layer were washed successively with H_2O (2 × 20 ml), 2 *N* HCl (2 × 20 ml), and 10% aq Na_2CO_3 (2 × 20 ml) and dried (Na_2SO_4).

Removal of solvent gave the oily 2-nitrile (0.67 g, 87%), which recrystd as colorless needles, mp 104–108°, from Me_2CO–Et_2O: ν_{max}^{Nujol} 2200 cm^{-1} (s) CN; P^+, *m/e* 226.146668 ($C_{15}H_{18}N_2$).

A soln of the nitrile (0.205 g) in 6% HCl (20 ml) was heated under reflux for 18 hr. The cooled soln was basified (NH_4OH) and extd with Et_2O (3 × 20 ml), and the Et_2O soln in turn was extd wih 2 *N* HCl (3 × 20 ml).

Basification (NH_4OH) of the acid soln followed by Et_2O (3 × 20 ml) extn, gave on evapn of the dried (Na_2SO_4) soln **9a**·base (0.14 g, 78%).** **3,5-Dimethyl-6,7-benzomorphan·HBr** crystd as prisms from EtOH–Et_2O and had mp 228–230°. *Anal.* ($C_{14}H_{20}BrN$) C, H, N.

4,5-Dimethyl-6,7-benzomorphan·HCl (9b·HCl).—By the method described above the base **8** (13.1 g) and CNBr (16.8 g) gave a cryst (plates) *N*-nitrile (8.3 g, 60%): ν_{max}^{film} 2200 cm^{-1} (s) CN; P^+, *m/e* 226,146887 ($C_{15}H_{18}N_2$). Hydrolysis of the nitrile (8.3 g) by aq 6% HCl (500 ml) gave 4,5-dimethyl-6,7-benzomorphan (4.36 g, 59%). The hydrochloride was recrystd from EtOH–Et_2O as colorless prisms, mp 215–219°. *Anal.* ($C_{14}H_{20}ClN$) C, H, N.

2-Cyclopropylmethyl-3,5-dimethyl-6,7-benzomorphan·HBr (14a·HBr).—To a soln of 3,5-dimethyl-6,7-benzomorphan (0.64 g) in a mixt of CH_2Cl_2 (35 ml) and Et_3N (6.0 ml) was added cyclopropanecarbonyl chloride (2.0 g). The mixt was refluxed for 12 hr, cooled, and washed successively with 2 *N* HCl (3 × 20 ml) and H_2O (3 × 20 ml). The CH_2Cl_2 soln was dried (K_2CO_3) and evapd to yield the cryst amide **12a** (0.336 g, 42%).

A dry Et_2O soln of **12a** (0.336 g, 20 ml) was added dropwise to a stirred suspension of LAH (1.0 g) in Et_2O. The mixt was refluxed for 6 hr, cooled, and quenched with H_2O. The Et_2O phase was decanted and the inorg gel washed with Et_2O (3 × 20 ml). The dried (Na_2SO_4) Et_2O solns gave, on evapn, the base **14a** (3.4 g, 79%) which solidified. The hydrobromide recrystd on colorless plates, mp 187–188°, from EtOH–Et_2O. *Anal.* ($C_{18}H_{26}BrN$) C, H, N.

2-Cyclopropylmethyl-4,5-dimethyl-6,7-benzomorphan·HCl (14b·HCl).—By the method described for **14a**, 4,5-dimethyl-6,7-benzomorphan (0.316 g) afforded **14b**·base (0.208 g, 52%). The HCl salt was recrystd from EtOH–Et_2O as colorless plates, mp 202–204°. *Anal.* ($C_{18}H_{26}ClN$) C, H, N.

