The hydrochloride, m.p. 225.6–226.4° (dec.) (corr., bath preheated to 210°), was recrystallized from an ethanol and ether mixture.

Anal. Calcd. for $C_8H_{11}BrClNO$: C, 38.04; H, 4.39; N, 5.55. Found: C, 37.87; H, 4.51; N, 5.65.

Method C. In a solution of 20 ml. of water and 16 ml. of 5% sodium hydroxide was dissolved 3.3 g. (0.02 mole) of *o*-azidobenzoic acid. To this solution was added a solution of 3.0 g. (0.080 mole) of sodium borohydride in 25 ml. of water. After being refluxed for 5 hr. the solution was cooled and made acidic with 10% hydrochloric acid. Following treatment with 10% sodium hydroxide until basic, the solution was made acidic with glacial acetic acid and upon storage in the refrigerator overnight crude anthranilic acid, m.p. and mixture m.p. 148–149°,[8] 1.9 g. (69%), was obtained. Extraction of the mother liquor with ether yielded an additional amount of the product. Upon recrystallization from hot water, a second crop of crystals weighing 0.5 g. (total yield 85%), m.p. and mixture m.p. 146–147°, was obtained.

Additional examples for each procedure are found in Table I.

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Hydrogenolysis of Fatty Acid Esters of 4-Desoxypyridoxine[1]

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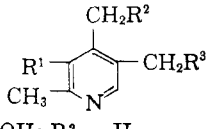
During the course of our investigation on the fatty acid esters of vitamin B_6, it was noted that the 5-ester linkage of 3,*O*-benzyl-4-desoxypyridoxine 5-palmitate (II) was cleaved when it was hydrogenated in the presence of platinum and palladium catalysts under 30 pounds pressure at room temperature. As was expected, debenzylation also took place during the treatment, and consequently free palmitic acid and 2,4,5-trimethyl-3-pyridinol (VII) were identified from the reaction mixture. Since this represented catalytic hydrogenolysis of the ester linkage, it appeared of interest to investigate further with some other derivatives of 4-desoxypyridoxine (I).



I, $R^1 = R^3 = OH$; $R^2 = H$
II, $R^1 = C_6H_5CH_2O—$; $R^2 = H$; $R^3 = CH_3(CH_2)_{14}COO—$
III, $R^1 = R^3 = CH_3COO—$; $R^2 = H$
IV, $R^1 = R^3 = CH_3(CH_2)_{14}COO—$; $R^2 = H$
V, $R^1 = CH_3(CH_2)_{14}COO—$; $R^2 = H$; $R^3 = OH$
VI, $R^1 = R^2 = OH$; $R^3 = H$
VII, $R^1 = OH$; $R^2 = R^3 = H$
VIII, $R^1 = CH_3(CH_2)_{14}COO—$; $R^2 = R^3 = H$

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When 4-desoxypyridoxine 3,5-dipalmitate(IV) or 4-desoxypyridoxine 3,5-diacetate(III) was similarly reduced, complete cleavage at the 5-position took place, and the 3-ester of 2,4,5-trimethyl-3-pyridinol(VII) was identified as a resultant compound. On the other hand, using 4-desoxypyridoxine(I) and 4-desoxypyridoxine 3-monopalmitate(V), it was found that when the 5-hydroxymethyl group was free, the reduction product was a mixture of compounds having a 5-hydroxymethyl group and a 5-methyl group. This indicates that cleavage of the 5-esters of 4-desoxypyridoxine(I) under 30 pounds hydrogen pressure in the presence of platinum and palladium catalysts at room temperature is direct hydrogenolysis and it is not catalytic hydrolysis of the ester linkage followed by reduction. Similar observation has been made with codecarboxylase, or vitamin B_6 5-phosphate.[2]

The ester linkage at the 3-position was hardly cleaved by hydrogenolysis. An attempt to isolate free palmitic acid from the hydrogenation mixture of 2,4,5-trimethyl-3-pyridinol palmitate(VIII) was unsuccessful, and the unchanged original compound was recovered.

