mol) of oxanilyl chloride dissolved in 50 ml of ethyl acetate. After refluxing for 4 hr under dry conditions, the reaction mixture was cooled and 2 g of solid was removed by suction filtration. The filtrate was evaporated to a syrup, the syrup was stirred with 95% ethanol, and the ethanolic solution was chilled in a freezer to give crystals of the desired product. A second crop was collected by concentrating the ethanolic filtrate, giving a total of 3.73 g (53%). Ir spectra of the products from methods A and B were identical.

Anal. Calcd: N, 10.08. Found: N (micro Kjeldahl), 10.33.

N-Oxanilyl-α-aminoisobutyric Acid (6).—The finely powdered ester (5.25 g, 0.018 mol) was suspended in 500 ml of 0.5 *N* sodium hydroxide solution plus 100 ml of 95% ethanol. After the mixture had been stirred for 1 hr at room temperature (28°), a small amount of unreacted material was removed by suction filtration. The filtrate was acidified to pH 2 with concentrated hydrochloric acid, the mixture being cooled in an ice bath. The precipitate was collected by filtration, washed with cold acidified water, and dried at 100°: yield, after recrystallization from 95% ethanol, 3.44 g (73%); mp 203–204°.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 56.45; H, 5.60; N, 11.18. Found: C, 56.97; H, 5.61; N, 11.31.

Attempted Cyclization of 6.—A sample of 2.0 g of **6** was added to 15 ml of acetic anhydride and the mixture was heated on a steam bath for 45 min. Excess acetic anhydride was distilled off at 24° (1.8 mm), and the syrupy residue remaining in the distillation flask was chilled in a freezer. The crystals which separated were obtained by suction filtration. Two crops were combined and recrystallized from benzene plus *n*-pentane, yielding 0.83 g (36%) of product which analyzed for the mixed anhydride **7**, mp 103–104°.

Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.60; H, 5.52; N, 9.57. Found: C, 57.63; H, 5.57; N, 9.23.

Registry No.—α-Aminoisobutyric acid ethyl ester hydrochloride, 17288-15-2; **1b** diethyl ester, 17288-16-3; **1b**, 17288-17-4; mixed anhydride from **1b** and acetic acid, 17288-18-5; **2b**, 17288-19-6; **3** diethyl ester, 17288-20-9; **3**, 17288-21-0; barium salt of **3**, 17288-22-1; **6** ethyl ester, 17288-23-2; **6**, 17288-24-3; **7**, 17288-25-4.

Synthesis of Fat-Soluble Analogs of Pyridoxal 5′-Phosphate[1]

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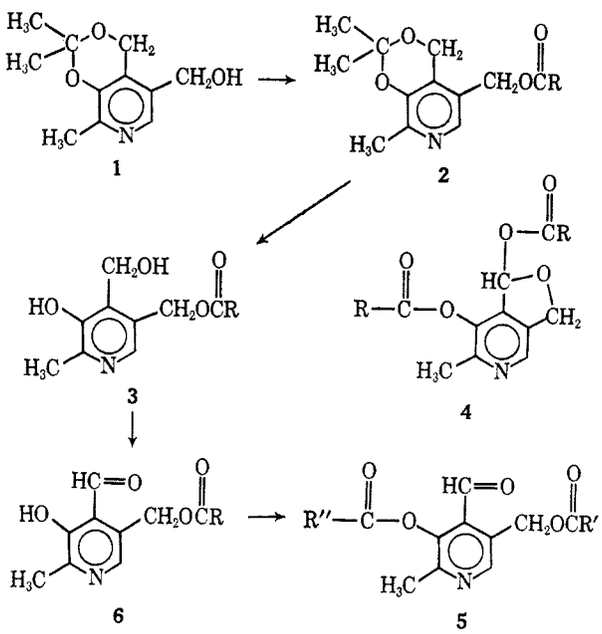
The coenzymatic form of vitamin B_6 is pyridoxal 5′-phosphate. Very few analogs of this compound in which the phosphate ester has been replaced by another acidic group[2] and none in which it has been replaced with a carboxylic acid have been reported. Our interest in the biological properties of such compounds prompted us to synthesize the compounds pyridoxal 5′-palmitate and pyridoxal 5′-benzoate (**6a** and **6b**). Furthermore, we converted these esters into 3,5′ diesters. Such diesters of pyridoxal have not been previously synthesized. The pyridoxal 5′ esters were prepared using methods reported for the synthesis of analogous compounds[3] (see Scheme I).