2-Phenethyl-3,5-dimethyl-6,7-benzomorphan·HBr (13a·HBr).—Phenylacetyl chloride (0.5 ml) in MeOH (2 ml) was added, during 5 min, to a stirred suspension of **9a** (0.51 g) in a mixt of K_2CO_3 (0.5 g), MeOH (8 ml), and H_2O (3 ml). The mixt was stirred for 4 hr and was then extd with Et_2O (4 × 20 ml). The exts were washed successively with 2 *N* HCl (2 × 20 ml) and 10% aq $NaHCO_3$ (2 × 20 ml) and dried (Na_2SO_4), and the solvent was evapd to give the intermediate amide.

The crude amide in dry Et_2O (45 ml) was added dropwise to a stirred suspension of LAH (1.0 g) in Et_2O (20 ml), and the mixt was refluxed for 6 hr. Excess LAH was destroyed by the addn of H_2O, and the ethereal supernatant was decanted. The Et_2O soln together with Et_2O washings (3 × 20 ml) of the inorganic residue was extd with 2 *N* HCl (3 × 50 ml), the exts were basified (0.88 ammonia) and extd with Et_2O (3 × 50 ml). Evapn of the dried (Na_2SO_4) ethereal soln afforded the *N*-phenethylbenzomorphan (0.52 g, 68%). The **hydrobromide hemihydrate** recrystd as colorless plates, mp 134–137°, from EtOH–Et_2O. *Anal.* ($C_{22}H_{28}BrN \cdot 0.5H_2O$) C, H, N.

2-Phenethyl-4,5-dimethyl-6,7-benzomorphan·HCl (13b·HCl).—Prepd by the method described for **13a, 9b** (0.25 g) gave 2-phenethyl-4,5-dimethyl-6,7-benzomorphan (0.295 g, 79%). The **hydrochloride** recrystd as colorless plates, mp 229–231°. *Anal.* ($C_{22}H_{28}ClN$) C, H, N.

2-(2-Methyl-3-butenyl)-3,5-dimethyl-6,7-benzomorphan·HCl (10a·HCl).—To a stirred suspension of **9a** (0.324 g) and NaHCO (0.5 g) in DMF (15 ml) was added 1-bromo-3-methylbut-2-ene (0.24 g) and the mixt was heated under reflux for 8 hr, cooled, and filtered. The filtrate, plus EtOH washings, was evapd to dryness, and the residue was dissolved in Et_2O, filtered, and extd with 2 *N* HCl (3 × 20 ml). Basification (NH_4OH) of the exts followed by Et_2O extn (3 × 20 ml), gave on evapn of dried (Na_2SO_4) soln, 0.294 g (68%) of the benzomorphan base **10a**. The hydrochloride was recrystd from EtOAc–petr ether (bp 40–60°) as prisms, mp 183–185°. *Anal.* ($C_{19}H_{28}ClN$) C, H, N.

2-(2-Methyl-3-butenyl)-4,5-dimethyl-6,7-benzomorphan·HCl (10b·HCl).—By the method described for **10a, 9b** (0.415 g) and 1-bromo-3-methylbut-2-ene (0.30 g) yielded 0.407 g (73%) of **10b**·base. The **hydrochloride** was recrystd from EtOH–Et_2O–petr ether (bp 40–60°) as colorless plates, mp 178–179°. *Anal.* ($C_{19}H_{28}ClN$) C, H, N.

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** It was sometimes necessary to distil the base over a short path [70° (0.7 mm)] before converting it to the HBr salt.

Vitamin B_6 Analogs. 4. 4-Desoxyisopyridoxal and the Phosphonic Acid Analog of 4-Desoxypyridoxine Phosphate[1,2]

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The phosphonic acid analogs II and III of 4-desoxypyridoxine phosphate and pyridoxine phosphate were synthesized from 4-desoxyisopyridoxal (IV) and pyridoxal, respectively, by means of the modified Wittig reaction. 4-Desoxyisopyridoxal (IV) and its 3-acetyl derivative XVI exhibited antivitamin B_6 activity against *Saccharomyces carlsbergensis* and cytotoxicity against human epidermoid cells in culture. No antileukemic activity was observed for the phosphonic acid analogs II and III or 4-desoxyisopyridoxal (IV) against mouse leukemia L1210.

