C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>) C, H, N. The parent dialdehyde 6 was obtained as an oil by preparative tlc (eluted with EtOAc): nmr (CDCl<sub>3</sub>)  $\delta$  1.67 (isopropylidene CH<sub>3</sub>'s), 5.38 (4-CH<sub>2</sub>), 10.38, 10.58 (2-, 5-CHO), 8.87 (C<sub>6</sub>-H).

**Experiment B.** Compound 4 (free base, 225 mg, 1 mmol) was dissolved in H<sub>2</sub>O (15 ml). MnO<sub>2</sub> (650 mg) was added, and the suspension was stirred for 3 hr. After the MnO<sub>2</sub> was filtered and was washed with H<sub>2</sub>O (200 ml), the combined filtrate and washings were concentrated *in vacuo*. Tlc (EtOAc) of the reaction mixture showed two aldehyde spots: *R*<sub>f</sub> 0.78 for the dialdehyde 6 (see ex-

periment A), and  $R_f$  0.48 for the monoaldehyde 7. The latter was isolated by preparative tlc (the upper spot yielded 20 mg of oily dialdehyde). The yield of monoaldehyde 7 was 60 mg; mp 65° (from Me<sub>2</sub>CO-Et<sub>2</sub>O); uv  $\lambda_{\max}$  (0.1 N NaOH) 250 nm ( $\epsilon$  8400), 285 (10,800), 320 (6800); ir  $\lambda_{\max}$  (KBr) 1695 (C=O), 3400 cm<sup>-1</sup> (broad, probably due to water of hydration) (OH); nmr (CDCl<sub>3</sub>)  $\delta$  1.65 (isopropylidene CH<sub>3</sub>'s), 4.80 and 5.08 (4- and 5-CH<sub>2</sub>'s), 8.40 (C<sub>6</sub>-H), 10.50 (2-CHO). *Anal.* (C<sub>11</sub>H<sub>13</sub>N<sub>2</sub>O<sub>4</sub>) C, H.

**3-*O*-Benzyl- $\alpha^2$ -hydroxypyridoxol (9).** To a solution of 1.67 g (72 mmol) of Na in absolute EtOH (100 ml), 3 (8.05 g, 36 mmol) was added. The solution was stirred for 1 hr and cooled to 0°, and to it was added dropwise a solution of benzyltrimethylphenylammonium chloride (8.95 g, 37 mmol) in 100 ml of absolute EtOH. The dark-colored mixture was stirred at room temperature for 2 hr, the solvent was removed *in vacuo*, and the residue was twice flash-evaporated with toluene and dried. Xylene (dry, 100 ml) was then added, and the mixture was refluxed for 2.5 hr. After evaporation of the xylene, the syrupy residue was dissolved in EtOAc (2 l.), and the EtOAc solution was washed with H<sub>2</sub>O and dried (Na<sub>2</sub>SO<sub>4</sub>). After removal of the EtOAc, the residue was dissolved in H<sub>2</sub>O and was subjected to steam distillation to remove dimethylaniline. The residue was extracted with EtOAc and dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed, and the residue was crystallized from EtOAc-Et<sub>2</sub>O, yielding 4.5 g (45%), mp 84°. *Anal.* (C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

**3-*O*-Benzyl- $\alpha^4, \alpha^5$ -*O*-isopropylidene- $\alpha^2$ -hydroxypyridoxol (8).** To a solution of 9 (4.0 g, 15 mmol) in Me<sub>2</sub>CO (dry, 150 ml), *p*-toluenesulfonic acid (8.0 g, 42 mmol) was added, and the solution was stirred for 16 hr at room temperature. The reaction mixture was neutralized with a 25% aqueous solution of NaHCO<sub>3</sub>, concentrated, and extracted with Et<sub>2</sub>O. After washing with H<sub>2</sub>O and drying (Na<sub>2</sub>SO<sub>4</sub>), the solvent was removed, and the residue was crystallized from MeOH, yielding 3.5 g (76%); mp 144°; ir  $\lambda_{\max}$  (KBr) 3160 cm<sup>-1</sup> (OH). *Anal.* (C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N. Benzoylation of 5 with benzyltrimethylphenylammonium chloride gave 8 in 76% yield.