SCHEME I



a, R = $(CH_2)_{14}CH_3$
b, R = C_6H_5
c, R′ = $(CH_2)_{14}CH_3$; R″ = CH_3
d, R′ = C_6H_5; R″ = CH_3
e, R′ = R″ = $(CH_2)_{14}CH_3$

When pyridoxal 5′ esters (**6a** and **6b**) were treated with acetic anhydride or palmitoyl chloride in pyridine, the corresponding pyridoxal 3,5′ diesters (**5c**, **5d**, and **5e**) were obtained. The diesters are of special interest in view of the recent work of Prosser, Sheppard, and Libby[4] who claimed to have synthesized pyridoxal 3,5′-diacetate by treating pyridoxal hydrochloride in pyridine–chloroform mixture with acetic anhydride. Korytnyk, *et al.*,[5,6] have conclusively established the structure of the compounds obtained when pyridoxal is treated with acetic anhydride or palmitoyl chloride as pyridoxal 3,4′ diesters (1,3-dihydro-1,7-diacyloxy-6-methylfuro[3,4-*c*]pyridine) (**4**), thus questioning the previously reported synthesis of pyridoxal 3,5′-dipalmitate.[7] However, Prosser, *et al.*,[4] to explain the nuclear magnetic resonance (nmr) spectrum of the compound which they had obtained (aldehydic proton signal and lack of acetal proton signal), attributed its pyridoxal 3,5′ diester structure to possible isomerization during the isolation procedure. It has been shown in the literature that, since pyridoxal exists predominantly in the cyclic hemiacetal form,[8] attempts to esterify[5,6] or etherify[9,10] it directly will result in the formation of the corresponding cyclic 4′ ester or acetal derivative. Nevertheless, the possibility existed that a rearrangement took place in the course of drying and neutralization, resulting in the formation of the free aldehyde form.

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TABLE I

SPECTRAL DATA

Compound	λ_{max}, mμ ($\epsilon_{max} \times 10^{-3}$) 0.01 *N* HCl–MeOH	0.01 *N* NaOH–MeOH	$CHCl_3$	λ_{max}, cm^{-1} (>C=O stretch) CCl_4	KBr	Nmr characteristics[a] 2-CH_3	4-CH_2	5-CH_2	6-H	Other
Isopropylidenepyridoxol 5′-palmitate (**2a**)	230 (sh) (5.0) 292 (9.1)	281 (5.8)			1745	2.40	4.85	4.98	8.03	1.25 (aliphatic CH_2) 1.53 (*gem*-dimethyl)
Isopropylidenepyridoxol 5′-benzoate (**2b**)	229 (18.7) 292 (9.5)	229 (18.2) 281 (6.9)			1724	2.43	4.93	5.23		1.53 (*gem*-dimethyl) 7.33–8.08 (phenyl + pyridine 6-H
Pyridoxol 5′-palmitate (**3a**)	230 (sh) (2.9) 292 (8.9)	247 (7.2) 310 (6.9)			1740	2.42	5.05[b]	4.98[b]	7.08	1.25 (aliphatic CH_2)
Pyridoxol 5′-benzoate (**3b**)	230 (17.1) 294 (9.7)	229 (17.3) 249 (sh) (6.4) 310 (5.8)			1720	Insoluble in $CHCl_3$				
Pyridoxal 5′-palmitate (**6a**)	230 (sh) (3.8) 296 (8.9)	232 (13.1) 312 (1.1) 390 (5.0)	251 (5.6) 292 (sh) (0.69) 352 (3.9)	1665, 1747	1660, 1682, 1730, 1741	2.57		5.41	8.28	1.25 (aliphatic CH_2) 10.40 (4-CHO) 11.33 (3-OH)
Pyridoxal 5′-benzoate (**6b**)	229 (10.7) 296 (7.8)	230 (15.2) 314 (2.0) 390 (3.4)	285 (2.0) 350 (2.4)	1665, 1727	1655, 1727	2.56		5.65	8.30	7.33–8.16 (phenyl) 10.50 (4-CHO)
Pyridoxal 3-acetate 5′-palmitate (**5c**)	276 (8.2)	250 (7.8)[c,d] 319 (7.7)	307 (3.7)	1712, 1745, 1783	1695, 1735, 1758	2.50		5.43	8.62	1.25 (aliphatic CH_2) 2.41 (acetate CH_3) 10.27 (4-CHO)
Pyridoxal 3-acetate 5′-benzoate (**5d**)	230 (14.1) 275 (8.2)	229 (19.3)[c,d] 249 (sh) (9.7) 319 (7.6)	285 (sh) (3.2) 308 (3.8)	1715, 1743, 1780	1695, 1725, 1775	2.50		5.66	8.53	2.40 (acetate CH_3) 7.16–8.16 (phenyl) 10.38 (4-CHO)
Pyridoxal 3,5′-dipalmitate (**5e**)	277 (7.0)	249 (6.1)[c,d] 309 (5.6)	309 (2.8)	1713, 1747, 1770	1702, 1725, 1750, 1770	2.48		5.40	8.57	1.25 (aliphatic CH_2) 10.26 (4-CHO)