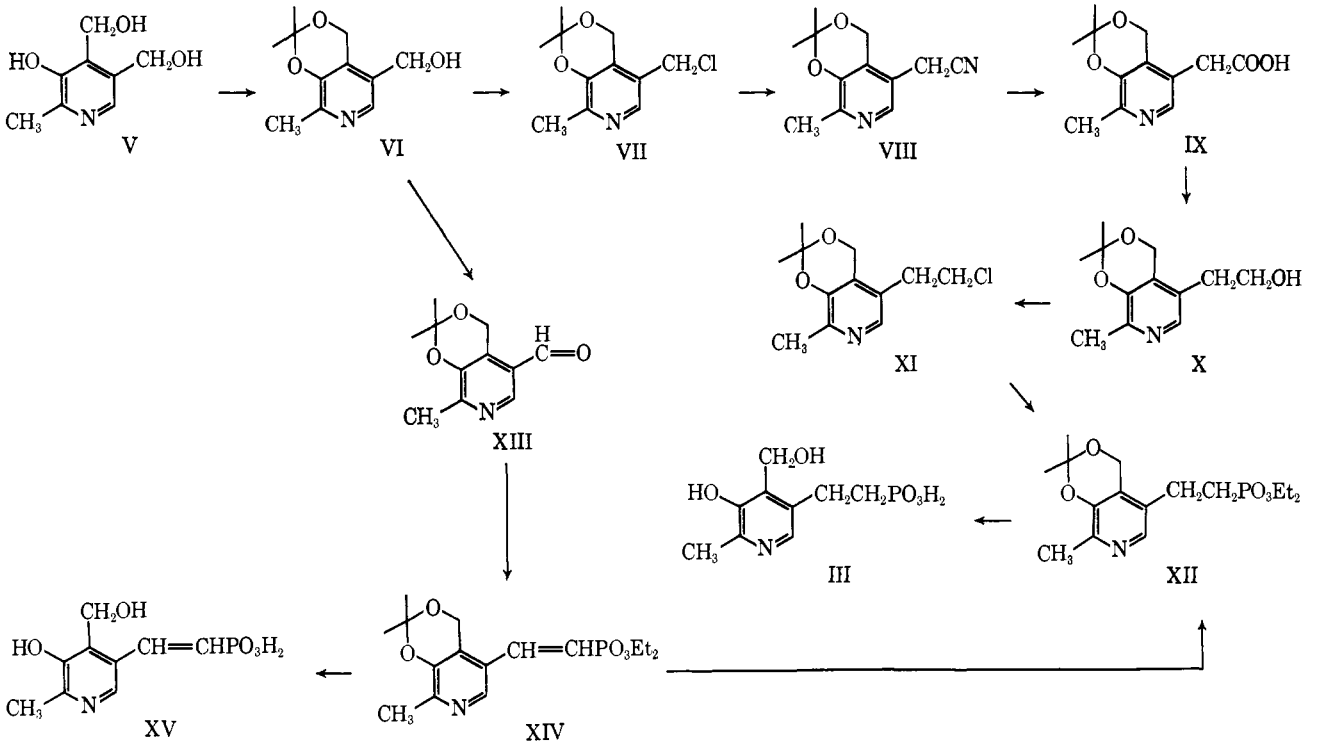
4-Desoxypyridoxine (I) has been shown to be an inhibitor of several types of tumors in animals maintained on a vitamin B_6 deficient diet. After phosphorylation the vitamin analog I can serve as a substrate for enzymes that use pyridoxal phosphate as a cofactor.[3] Because I shows only weak competitive inhibition, as shown by the fact that a deficient diet is necessary for *in vivo* activity, we are engaged in a program of synthesis of analogs of I that might be effective antineoplastic agents on a complete diet.

(1) This investigation was supported by Contract PH43-64-51 with Chemotherapy, National Cancer Institute, National Institutes of Health.