**3-*O*-Benzyl-2-formyl- $\alpha^4, \alpha^5$ -isopropylidene-2-norpyridoxol (15).** To a solution of 8 (630 mg, 2 mmol) in CHCl<sub>3</sub> (60 ml), MnO<sub>2</sub> (2.25 g) was added, and the suspension was stirred for 24 hr at room temperature. The reaction mixture was worked up in the usual way. The oily residue was crystallized from a mixture of Et<sub>2</sub>O and petroleum ether, yielding 500 mg (80%); mp 52°; ir  $\lambda_{\max}$  (KBr) 1705 cm<sup>-1</sup> (C=O); nmr  $\delta$  (CDCl<sub>3</sub>) 5.08 (CH<sub>2</sub>), 4.94 (CH<sub>2</sub>), 4.86 (CH<sub>2</sub>), 10.30 (CHO), 7.50 (C<sub>6</sub>H<sub>5</sub>), 8.40 (C<sub>6</sub>-H). *Anal.* (C<sub>18</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

The oxime of 15 was obtained by heating 15 in aqueous EtOH solution with NH<sub>2</sub>OH-HCl and NaOAc on a steam bath for 1 hr: mp 114-115° (from Et<sub>2</sub>O-petroleum ether). *Anal.* (C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

**$\alpha^4, \alpha^5$ -*O*-Isopropylidene-pyridoxol (10).** To pyridoxol (free base, 100 mg, 0.59 mmol) in Me<sub>2</sub>CO (2 ml, dried over CaSO<sub>4</sub>), 0.5 ml of 2,2-dimethoxypropane and finally 112 mg (0.59 mmol) of *p*-toluenesulfonic acid were added, and the solution was stirred for 20 hr. The resulting precipitate was filtered, washed with a little Me<sub>2</sub>CO, and poured into a cold saturated NaHCO<sub>3</sub> solution while it was being stirred. The resulting solution was extracted with EtOAc continuously for 6 hr, and the EtOAc was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated. Tlc gave a single product: mp 182° (lit.<sup>9</sup> mp 185°); yield 120 mg (94%). The compound was identical with an authentic sample in ir and nmr spectra.

**$\alpha^4, \alpha^5$ -*O*-Isopropylidene-*d*<sub>6</sub>-pyridoxol** was prepared exactly like the nondeuterated compound, except that acetone-*d*<sub>6</sub> (99.5%) was used. The melting point was identical with that of the nondeuterated compound, and the degree of isotopic purity was 88%.

**$\alpha^4, 3$ -*O*-Isopropylidene-pyridoxol (11).** To a suspension of pyridoxol hydrochloride (1.0 g, 4.86 mmol) in Me<sub>2</sub>CO (25 ml, dried over CaSO<sub>4</sub>) and 2,2-dimethoxypropane (15 ml), *p*-toluenesulfonic acid (3.7 g, 19.4 mmol) was added, and the mixture was stirred for 16 hr. The resulting dark-brown solution was neutralized with K<sub>2</sub>CO<sub>3</sub> and then concentrated *in vacuo*. After extraction with CHCl<sub>3</sub>, washing with H<sub>2</sub>O, and drying (Na<sub>2</sub>SO<sub>4</sub>), the CHCl<sub>3</sub> was removed, and the residue was crystallized from EtOH-Et<sub>2</sub>O: yield 0.64 g (63%). The compound was identical with authentic material in ir and nmr spectra.<sup>13</sup> The preparation has been scaled up, starting with 41 g (0.2 mol) of pyridoxol hydrochloride, and yielding 31.8 g (76%) of 11.