It is known that pyridoxine can be directly reduced to 4-desoxypyridoxine(I)[3] or to a mixture of 4- and 5-desoxypyridoxines (I,VI).[2] Under the conditions presently employed, reduction of pyridoxine resulted in the formation of, among other compounds, 2,4,5-trimethyl-3-pyridinol(4,5-bisdesoxypyridoxine)(VII). 4-Desoxypyridoxine(I) as well as 5-desoxypyridoxine(VI) is a potential antivitamin B_6.[4] In the present study, 2,4,5-trimethyl-3-pyridinol(VII) was also found to be a reversible antagonist of pyridoxine to *Saccharomyces carlsbergensis*(ATCC 4228), and its inhibition potency was $^1/_8$ that of 4-desoxypyridoxine(I) on a molar basis.[5] The preparations of 2,4,5-trimethyl-3-pyridinol(VII) used for the test were obtained from 4-desoxypyridoxine(I) and from pyridoxine *via* bromination of the hydroxymethyl groups[6,7] followed by reduction.[3] The two preparations thus obtained showed an identical inhibition pattern for the growth of the assay organism eliminating the possibility that the inhibition might have been due

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to contamination with 4-desoxypyridoxine(I) or the apparent inhibition might have been hindered by the presence of unchanged pyridoxine.

EXPERIMENTAL

3,O-Benzyl-4-desoxypyridoxine 5-palmitate (II). 3,O-Benzyl-4-desoxypyridoxine hydrochloride was prepared according to the procedure reported previously.[8] M.p. 201.0–202.0°. (Lit.,[8] 183–185°).

Anal. Calcd. for $C_{15}H_{17}NO_2 \cdot HCl$: C, 64.39; H, 6.48; N, 5.01. Found: C, 64.72; H, 6.45; N, 4.85.

Four hundred milligrams of 3,O-benzyl-4-desoxypyridoxine hydrochloride was acylated with palmitoyl chloride by the conventional procedure in a chloroform-pyridine mixture. The resulting product was recrystallized from acetone-water. Yield: 370 mg. (54%). M.p. 46.0–47.0°.

Anal. Calcd. for $C_{31}H_{47}NO_3$: C, 77.29; H, 9.84; N, 2.91. Found: C, 77.47; H, 9.94; N, 2.79.

Hydrochloride of 4-desoxypyridoxine 3,5-diacetate (III). Two hundred milligrams of 4-desoxypyridoxine hydrochloride (I) was suspended in a mixture of 3 ml. of acetic anhydride and 3 ml. of glacial acetic acid. The suspension was refluxed for one hour. By the end of this period of time, a clear mixture was obtained. 4-Desoxypyridoxine diacetate hydrochloride (III) was precipitated upon addition of ether. Recrystallization was effected from methanol-ether as needles. The product was negative to the *N*,2,6-trichloro-*p*-quinoneimine test. Yield: 200 mg. (70%). M.p. 157.5–159.0°.

Anal. Calcd. for $C_{12}H_{15}NO_4 \cdot HCl$: N, 5.12. Found: N, 5.10.

Hydrochloride of 4-desoxypyridoxine 3-monopalmitate (V). Nine hundred fifty milligrams of 4-desoxypyridoxine hydrochloride(I) was dissolved in 30 ml. of water containing 450 mg. of sodium hydroxide. With stirring, approximately 25 ml. of acetone containing 1.37 g. of palmitoyl chloride was added in one portion at room temperature. Stirring was continued for 2 hr. The product was extracted with ether and the extract was washed with 5% potassium carbonate solution and water successively. After drying over anhydrous sodium sulfate, the solvent was removed and the residue was recrystallized from ethanol. The product was negative to the *N*,2,6-trichloro-*p*-quinoneimine test. It had a m.p. of 89.0–91.0°.