[a] In parts per million (δ) units from TMS internal standard, with all peaks singlets except phenyl proton signals which were complex multiplets. [b] Tentative assignment. [c] Such absorption is usually indicative of a dissociable phenolic group,[d] which should not be present in these structures. In each case, after the spectra were run in alkaline methanol, the solutions in the cuvettes were acidified with methanolic hydrochloric acid and their spectra were run again. With each of these compounds, the new absorption maximum in acidic solution was at about 295 mμ, again suggesting a free phenolic group.[d] A reaction had apparently taken place in alkaline solution which resulted in the formation of a compound with a free 3-OH group. The possibility of simple saponification of the esters was unlikely, since the alkaline spectra did not resemble those of the parent pyridoxal 5′ esters or pyridoxal. In spite of this anomalous behavior, the alkaline spectra were reproducible and characteristic of the compounds. Further work to investigate this phenomenon is in progress. [d] J. Baddiley and A. P. Mathias, *J. Chem. Soc.*, 2583 (1952).

To clarify the structure of the product obtained from pyridoxal and acetic anhydride by the procedure of Prosser, *et al.*,[4] we repeated their synthesis. As stated, the product first appeared as a "light brown oily residue," but crystallized after standing awhile. The solid residue was recrystallized from ether–petroleum ether to give a compound of mp 106–108°[6] which had similar ultraviolet (uv) and infrared (ir) spectra to those reported by Prosser, *et al.*, for the "oily residue." Its nmr spectrum in chloroform-*d* though, was somewhat different from that reported by them and similar to that reported by Korytnyk, *et al.*,[5,6] for pyridoxal 3,4′-diacetate and -dipalmitate (**4**). Moreover, the uv spectra in chloroform solution of the pyridoxal 3,5′ diesters which we have synthesized show maximum absorptions at about 310 mμ, and their ir spectra in carbon tetrachloride show three well-resolved absorption peaks in the 1600–1800-cm^{-1} region, two for the esters (phenolic and benzylic), and one for the free 4-formyl group. This was considerably in variance with the 270-mμ absorption and the weak poorly resolved shoulders on the 1755-cm^{-1} peak reported by Prosser, *et al.*[4]