**"Isomerization" of  $\alpha^4, \alpha^5$ -*O*-Isopropylidene-*d*<sub>6</sub>-pyridoxol.** To a solution of 11-*d*<sub>6</sub> (50 mg, 0.23 mmol) in acetone (dried over CaSO<sub>4</sub>, 2.5 ml), 0.177 g (0.93 mmol) of *p*-toluenesulfonic acid was added, and the mixture was stirred for 2 days. The mixture was then neutralized (Na<sub>2</sub>CO<sub>3</sub>) and was extracted with CHCl<sub>3</sub>. Evap-

oration yielded 30 mg (62%) of  $\alpha^4, 3$ -*O*-isopropylidene-pyridoxol without the deuterium label, as shown by ir and nmr spectroscopy.

**3-*O*-Benzylpyridoxol (12).** Pyridoxol hydrochloride (2.0 g, 0.97 mmol) was added to a solution of NaOEt [from Na (0.5 g) in 25 ml of absolute EtOH], and the resulting solution was stirred at room temperature for 1 hr. The latter solution was cooled in ice, and a solution of dimethylphenylbenzylammonium chloride (3 g) in EtOH (25 ml) was added slowly, with stirring. The mixture was stirred at room temperature for 2 hr and was then evaporated *in vacuo*. Twice, dry C<sub>6</sub>H<sub>6</sub> was added to the residue and evaporated to remove traces of EtOH. Dry benzene (25 ml) was added to the residue, and the reaction mixture was gently refluxed for 0.5 hr and was then evaporated completely *in vacuo*. Water (25 ml) was added, and the mixture was extracted several times with CHCl<sub>3</sub>. The combined CHCl<sub>3</sub> extracts were dried over CaSO<sub>4</sub> and evaporated *in vacuo*, when crystalline material separated out. It was cooled, filtered, washed with a little Et<sub>2</sub>O, and dried: yield 1.43 g (57%); mp 113-114° (lit.<sup>21</sup> mp 118-120°). *Anal.* (C<sub>15</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N. The hydrochloride had a melting point of 198-199° (lit.<sup>21</sup> mp 178°).

**3-*O*-Benzyl- $\alpha^4, \alpha^5$ -*O*-isopropylidene-pyridoxol (13).** To a solution of 12 (9.2 g, 35.5 mmol) in Me<sub>2</sub>CO (dried over CaSO<sub>4</sub>, 100 ml), 2,2-dimethoxypropane (15 ml) and *p*-toluenesulfonic acid (6.98 g, 36.8 mmol) were added, and the mixture was stirred at room temperature for 4.5 days, until only a trace of the starting material could be detected by tlc. The reaction mixture was poured into ice-cold 10% aqueous Na<sub>2</sub>CO<sub>3</sub> with rapid stirring, and the alkaline solution was extracted with CHCl<sub>3</sub>, washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The oily product did not crystallize and was used for preparing the *N*-oxide.

**3-*O*-Benzyl- $\alpha^4, \alpha^5$ -*O*-isopropylidene-pyridoxol *N*-Oxide (14).** The oily product 13 from the previous experiment was dissolved in CHCl<sub>3</sub> (100 ml, dried over CaSO<sub>4</sub>), and the solution was cooled to 0°. To this solution, rapidly stirred, was added *m*-chloroperbenzoic acid (7.22 g, 0.0355 mol on the basis of 85% purity of the reagent). After being stirred at room temperature for 2 hr, until no starting material was detected by tlc, the reaction mixture was extracted with Na<sub>2</sub>SO<sub>3</sub> (10%, 2 × 100 ml), NaHCO<sub>3</sub> (5%, 2 × 100 ml), and H<sub>2</sub>O. After drying (Na<sub>2</sub>SO<sub>4</sub>), CHCl<sub>3</sub> was evaporated, and the residual oil was used in the next experiment. Part of the oil was crystallized (Et<sub>2</sub>O-petroleum ether) and recrystallized (EtOH-Et<sub>2</sub>O): mp 109-112°. *Anal.* (C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