Anal. Calcd. for $C_{24}H_{41}NO_3$ (4-desoxypyridoxine monopalmitate): C, 73.61; H, 10.55; N, 3.58. Found: C, 74.72; H, 10.64; N, 2.70.

These data indicated that the reaction product was a mixture of 4-desoxypyridoxine 3-monopalmitate (V) and 4-desoxypyridoxine 3,5-dipalmitate (IV).

The reaction product was dissolved in a mixture of isopropyl alcohol and absolute ether (1:5, v/v), and treated with hydrogen chloride gas. The hydrochloride of 4-desoxypyridoxine 3-monopalmitate (V) precipitated immediately, whereas 4-desoxypyridoxine 3,5-dipalmitate (IV) remained in solution. The precipitate was collected and washed with ether thoroughly. M.p. 172.0–172.5°.

Anal. Calcd. for $C_{24}H_{41}NO_3 \cdot HCl$: N, 3.27; Cl, 8.28. Found: N, 3.24; Cl, 8.05.

2,4,5-Trimethyl-3-pyridinol palmitate (VIII). 2,4,5-Trimethyl-3-pyridinol (VII) was prepared from 2-methyl-3-hydroxy-4,5-dibromomethylpyridine,[6] or from 2,4-dimethyl-3-hydroxy-5-bromomethylpyridine[7] through reduction.[3] The pyridinol was esterified with palmitoyl chloride in a mixture of chloroform-pyridine. The product was recrystallized from methanol. Yield: 800 mg. (64%) from 750 mg. of 2,4,5-trimethyl-3-pyridinol (VII). M.p. 58.0–60.0°.

Anal. Calcd. for $C_{24}H_{41}NO_2$: C, 76.74; H, 11.00; N, 3.73. Found: C, 76.77; H, 10.84; N, 3.41.

The hydrochloride of 2,4,5-trimethyl-3-pyridinol palmitate (VIII) was recrystallized from ethanol-ether. M.p. 139.0–140.0°.

Anal. Calcd. for $C_{24}H_{41}NO_2 \cdot HCl$: Cl, 8.61. Found: Cl, 8.82.

Paper chromatography. For the detection of 4-desoxypyridoxine hydrochloride (I) and 2,4,5-trimethyl-3-pyridinol hydrochloride (VII), a descending system on Whatman No. 1 filter paper using 1-butanol saturated with water at room temperature was employed. The chromogenic reagent was a 0.1% solution of *N*,2,6-trichloro-*p*-quinoneimine in benzene. The paper strip was sprayed with the reagent and then was exposed, after drying, to ammonia vapor. 2,4,5-Trimethyl-3-pyridinol (VII) revealed a violet spot in contrast to 4-desoxypyridoxine (I) which appeared as a blue spot. Typical R_f values were 0.63–0.65 for 4-desoxypyridoxine hydrochloride (I) and 0.78–0.83 for 2,4,5-trimethyl-3-pyridinol hydrochloride (VII). Throughout this study, reference compounds were run concurrently with the unknown on the same strip.

Reduction and hydrogenolysis. The sample was dissolved in methanol, ethanol, or isopropanol, and hydrogenated under 30 pounds pressure at room temperature for 2 hr. in the presence of about half the weight each of platinum oxide and 5% palladium on charcoal.

Hydrogenolysis of 3,O-benzyl-4-desoxypyridoxine 5-palmitate (II). Three hundred fifty milligrams of 3,O-benzyl-4-desoxypyridoxine 5-palmitate (II) was hydrogenated in 10 ml. of 95% ethanol. After hydrogenation, the catalysts were removed by filtration and the solvent was removed until dryness. The residue was recrystallized from acetone-water. The product (90 mg.) was identified as free palmitic acid by mixed melting point with an authentic specimen and by neutralization equivalent. The hydrogenated mixture was also paper chromatographed; the only fraction observed was 2,4,5-trimethyl-3-pyridinol (VII).