Although it was not specified in the Prosser, Sheppard, and Libby report,[4] it was assumed that they determined their nmr spectra in chloroform. While the nmr spectrum of the proposed pyridoxal 3,5′-diacetate is basically as reported by these authors, two significant points were overlooked. Prosser, *et al.*,[4] stated that no peak was found at −255 cps (δ 4.83 ppm) to account for the acetal proton. Indeed there was none in our spectrum, but there was one at δ 7.33 ppm which is where one would expect to find it by using pyridoxal 3,4′-dipalmitate (**4**) as a model compound.[5] This might be easily overlooked, as it overlaps that of the $CHCl_3$ naturally occurring in the $CDCl_3$ solvent. Close examination of the peak attributed to the 5-CH_2 group showed it to be a portion of an AB quartet with the two outside peaks very small and almost hidden by background noise. It seems, therefore, that the peak at −617 cps (δ 10.28 ppm) was due to an impurity, since the preparation did not provide for purification of the sample. Thus, it must be concluded that the presumed pyridoxal 3,5′-diacetate,[4] like the previously reported pyridoxal 3,5′-dipalmitate,[7] was in fact the cyclic diester with structure (**4**).

An unambiguous synthesis of pyridoxal 3,5′-dipalmitate is presented herein. Verification of the structures of the new compounds was generally straightforward, the only exception being the anomalous infrared spectra of pyridoxal 5′-palmitate and pyridoxal 3,5′-dipalmitate in potassium bromide pellets. With these compounds some of the carbonyl peaks appeared as doublets in potassium bromide pellets, but collapsed to sharp singlets when run in carbon tetrachloride solution. Compounds **1** and **2** gave negative Gibbs tests,[11] while **3** and **6** gave positive ones. Pyridoxal 5′-palmitate and -benzoate produced the blue coloration very slowly (in about 1 min).

The pyridoxal 3,5′ diesters were all sensitive to moisture and very susceptible to hydrolysis. They would in fact hydrolyze very slowly upon contact with atmospheric moisture.

Spectral data are given in Table I.

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Experimental Section[12]

5-(Palmitoxymethyl)-2,2,8-trimethyl-4H-*m*-dioxino[4,5-*c*]pyridine (Isopropylidenepyridoxol 5′-Palmitate) (2a).—Isopropylidenepyridoxol (1,[13] 1.68 g) was dissolved in 100 ml of anhydrous pyridine, and 3 ml of palmitoyl chloride was added quickly. The mixture was stirred at room temperature overnight, at which time 100 ml of petroleum ether (bp 30–60°) was added. This solution was washed twice with 0.1 *N* aqueous hydrochloric acid, with 1.0 *M* aqueous potassium carbonate until no further interfacial emulsion was formed (about ten times), dried over sodium sulfate, and evaporated to dryness at room temperature. The resulting white residue of isopropylidenepyridoxol 5′-palmitate weighed 2.34 g (65%, mp 45–48°). Recrystallization from methanol raised the melting point to 50–51° (lit.[14] mp 43–44°).

2-Methyl-3-hydroxy-4-hydroxymethyl-5-palmitoxymethylpyridene (Pyridoxol 5′-Palmitate) (3a).—This compound was prepared by the method of Korytnyk and Paul[14] except that the product was crystallized from methanol–water and then acetone–petroleum ether: mp 104–105° (lit.[7,14] mp 72–76 and 99–100°).

2-Methyl-3-hydroxy-4-formyl-5-palmitoxymethylpyridine (Pyridoxal 5′-Palmitate) (6a) and 2-Methyl-3-hydroxy-4-formyl-5-benzoxymethylpyridine (Pyridoxal 5′-Benzoate) (6b).—Pyridoxol 5′-palmitate (**3a**) or -benzoate[15] (**3b**, 0.25 g) was dissolved in 20 ml of chloroform or anhydrous methanol, respectively. Manganese dioxide "B" [16] (1 g) was added, and the suspension was stirred 36 hr at room temperature. Most of the manganese dioxide was removed by filtering the mixture through a fine paper filter. The solvent was evaporated to a volume of about 1 ml and applied to a 2 in. × 1 in. silicic acid chromatographic column. The pyridoxal 5′-palmitate or -benzoate was eluted with chloroform. The elution could be monitored visually owing to the yellow color of the product. As the desired products passed through the column, the manganese dioxide remained on top. The chloroform eluate was evaporated at room temperature, and the residue was taken up in acetone. The products were precipitated with water, filtered, and dried. The yield of the palmitate was 0.18 g (72%) with mp 66–68°, which was raised to 68–70° by recrystallization from methanol. A yield of 0.77 g (77%) was obtained with the benzoate. Its melting point was 95–106°, which was raised to 106–108° with recrystallization from methanol.