(2) Part 3, J. L. Greene, Jr., A. N. Williams, and J. A. Montgomery, *J. Med. Chem.*, **7**, 20 (1964).

(3) J. A. Montgomery, T. P. Johnston, and Y. F. Shealy, "Medicinal Chemistry," A. Burger, Ed., 3rd ed, Wiley, New York, N. Y., 1970, Chapter 28, pp 680–783.

SCHEME I



We report herein the synthesis and antitumor evaluation of phosphonic acid analogs II and III of 4-desoxypyridoxine phosphate and pyridoxine phosphate. Replacement of the phosphate ester oxygen with a methylene group to generate a nonhydrolyzable phosphate analog has been accomplished for several biologically important classes of compounds.[4] While our synthesis of II and III was in progress, Hullar[4] described the synthesis of II and XV and observed significant inhibitory activity against aspartate aminotransferase.

Two routes were followed for the synthesis of III as shown in Scheme I. Because of the low yield of XII obtained by means of the Korytnyk[5]–Arbuzov route (VI → VII → XI → XII), the Hullar[4]-modified Wittig route (VI → XIII → XIV → XII) was investigated and found to be greatly superior as a means of obtaining sufficient amounts of intermediates and final product for antitumor evaluation.

The synthesis of II was accomplished in a similar fashion, as shown in Scheme II, from the heretofore unreported 4-desoxyisopyridoxal[6] (IV).

The vitamin B_6 analogs were tested for cytotoxicity against human epidermoid cells in culture (Table I). Only IV and XVI were significantly inhibitory, and their cytotoxicity was apparent only at the highest level tested.

4-Desoxyisopyridoxal (IV) and its 3-acetyl derivative XVI, as well as the target compounds II and III, were evaluated for antivitamin B_6 activity in cultures of *Saccharomyces carlsbergensis*.[7] Figure 1 shows that normal growth (A) is altered by the presence of IV (B and C) and XVI (D and E), indicating some inhibitory effect by the two analogs, whereas no inhibitory effect was observed for 4-desoxypyridoxine (I), II, and III under identical conditions. At concentrations of pyridoxine that were too low to support growth ($0–1 \times 10^{-4}$ μg/ml) of *S. carlsbergensis*, a high concentration of III (100 μg/ml) permitted normal growth, thus suggesting the ability of III to serve as a weak substrate for enzymes that use pyridoxine phosphate as a cofactor.

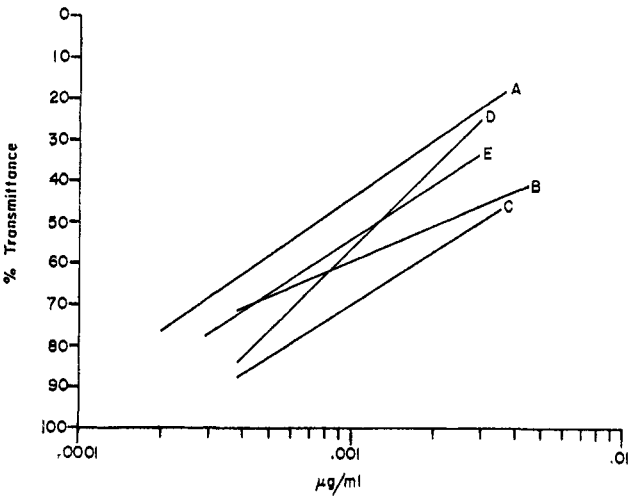


Figure 1.—Inhibition of growth of *Saccharomyces carlsbergensis:* A, pyridoxine; B and C, pyridoxine plus 1 μg and 10 μg, respectively, of 4-desoxyisopyridoxal; D and E, pyridoxine plus 1 μg and 10 μg, respectively, of 3-acetyl-4-desoxyisopyridoxal.

