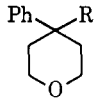
TABLE I

TETRAHYDROPYRANS



R	Method of prepn	Yield, % of theory	Bp (mm) or mp, °C	Form[a]	Crystn solvent[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_2NH_2	A	83	126–128 (2)	a	...	$C_{12}H_{17}NO$	75.35	9.0	7.3	75.3	9.1	7.3
HCl		67	285–287	b	A	$C_{12}H_{18}ClNO$	63.3	8.0	6.15	63.7	8.3	6.1
$CH_2NHCOMe$	c	60	170 (0.5), 97–99	b	...	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	71.8	8.5	5.9
$CH_2N(COMe)(CH_2)_2$-morph	B	53	208–211 (0.5)	c	...	$C_{20}H_{30}N_2O_3$	69.3	8.7	8.1	69.3	8.8	8.4
HCl		86	210–211	b	B	$C_{20}H_{31}ClN_2O_3$	62.7	8.2	7.3	62.9	7.8	7.15
$CH_2NH(CH_2)_2$-morph 2HCl	B	49	257–259 dec	b	A	$C_{18}H_{36}Cl_2N_2O_2$	57.3	8.0	7.4	57.0	7.8	7.1
NH_2	C	8	158–160 (20)	c	...	$C_{11}H_{15}NO$	74.5	8.5	7.9	74.9	8.5	8.4
HCl		75	287	d	C	$C_{11}H_{16}ClNO$	61.8	7.55	6.6	61.8	7.7	6.8
$CONH(CH_2)_2NEt_2$	D	76	165–167 (0.4), 61–62	c	...	$C_{18}H_{28}N_2O_2$	71.0	9.3	9.2	70.7	9.2	9.1
HCl		88	164–165	d	C	$C_{18}H_{29}ClN_2O_2$	63.4	8.6	8.2	63.4	8.3	8.0
C(=NH)Et	E	79	122–124 (0.8)	a	...	$C_{14}H_{19}NO$	77.4	8.8	6.4	77.2	9.2	6.5
C(=NH)Ph	E	62	158–162 (0.4)	c[d]	...	$C_{18}H_{19}NO$	81.5	7.2	5.3	81.2	7.3	5.0
HCl		68	210–213	b	C	$C_{18}H_{20}ClNO \cdot H_2O$	67.6	6.9	4.4	67.8	7.3	4.5
COEt	F	90	123–125 (1.0)	a	...	$C_{14}H_{18}O_2$	77.0	8.3	...	77.4	7.9	...
C(=NOH)Et		40	149–151	d	D	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	72.2	8.3	5.8
$CO(CH_2)_3NMe_2$	F	61	142–143 (0.4)	c	...	$C_{17}H_{25}NO_2$	74.1	9.2	5.1	73.8	9.0	5.2
HCl		82	165–167	d	C	$C_{17}H_{26}ClNO_2$	65.4	8.4	4.5	65.6	8.4	4.4
$COC_6H_4(p\text{-}NMe_2)$	F	73	Decomp at 250	b	...	$C_{20}H_{23}NO_2$	77.6	7.5	4.5	77.5	7.6	4.7
CH(OH)Et	G	77	114.5–116	e	E	$C_{14}H_{20}O_2$	76.3	9.2	...	76.7	9.0	...
$CH(OH)C_6H_4(p\text{-}NMe)$	G	86	139.5–140.5	b	E	$C_{26}H_{25}NO_2$	77.1	8.1	4.5	76.9	8.5	4.4
$C(OH)Et_2$	E	59	106–108	b	E	$C_{18}H_{24}O_2$	77.4	9.7	...	77.4	9.4	...

[a] a, colorless oil; b, prisms; c, yellow oil; d, needles; e, plates. [b] A, ethyl methyl ketone; B, ethanol; C, ethanol–ether; D, benzene–petroleum ether (bp 60–80°); E, cyclohexane. [c] The amino methyl compound was acetylated with Ac_2O in acetic acid in the presence of sodium acetate. The mixture was refluxed for 2 hr. [d] Solidified on standing.

Vitamin B_6 Analogs. An Improved Synthesis of 5-Deoxypyridoxal[1]

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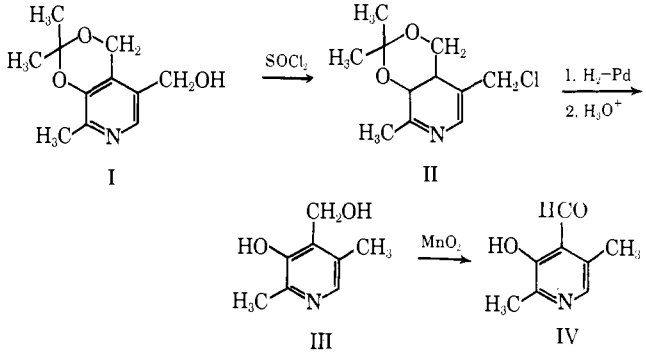
Unlike pyridoxal, 5-deoxypyridoxal (IV) cannot form an internal hemiacetal, but closely resembles instead in spectrum and reactivity the coenzyme form of vitamin B_6, pyridoxal 5′-phosphate.[2,3] For this and other reasons, this vitamin antagonist



should prove useful in the study of model reactions related to enzymatic pyridoxal phosphate dependent reactions.[4] Although two methods for synthesis of 5-deoxypyridoxal have been reported,[2,5] the compound is not readily available. We describe herein a simple four-step synthesis which gives the desired product in 35% over-all yield from pyridoxine.