**3-*O*-Benzyl- $\alpha^4, \alpha^5$ -*O*-isopropylidene- $\alpha^2$ -hydroxypyridoxol (8).** A solution of 14 (the total amount of the oily material from the preceding experiment) in CH<sub>2</sub>Cl<sub>2</sub> (dried over CaSO<sub>4</sub>, 75 ml) was cooled (ice bath). Trifluoroacetic anhydride (2.0 ml) was added while the solution was being stirred, and more (5.0 ml) was added after 5 min. The reaction mixture was stirred for 8 hr at room temperature, until no starting material could be detected by tlc. Then it was cooled to 0°, and MeOH (30 ml) was added while stirring was continued. The solvents were then evaporated. The oil was taken up in CHCl<sub>3</sub> and was washed with Na<sub>2</sub>CO<sub>3</sub> (20%), followed by H<sub>2</sub>O until neutral. It was then crystallized from EtOH-CHCl<sub>3</sub>, yielding 8.24 g (74%, based on amount of 12). The material was identical with 8 obtained by the other two methods already described.

**2-Formyl-2-norpyridoxol (1, R<sub>2</sub> = CHO).** A solution of 74 mg (0.24 mmol) of 15 in trifluoroacetic acid (10 ml) was stirred at room temperature for 3 hr, and then the acid was removed *in vacuo*. The residue was dissolved in H<sub>2</sub>O (1 ml), applied to an Amberlite CG-50 (200-400 mesh, H<sup>+</sup> form, 1.1 × 15 cm) column, and eluted with H<sub>2</sub>O. The acid fractions emerged first and were followed by neutral fractions containing the aldehyde. The neutral fractions were combined, and the aldehyde was crystallized from H<sub>2</sub>O-Me<sub>2</sub>CO: yield 15 mg (35%); mp 123-125°; uv  $\lambda_{\max}$  (pH 6.8) 248, 327, 386 nm; uv  $\lambda_{\max}$  (0.1 N NaOH) 243, 384 nm. *Anal.* (C<sub>8</sub>H<sub>9</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

**3-*O*-Benzyl- $\alpha^4, \alpha^5$ -*O*-isopropylidene-2-vinyl-2-norpyridoxol (16).** Triphenylmethylphosphonium bromide (900 mg, 3.43 mmol) was added under N<sub>2</sub> to a stirred and cooled (0°) mixture of a 1.6 M solution of *n*-butyllithium (1.5 ml) and a solution of 0.5 g of a 1:1 mixture of potassium *tert*-butoxide and *tert*-butyl alcohol in 8 ml of Et<sub>2</sub>O. The resulting mixture was stirred at room temperature for 2 hr. Then 15 (450 mg, 1.43 mmol) in Et<sub>2</sub>O (3 ml) was added within 15 min, and stirring was continued for another 12 hr. The reaction mixture was filtered, and the filtrate was diluted with Et<sub>2</sub>O. The dilute solution was treated with saturated NaHSO<sub>3</sub> and NH<sub>4</sub>Cl solutions, and finally with H<sub>2</sub>O. After drying (MgSO<sub>4</sub>), the solvent was evaporated to an oil, and the vinyl compound was separated from (C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>PO by chromatogra-

phy on silica gel, using EtOAc as the eluent: yield 358 mg (80%); nmr (CDCl<sub>3</sub>)  $\delta$  1.47 [(CH<sub>3</sub>)<sub>2</sub>C], 4.89 (3  $\times$  CH<sub>2</sub>), 5.43-6.67 (2-CH=CH<sub>2</sub>), 7.00-7.73 (2-CH=CH<sub>2</sub>), 7.50 (C<sub>6</sub>H<sub>5</sub>), 8.23 (C<sub>6</sub>-H); ir  $\lambda_{\max}$  (neat) 1605 cm<sup>-1</sup> (C=C). *Anal.* (C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>) C, H.