The analogs were evaluated at a starting dose of 400 mg/kg against leukemia L1210 in mice on a normal diet. Administration was by the intraperitoneal route on the first day of the test in mice inoculated with 10^5 cells. No antileukemic activity was found for any of the compounds tested. Some toxicity was observed for IV and XVI; the highest nontoxic doses administered were 75 and 150 mg/kg, respectively.

(4) T. L. Hullar, *J. Med. Chem.*, **12**, 58 (1969), and ref cited therein.
(5) W. Korytnyk, B. Paul, A. Bloch, and C. A. Nichol, *ibid.*, **10**, 345 (1967).
(6) The thiosemicarbazone of 4-desoxyisopyridoxal has been reported: T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, **16**, 1121 (1951).
(7) E. E. Snell and J. C. Rabinowitz, *Anal. Chem.*, **19**, 277 (1947).

SCHEME II

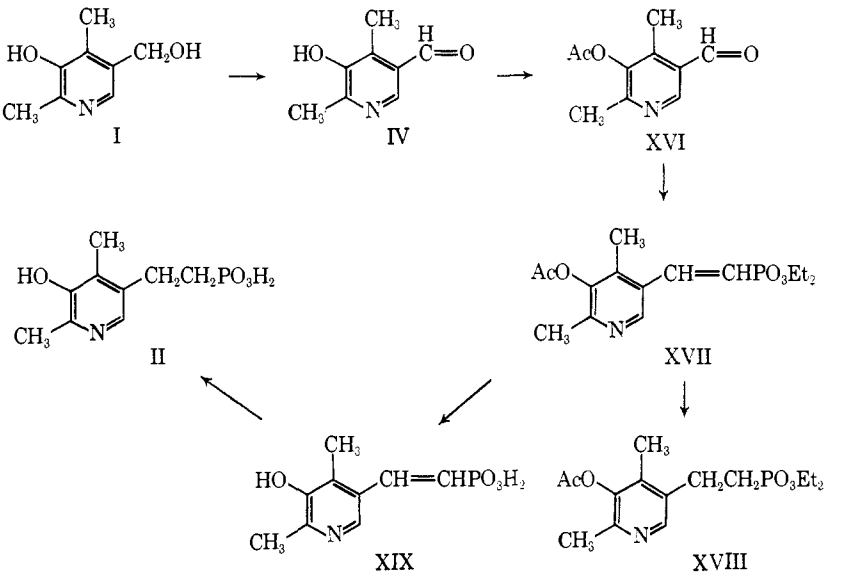


TABLE I

CYTOTOXICITY[a]

Compd	$T - C_0/C - C_0$[b]
II	0.79
III	0.78
IV	−0.10
VII	0.72
VIII	0.51
XI	1.21
XII	0.79
XIV	0.70
XV	0.94
XVI	−0.15
XVII	0.76
XIX	0.98

[a] HEp 2 cells. [b] $T - C_0$ and $C - C_0$ represent μg of protein in treated and control systems in tests at a dose level of 100 μg/ml.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values. Melting points were determined with a Kofler Heizbank apparatus. Nmr data were determined with a Varian A-60A spectrometer and are given in ppm downfield from Me_4Si. Mass spectra were obtained with a Hitachi RMU-6D spectrometer equipped with mass marker and peak matching device.

5-(2-Chloroethyl)-2,2,8-trimethyl-4*H*-*m*-dioxino[4,5-*c*]pyridine·HCl (XI).—α^4,3-*O*-Isopropylidene-α^5-pyridoxylmethanol (X) was prepd from pyridoxine (I) according to the method of Korytnyk, *et al.*[5] X (1.9 g, 8.53 mmoles) in 125 ml of dry, refluxing C_6H_6 was treated dropwise with stirring in 10 min with a soln of $SOCl_2$ (1.5 ml, 2.4 g, 20 mmoles) in 5 ml of dry C_6H_6. A ppt formed during the $SOCl_2$ addition but dissolved before the addition was complete. The soln was refluxed 1 hr after the addition and allowed to stand overnight at room temp. The pptd solid was collected by filtration and dried *in vacuo:* mp 172–174° dec; yield 1.87 g (79%). The solid was dissolved in 50 ml of dry C_6H_6 contg a small amt of EtOH. The soln was filtered and the filtrate treated with excess Et_2O; the crystalline ppt was collected by filtration and dried *in vacuo:* mp 175–177° dec; yield 1.6 g (68%). *Anal.* ($C_{12}H_{17}Cl_2NO_2$) C, H, Cl, N.