Hydrogenolysis of 4-desoxypyridoxine 3,5-diacetate (III). Thirty milligrams of the hydrochloride of 4-desoxypyridoxine 3,5-diacetate (III) in 10 ml. ethanol was hydrogenated. The hydrogenated solution was negative to the *N*,2,6-trichloro-*p*-quinoneimine test indicating that the acyl group at the 3-position remained intact. After removing the catalysts, an equal volume of 4*N* ethanolic potassium hydroxide was added and the mixture refluxed for 30 min. The solution was acidified using Congo red with ethanolic hydrogen chloride and applied to a papergram. The only spot observed was 2,4,5-trimethyl-3-pyridinol (VII) free from 4-desoxypyridoxine (I).

Hydrogenolysis of 4-desoxypyridoxine 3,5-dipalmitate (IV). Five hundred milligrams of 4-desoxypyridoxine 3,5-dipalmitate (IV)[6] was dissolved in 30 ml. of isopropyl alcohol and hydrogenated. The hydrogenated solution was negative to the *N*,2,6-trichloro-*p*-quinoneimine test. After removing the catalysts, the solvent was evaporated until dryness. The residue was extracted with ether and the ether extract was washed with potassium carbonate solution. The ether layer was dried over anhydrous sodium sulfate and the solvent was removed. The residue was recrystallized from ethanol–water. The product (27.5 mg.) melted at 58.0–60.0°. A mixed melting point with 2,4,5-trimethyl-3-pyridinol palmitate (VIII) was also 58.0–60.0°. Paper chromatography of the alkali hydrolysate of this product confirmed the presence of 2,4,5-trimethyl-3-pyridinol (VII) free from 4-desoxypyridoxine (I).

The alkali wash was acidified with hydrochloric acid; the precipitate was collected, and was recrystallized from methanol. The product (110 mg.) was identified as free palmitic acid.

Reduction of 4-desoxypyridoxine (I). Three hundred milligrams of 4-desoxypyridoxine hydrochloride (I) was hydrogenated in 30 ml. of methanol. After removing the catalysts,

(8) R. F. Long and A. L. Morrison, *J. Chem. Soc.*, 3854 (1954).

the solution was tested by paper chromatography, which revealed two spots, one for 4-desoxypyridoxine (I) and the other for 2,4,5-trimethyl-3-pyridinol (VII). The solvent was then removed, and the residue was separated into two fractions: one was soluble in isopropyl alcohol and the other was insoluble. The former fraction was precipitated by adding ether. Yield: 25 mg. M.p. 215.0–216.0°. This was identified as 2,4,5-trimethyl-3-pyridinol hydrochloride (VII) by mixed melting point and by paper chromatography. The insoluble fraction was recrystallized from methanol-ether as fine needles (30 mg.). M.p. 267.0–268.0°. A mixed melting point with authentic 4-desoxypyridoxine hydrochloride (I) was also 267.0–268.0°. Paper chromatography showed that this fraction was 4-desoxypyridoxine hydrochloride (I).

Reduction of 4-desoxypyridoxine 3-monopalmitate (V). Five hundred milligrams of 4-desoxypyridoxine 3-monopalmitate (V) was hydrogenated in 30 ml. of isopropyl alcohol. The hydrogenated mixture was negative to the *N*,2,6-trichloro-*p*-quinoneimine test. After removal of the catalysts and the solvent, the residue was extracted with approximately 50 ml. of absolute ether. To this extract, ethanolic dry hydrogen chloride was added. The precipitate (75 mg.) melted at 153–159°. This product appeared to be a mixture of the hydrochlorides of 4-desoxypyridoxine 3-monopalmitate (V) and 2,4,5-trimethyl-3-pyridinol palmitate (VIII). This product after being refluxed in 2*N* ethanolic potassium hydroxide solution for 30 min. followed by acidification with alcoholic hydrogen chloride to Congo red gave two spots for 4-desoxypyridoxine hydrochloride (I) (intense) and 2,4,5-trimethyl-3-pyridinol hydrochloride (VII) (weak) upon paper chromatography.