**2-Vinyl-2-norpyridoxol [1c (1, R<sub>2</sub> = CH=CH<sub>2</sub>)] Hydrochloride.** A solution of 16 (300 mg) in 1 N HCl (10 ml) was heated on a steam bath for 1 hr. After evaporation *in vacuo*, the residue was evaporated several times with H<sub>2</sub>O to remove excess HCl and benzyl alcohol: mp 201-203° dec from EtOH; yield 170 mg (77%); nmr (D<sub>2</sub>O)  $\delta$  4.78 (5-CH<sub>2</sub>), 5.02 (4-CH<sub>2</sub>), 5.90-6.50 (2-CH=CH<sub>2</sub>), 6.83-7.35 (2-CH=CH<sub>2</sub>), 8.27 (C<sub>6</sub>-H); ir  $\lambda_{\max}$  (KBr) 3340, 3200, 3100 (OH), 1612 cm<sup>-1</sup> (C=C); uv  $\lambda_{\max}$  (0.1 N HCl) 324 nm ( $\epsilon$  6485); uv  $\lambda_{\max}$  (0.1 N NaOH) 353 nm ( $\epsilon$  6360); uv  $\lambda_{\max}$  (pH 7) 367 nm ( $\epsilon$  6800). *Anal.* (C<sub>9</sub>H<sub>12</sub>ClNO<sub>3</sub>) C, H, Cl.

**$\alpha^2$ -Methylpyridoxol Hydrochloride.** To a solution of 18 in EtOH (5 ml), 5% Pd/C (12 mg) was added, and the mixture was hydrogenated for 30 min. After filtration and evaporation of the solvent, the product was crystallized from EtOH-Et<sub>2</sub>O: mp 192-195° (lit.<sup>17a</sup> mp 192°); yield 32 mg (79%).

**2-Ethyl-3-hydroxy-4,5-dimethylpyridine Hydrochloride.** To a solution of 2-vinyl-2-norpyridoxol hydrochloride (50 mg) in EtOH (3 ml) 10% Pd/C (30 mg) was added, and the solution was stirred for 24 hr in an atmosphere of H<sub>2</sub>. After filtration and evaporation the compound was crystallized from EtOH-petroleum ether: yield 32 mg (74%); mp 154-156°. *Anal.* (C<sub>9</sub>H<sub>14</sub>ClNO) C, H, N. This compound has also been obtained from  $\alpha^2$ -methylpyridoxol hydrochloride on hydrogenolysis under the conditions described here.

**3-O-Benzyl- $\alpha^4, \alpha^5$ -isopropylidene-2-( $\beta$ -chlorovinyl)-2-norpyridoxol (17).** The reaction conditions were similar to those described for 16, except that the ylide was generated from (chloromethyl)triphenylphosphonium chloride (1.9 g, 5.47 mmol) and was allowed to react with 15 (1.0 g, 2.9 mmol). Chromatography (silica gel, EtOAc as eluent) gave an oil (782 mg, 67%); nmr (CDCl<sub>3</sub>)  $\delta$  1.45 [(CH<sub>3</sub>)<sub>2</sub>C], 4.87 (3  $\times$  CH<sub>2</sub>), 5.83-7.33 (CH=CHCl), 7.50 (C<sub>6</sub>H<sub>5</sub>), 8.17 (C<sub>6</sub>-H); ir  $\lambda_{\max}$  (neat) 1610 cm<sup>-1</sup> (C=C). The compound was also characterized by the two hydrolysis products obtained as described in the next two paragraphs.