Diethyl α^4,3-*O*-Isopropylidene-α^5-pyridoxylmethylphosphonate·HCl (XII).—Diethyl α^4,3-*O*-isopropylidene-α^5-pyridoxylidenemethylphosphonate·HCl (XIV) (1 g), prepd by the method of Hullar,[4] in 100 ml of EtOH was treated with 1 g of 5% Pd/C and hydrogenated with shaking for 4 hr at room temp at an initial pressure of 3.5 kg/cm². The catalyst was removed by filtration, and the filtrate was evapd to dryness *in vacuo*. Trituration of the residue with ether and filtration gave a solid: mp 105–107°; yield 650 mg (65%). Crystn from EtOAc gave XII in analytical purity: mp 114–116°; yield 500 mg (50%); nmr (DMSO-d_6), 1.2 (triplet, OCH_2CH_3), 1.53 ($>C(CH_3)_2$), 2.5 (2-CH_3-pyridine), 2.5 (multiplet, CH_2CH_2), 4.0 (multiplet, OCH_2CH_3), 5.1 (OCH_2-pyridine), 8.2 (H-pyridine), *ca.* 12 (HCl). *Anal.* ($C_{16}H_{26}NO_5P\cdot HCl$) C, H, Cl, N, P.

XII was also prepd from XI by means of the Arbuzov reaction by refluxing XI for 40 hr in (i-PrO)$_3$P according to the procedure of Bennett, *et al.*[8] Yield and purity of XII obtained by this method were inferior to that obtained from XIV.

2-[5-Hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridyl]ethylphosphonic Acid[4] (III).—XII (200 mg) was refluxed 12 hr in concd HCl, and the resulting soln was evapd to dryness *in vacuo*. The syrupy residue was purified as described by Hullar and gave a product whose ir spectrum was in agreement with that reported.[4] Further characterization was provided by mass spectral analysis. Although no definitive spectrum was obtained for III itself, trimethylsilylation generated a volatile derivative that showed the following peaks (m/e): 463 (M^+, tri-TMS derivative), 448 (M^+ 463 − CH_3), 447 (m/e 448 − H), 432 (M^+ 463 − CH_2OH), 391 (M^+, di-TMS derivative), 390 (M^+ 391 − H), 376 (M^+ 391 − CH_3), 375 (m/e 376 − H), 360 (M^+ 391 − CH_2OH).

2-[5-Hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridyl]vinylphosphonic Acid[4] (XV).—XIV[4] (350 mg) in 10 ml of concd HCl was refluxed 1 hr and the soln was freed of H_2O by C_6H_6 azeotropic drying. The residue (mp > 260°) was crystallized from EtOH–H_2O: mp > 260°; yield 60 mg. *Anal.* ($C_9H_{12}NO_5P$) C, H, N, P.

4-Desoxyisopyridoxal (IV).—Following the procedure of Korytnyk, *et al.*,[9] CrO_3 (31.7 g) was added batchwise to 1500 ml of pyridine (distilled from $KMnO_4$) in 10 min with vigorous stirring under N_2. After stirring 20 min at room temp, desoxypyridoxine (3 g) in 100 ml of pyridine was added in one batch. The mixt was stirred at room temp 1 hr, heated slowly to reflux in 1 hr, and refluxed 2 hr. After cooling to room temp, H_2O (2.5 l) was added, and the mixt was extd continuously with ether for 4 days. Evapn of the ext gave a solid residue (1 g) which was crystd twice from C_6H_6–EtOH and yielded an analytical sample: mp 160°; yield 780 mg. *Anal.* ($C_8H_9NO_2$) C, H, N.