Reduction of 2,4,5-trimethyl-3-pyridinol palmitate (VIII). Five hundred milligrams of 2,4,5-trimethyl-3-pyridinol palmitate (VIII) in 35 ml. of ethanol was hydrogenated. After removing the catalysts, the solvent was removed until dryness. The residue was extracted with ether, and the solution added to dry ether which contained hydrogen chloride. The precipitate (400 mg.) melted at 140.0–141.0°; a mixed melting point with the hydrochloride of 2,4,5-trimethyl-3-pyridinol palmitate (VIII) was 139.0–140.0°. No palmitic acid was isolated from the remaining ether extract.

Reduction of pyridoxine. One gram of pyridoxine hydrochloride was hydrogenated in 80 ml. of methanol. The catalysts were removed by filtration and the solution was evaporated until dryness. The residue had a melting point (241°) which was higher than any of the possible products, pyridoxine hydrochloride (206–208°), 5-desoxypyridoxine hydrochloride (VI) (143–143.5°),[2] and 2,4,5-trimethyl-3-pyridinol hydrochloride (VII) (216°). This suggested that the residue might contain 4-desoxypyridoxine hydrochloride (I) (267–268°). Upon paper chromatography, the residue revealed two spots corresponding to 4-desoxypyridoxine hydrochloride (I) and 2,4,5-trimethyl-3-pyridinol hydrochloride (VII).

The residue was dissolved in 5 ml. of water. Excess of potassium carbonate was added to make the solution alkaline, and the solution extracted with chloroform. The chloroform extract was thoroughly washed with water and after drying over anhydrous sodium sulfate, the solvent was removed. The residue was taken up in ethanol and upon addition of ether containing dry hydrogen chloride, a precipitate was obtained. Recrystallization was effected from approximately 3 ml. of absolute ethanol at −5°. Yield: 150 mg. M.p. 216.0–217.0°. A mixed melting point with authentic 2,4,5-trimethyl-3-pyridinol hydrochloride (VII) was 215.0–216.0°. This product was paper chromatographically homogeneous and showed an inhibition potency equivalent to that of authentic 2,4,5-trimethyl-3-pyridinol (VII) for the growth of *Saccharomyces carlsbergensis* (ATCC 4228).[5]

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Reduction of Polycyclic Phenols to Hydrocarbons

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In the course of studies on the Veratrum alkaloids, we recently had occasion[1] to reduce to the parent aromatic hydrocarbon a small amount of a phenolic degradation product,[2,3] $C_{18}H_{16}O$, derived from rubijervine[4,5] by selenium dehydrogenation. Experiments with zinc dust distillation showed that at temperatures high enough to effect reduction the only hydrocarbon isolated was chrysene, and this was subsequently shown to be a rearrangement product.[1] These circumstances, and the experience of other workers who have encountered unidentified phenols[6–10] during dehydrogenations, called to our attention the fact that few methods[9,11,12] are available to the natural product chemist for the reduction of small quantities (50–200 mg.) of phenols by procedures mild enough to preclude rearrangement.

In searching for a method which might be applicable to the small-scale reduction of phenols, we noted the recent paper of Kenner and Williams[13] which describes the conversion of phenols to aryl diethyl phosphates and their subsequent reduction to aromatic hydrocarbons with sodium or lithium in liquid ammonia.

$$\mathrm{ArOH} + \mathrm{HO{-}P(O)(OC_2H_5)_2} + \mathrm{CCl_4} + (\mathrm{C_2H_5})_3\mathrm{N} \longrightarrow \mathrm{ArOP(O)(OC_2H_5)_2} + \mathrm{CHCl_3} + (\mathrm{C_2H_5})_3\mathrm{N{\cdot}HCl}$$

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