**3-O-Benzyl-2-( $\beta$ -chlorovinyl)-2-norpyridoxol Hydrochloride.** A solution of 17 in Et<sub>2</sub>O was treated with ethereal HCl. The precipitated hydrochloride was crystallized from hot EtOH, which resulted in cleavage of the isopropylidene group: mp 166-168° dec; nmr  $\delta$  (CDCl<sub>3</sub>) 4.82, 4.70, 5.02 (3  $\times$  CH<sub>2</sub>), 6.67-7.67 (CH=CHCl), 7.48 (C<sub>6</sub>H<sub>5</sub>), 8.25 (C<sub>6</sub>-H); ir  $\lambda_{\max}$  (KBr) 3380, 3310 (-OH), 1615 cm<sup>-1</sup> (C=C). *Anal.* (C<sub>16</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>3</sub>) C, H, Cl.

**2-( $\beta$ -Chlorovinyl)-2-norpyridoxol (1, R<sub>2</sub> = CH=CHCl) Hydrochloride.** The blocking groups in 19 were hydrolyzed as described for 16: yield 73%; mp 177-179° dec; nmr (D<sub>2</sub>O)  $\delta$  4.87 and 5.02 (4- and 5-CH<sub>2</sub>), 6.70-7.83 (CH=CHCl), 8.47 (C<sub>6</sub>-H); ir  $\lambda_{\max}$  (KBr) 1612 cm<sup>-1</sup>. *Anal.* (C<sub>9</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>3</sub>) C, H, N.

**3-O-Benzyl- $\alpha^4, \alpha^5$ -O-isopropylidene-2-ethynyl-2-norpyridoxol (18).** Fresh NaNH<sub>2</sub> was prepared according to the method of Vaughn, *et al.*,<sup>22</sup> from Na (69 mg), liquid NH<sub>3</sub> (10 ml), and Fe(NO<sub>3</sub>)<sub>2</sub> (0.6 mg). A solution of 17 (346 mg, 1 mmol) in Et<sub>2</sub>O (anhydrous, 10 ml) was added dropwise to the NaNH<sub>2</sub> solution during 1 hr. The reaction mixture was left at room temperature for 15 hr. The sodium acetylide formed was hydrolyzed by careful addition of 10% NH<sub>4</sub>Cl solution, and the products were extracted with Et<sub>2</sub>O, washed with H<sub>2</sub>O, and dried (MgSO<sub>4</sub>). The oily mixture obtained on evaporation of Et<sub>2</sub>O was separated on a silica gel column (eluted with 1:1 C<sub>6</sub>H<sub>6</sub>-Et<sub>2</sub>O), yielding 96 mg (30%) of 18 as an oil: nmr (CDCl<sub>3</sub>)  $\delta$  1.42 [(CH<sub>3</sub>)<sub>2</sub>C], 4.77 and 4.93 (4- and 5-CH<sub>2</sub>), 5.20 (CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 3.45 (C $\equiv$ CH), 7.47 (C<sub>6</sub>H<sub>5</sub>), 8.07 (C<sub>6</sub>-H);

ir  $\lambda_{\max}$  (neat) 3290 (C $\equiv$ CH stretching), 2210 cm<sup>-1</sup> (C $\equiv$ C). *Anal.* (C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>) C, H.

**2-Ethynyl-2-norpyridoxol [1d (1, R<sub>2</sub> = C $\equiv$ CH)] Hydrochloride.** The blocking groups in 18 were hydrolyzed with 1 N HCl as described for 16. The yield was only 32%; mp 155-157° dec, from EtOH-Et<sub>2</sub>O, with some difficulty; nmr (D<sub>2</sub>O)  $\delta$  4.52 (C $\equiv$ CH), 4.84 and 4.88 (4- and 5-CH<sub>2</sub>), 8.37 (C<sub>6</sub>-H); ir  $\lambda_{\max}$  (KBr) 3260 (C $\equiv$ CH stretching), 2120 cm<sup>-1</sup> (C $\equiv$ C). *Anal.* (C<sub>9</sub>H<sub>10</sub>ClNO<sub>3</sub>) C, H.

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