5-Hydroxy-4,6-dimethylnicotinaldehyde Acetate Ester (3-Acetyl-4-desoxyisopyridoxal) (XVI).—IV (500 mg) in 10 ml of Ac_2O was stirred 3 days at room temp and evapd to dryness *in vacuo*. Crystn of the solid residue from C_6H_6 gave an analytical sample: mp 79–80°; yield 220 mg (34%); nmr (DMSO-d_6), 2.4 (partially resolved triplet, 2- and 4-CH_3-pyridine, CH_3CO),

(8) R. Bennett, A. Burger, and W. W. Umbreit, *J. Med. Pharm. Chem.*, **1**, 213 (1959).

(9) W. Korytnyk, E. J. Kris, and R. P. Singh, *J. Org. Chem.*, **29**, 574 (1964).

8.75 (H-pyridine), 10.25 (CH=O). *Anal.* ($C_{10}H_{11}NO_3$) C, H, N.

Diethyl [2-(5-Acetoxy-4,6-dimethyl-3-pyridyl)vinyl]phosphonate·HCl (XVII).—Tetraethyl methylenediphosphonate[10] (11.5 g, 0.04 mole) was added dropwise in 15 min at room temp to a stirred mixt of NaH (1.92 g, 50% oil dispersion, 0.04 mole) in 200 ml of dry 1,2-dimethoxyethane. After stirring 1 hr, the homogeneous system was treated with XVI (6 g, 0.031 mole) batchwise in 5 min, and the soln was stirred overnight. A syrup pptd during the stirring period. Evapn of the solvent, addn of 50 ml of H_2O, and overnight extn with EtOAc yielded the crude product in the org layer. The solvent was removed, and the residue in Et_2O was treated with dry HCl until pptn of an oil was complete. After stirring 15 min, the ppt (now crystalline) was collected by filtration: yield 6.5 g (45%). Crystn from Et_2O–EtOAc gave the purified product: mp 125–127°; mass spectrum (*m/e*), 327 (M^+), 285 ($M^+ - COCH_3 + H$), 282 ($M^+ - OEt$), 248.4 (metastable, 327 → 285), 177 ($M^+ - CHPO_3Et_2$), 176 (177 − H), 149 (177 − CO), 148 (177 − HCO), 36 (base peak, HCl).

Diethyl [2-(5-Hydroxy-4,6-dimethyl-3-pyridyl)ethyl]phosphonate Acetate Ester·HCl (XVIII).—XVII (1 g) in 50 ml of EtOH was treated with 1 g of 5% Pd/C and hydrogenated at room temp with shaking for 7 hr at an initial pressure of 3.5 kg/cm². Removal of the catalyst by filtration and evapn of the filtrate gave a syrup. This was sublimed *in vacuo* (*ca.* 0.02 mm) at 100° and yielded a white, cryst sublimate: mp 100–102°; yield 180 mg; mass spectrum (*m/e*) 329 (M^+), 314 ($M^+ - CH_3$), 300 ($M^+ - C_2H_5$), 287 ($M^+ - COCH_3 + H$), 272 (*m/e* 287 − CH_3), 258 (*m/e* 287 − C_2H_5), 242 (*m/e* 287 − OC_2H_5), 192 ($M^+ - PO_3Et_2$), 150 (*m/e* 287 − PO_3Et_2). *Anal.* ($C_{15}H_{24}NO_5P·HCl$) C, H, Cl, N, P.

[2-(5-Hydroxy-4,6-dimethyl-3-pyridyl)vinyl]phosphonic Acid (XIX).—XVII (200 mg) in 10 ml of concd HCl was refluxed for 5 hr, and the resulting soln was evapd to dryness *in vacuo*. Trituration of the residue with Et_2O and filtration gave a white solid: mp > 260°; yield 130 mg. The solid was crystd from EtOH–H_2O: mp >260°; yield 50 mg (40%); nmr (DMSO-d_6), 2.4, 2.65 (2- and 4-CH_3-pyridine), 7.05 (multiplet, *trans*-HC=CH), 8.45 (H-pyridine), 10.7 (OH and H_2O). *Anal.* ($C_9H_{12}NO_4P·H_2O$) C, H, N, P.