Anal. Calcd for $C_{24}H_{39}NO_4$: C, 71.07; H, 9.69; N, 3.45. Found: C, 71.27; H, 9.63; N, 3.64. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.13. Found: C, 66.10; H, 4.92; N, 5.14.

2-Methyl-3-acetoxy-4-formyl-5-palmitoxymethylpyridine (Pyridoxal 3-Acetate 5′-Palmitate) (5c), 2-Methyl-3-acetoxy-4-formyl-5-benzoxymethylpyridine (Pyridoxal 3-Acetate 5′-Benzoate) (5d), and 2-Methyl-3-palmitoxy-4-formyl-5-palmitoxymethylpyridine (Pyridoxal 3,5′-Dipalmitate) (5e).—To a solution of 0.25 g of pyridoxal 5′-palmitate or benzoate in 20 ml of dry pyridine was added 1.2 equiv of acetic anhydride or palmitoyl chloride. The solution was allowed to stand 3–4 hr at room temperature. The solvent was removed under reduced pressure, and the residue was taken up in dry acetonitrile. Upon refrigeration for several hours, 0.21 g (77%, mp 63–65°), 0.22 g (77%, mp 98–100°), 0.36 g (90%, mp 64–69°), respectively, of pyridoxal 3-acetate 5′-palmitate, pyridoxal 3-acetate 5′-benzoate, and pyridoxal 3,5′-dipalmitate were obtained. The melting points were raised to 65–67°, 108–109°, and 68–69° with two recrys tallizations from dry acetonitrile.

Anal. Calcd for $C_{26}H_{41}NO_5$: C, 69.77; H, 9.23; N, 3.13. Found: C, 69.73; H, 9.37; N, 3.41. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.73; H, 4.99; N, 4.69. Calcd for $C_{40}H_{69}NO_5$: C, 74.60; H, 10.80; N, 2.17. Found: C, 74.61; H, 10.84; N, 1.89.

(12) Ultraviolet spectra were determined with a Cary recording spectrometer, Model 11M. Nuclear magnetic resonance spectra were obtained using a Varian A-60A instrument at 60 Mcps. Compounds were used as 30% solutions in deuterated chloroform. Results are expressed in parts per million (δ) units from tetramethylsilane as internal standard. Infrared spectra were recorded with a Beckman IR-7 spectrometer, with samples used as potassium bromide pellets or 10% solutions in carbon tetrachloride. Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill. All melting points are corrected.

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Registry No.—**2a**, 14320-27-5; **2b**, 17288-58-3; **3a**, 14210-75-4; **3b**, 17288-60-7; **5c**, 17288-61-8; **5d**, 17288-62-9; **5e**, 1961-81-5; **6a**, 17288-64-1; **6b**, 17288-65-2.

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A Synthesis of Sempervirine[1]

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Sempervirine, an interesting indole alkaloid obtained from *Gelsemium sempervirens*, Ait.,[2,3] has been the subject of several communications relating to its synthesis.[4–7] We now wish to report a very convenient route to sempervirine that should be capable of extension to related ring systems.

Condensation of α-picolinium salts having an active methylene group as part of the substituent on the nitrogen atom, as, *e.g.*, in 2-methyl-1-ethoxycarbonylmethylpyridinium halides, with suitable α diketones has been shown[8] to be a very effective route to quinolizinium salts. In most instances, spontaneous hydrolysis and decarboxylation of the original ester function occurred but under certain conditions,[8] the ester group could be retained in the resulting quinolizinium salt. As sempervirine contains the quinolizinium nucleus, this procedure should provide a simple route for its synthesis and this expectation was borne out as described below.

Quaternization of harman with ethyl bromoacetate occurred in excellent yield, either at the reflux temperature in benzene, or at room temperature in ethanol. Similarly, reaction of harman with methyl iodide was found to give the corresponding methiodide in good yield. That reaction had occurred at N-2 in both cases was indicated by the analytical data and also by the visible and ultraviolet absorption spectral characteristics of these salts. The development of anhydro-

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