[2-(5-Hydroxy-4,6-dimethyl-3-pyridyl)ethyl]phosphonic Acid (II).—XIX (500 mg) suspended in 25 ml of H_2O was treated dropwise with 1 *N* KOH until homogeneous. To the soln (pH 7–8) was added 500 mg of 5% Pd/C, and the mixt was hydrogenated at room temp with shaking for 12 hr at an initial pressure of 3.5 kg/cm². The catalyst was removed by filtration, and the reduced product was isolated from the filtrate as described by Hullar[4] for the corresponding pyridoxine analog: mp >260°; yield 100 mg (20%); nmr (CF_3COOD), 2.4, 3.2 (pair of complex multiplets, CH_2CH_2), 2.6, 2.75 (2- and 4-CH_3-pyridine), 8.1 (H-pyridine), 11.25 (OH). *Anal.* ($C_9H_{14}NO_4P$) C, H, N.

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(10) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 1500 (1953).

Alkaloid Studies. 7.[1] Reactions of 18-Hydroxymethyleneyohimban-17-one and the Preparation of Yohimbano[17,18-*c* and 18,17-*d*]pyrazoles

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Some reactions of 18-hydroxymethyleneyohimban-17-one (**1**) were investigated. Hydrazine and **1** gave yohimbanopyrazole **2**, acylation of which produced acetyl and 3,4,5-trimethoxybenzoyl derivatives **8** and **9**. Phenylhydrazine and **1**, or its isobutyl ether **5**, produced isomeric phenylyohimbano[17,18-*c* and 18,17-*d*]-pyrazoles **3** and **4**. Methylhydrazine and **1** produced isomeric methylyohimbano[17,18-*c* and 18,17-*d*]-pyrazoles **11** and **10**. Structural assignments of N-substituted pyrazoles based on pmr measurements are discussed. *O*-Benzoyl and *O*-3,4,5-trimethoxybenzoyl derivatives **12** and **13** were prepared by acylation of **1**. Potent CNS depressant activity in laboratory animals was exhibited by **1**, **2**, **5**, **10**, and **11**.

Our interest in the introduction of substituents into the E ring of yohimbanones and in further modification of the E ring led us to study the chemistry of C-18 substituted yohimban-17-ones. In a previous publication[2] we have described the synthesis of C-18 substituted yohimban-17-ones and presented evidence for substitution at C-18 in carboxylation and formylation of yohimban-17-one. A study of the chemistry of 18-hydroxymethyleneyohimban-17-one[2] (**1**) was undertaken since hydroxymethylene ketones[3] are reactive intermediates which undergo numerous condensation reactions. Reactions with amines give aminomethylene derivatives,[4,5] while reactions with alcohols afford alkoxymethylene ketones; heterocyclic pyrazoles are

(1) Alkaloid Studies. VI: J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Heterocycl. Chem.*, **7**, 623 (1970).

(2) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963).

(3) For the preparation of 2-hydroxymethylene 3-ketosteroids see: (a) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Amer. Chem. Soc.*, **81**, 427 (1959); (b) F. L. Weisenborn and H. E. Appelgate, *ibid.*, **81**, 1960 (1959).

(4) For the preparation of 2-aminomethylene 3-ketosteroids see: (a) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, H. Jimenez, A. Bowers, and H. J. Ringold, *Chem. Ind. (London)*, 1625 (1960); (b) G. de Stevens and A. Halamandaris, *J. Org. Chem.*, **26**, 1614 (1961).

(5) Reactions of 18-hydroxymethyleneyohimban-17-one (**1**) with amines will be described in a forthcoming publication.