Experimental Section

α^4-3-O-Isopropylidenepyridoxine (I).[6]—Dry HCl was bubbled into a cooled suspension of 24.0 g of pyridoxine·HCl in 500 ml of dry acetone. After 1.5 hr, 220 g of HCl had been taken up. The solution was stirred for another hour and then kept in the cold overnight. If no crystals appeared at this stage, the solution was reduced to 80% of its volume under vacuum. Crystallization began in the slightly orange solution and was complete after 1 hr at −20°. The yield of I·HCl was 24.6 g (86%). After one recrystallization from hot absolute ethanol, the product melted at 205–211° dec.

α^4-3-O-Isopropylidene Derivative of 2-Methyl-3-hydroxy-4-hydroxymethyl-5-chloromethylpyridine (II).[7]—To a stirred suspension of 23.1 g of I in 250 ml of anhydrous ether, 53 ml of $SOCl_2$ was added in 15 min. After refluxing for 5 hr, the precipitate was filtered, washed with ether, and dried at 100°. The crude product (24.5 g) was recrystallized from boiling absolute methanol to give 19.8 g (80%) of II. The white prisms decomposed at about 310°. From the mother liquor another crop of crystals (3.1 g) could be obtained after addition of ether. The infrared spectrum of II (in KBr) shows a new band at 13.1 μ as one would expect from the C–Cl stretching vibration.

5-Deoxypyridoxine (III) Hydrochloride.—A solution of 19.8 g of II in 350 ml of absolute methanol was hydrogenated in the presence of 2 g of 10% Pd–C and 6.15 g of anhydrous NaOAc. After 2 hr when 96% of the theoretical amount of H_2 had been absorbed, the catalyst and NaCl were filtered off. The filtrate was concentrated *in vacuo* to 75 ml, diluted with 200 ml of aqueous 1 *N* HCl, and held overnight at room temperature. After filtering out a slight precipitate, the solution was heated for 15 min at 80°, then taken almost to dryness *in vacuo*. The residue was extracted with absolute ethanol. On addition of ether to the

(1) Supported in part by Grant AM-1448 from the National Institutes of Health, U. S. Public Health Service.

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(3) D. E. Metzler and E. E. Snell, *ibid.*, **77**, 2431 (1955).

(4) E. E. Snell, *Vitamins Hormones*, **16**, 77 (1958).

(5) T. Kuroda, *Bitumin*, **29**, 116 (1964); *Chem. Abstr.*, **62**, 515g (1965).

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TABLE I

PURIFICATION OF 5-DEOXYPYRIDOXAL BY ADSORPTION CHROMATOGRAPHY ON SILICA GEL

Fraction[a]	Eluent — Benzene	$CHCl_3$	Wt, g
1–3	100	...	...
4–5	99	1	...
6–7	97	3	...
8–9	95	5	...
10–12	90	10	...
13–21	80	20	1.59
22–24	50	50	0.54
25–33	0	100	2.00

[a] Fractions of approximately 300 ml were collected.

ethanol extract, crystalline III·HCl 19.94 g with double melting points at 139–142° and 146–148°) precipitated. From the mother liquor another 2.47 g of crystals (mp 140–142°) was obtained. The total yield was 87%.

5-Deoxypyridoxal (IV).—Chloroform (50 ml) was overlaid with a solution of 10.2 g of III·HCl in 50 ml of water and stirred at 55°. A thick aqueous suspension of MnO_2 prepared[8] from 13.0 g of $KMnO_4$, and 2.44 ml of concentrated H_2SO_4 were added alternately in small portions over 6 hr so that the pH remained at about 4.5. The lower chloroform layer (which extracts the product as formed) was siphoned off each hour and replaced by fresh chloroform. The course of the oxidation was followed by measuring the absorbance of samples of the two layers in 0.1 *N* aqueous NaOH at 307 mμ (λ_{max} for III) and 390 mμ (λ_{max} for IV).

The chloroform extracts were combined and evaporated *in vacuo*. The residue was extracted with petroleum ether (bp 30–60°) and yielded 4.76 g (58%) of IV, mp 104–110°. The material was further purified by dissolving in benzene, applying to a column containing 150 g of silica gel (Merck, 0.05–0.20 mm), and eluting with benzene containing increasing amounts of chloroform. The desired product appeared in fractions 13–33 (Table I). These fractions were combined and evaporated to dryness, and the residue was crystallized from hot methanol and washed with ether: mp 111.5–113°.

Anal. Calcd for $C_8H_9NO_3$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.62; H, 6.26; N, 9.34.

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N-Oxides of 9-(β-D-Xylofuranosyl)adenine and 9-(β-D-Arabinofuranosyl)adenine[1]

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The antitumor effects of 9-(β-D-arabinofuranosyl)adenine and 9-(β-D-xylofuranosyl)adenine are decreased by their conversion to the biologically inactive hypoxanthine derivatives through enzymatic deamination.[2] A similar result has been observed for 3′-deoxyadenosine[3] (cordycepin), but this deamination could be nearly eliminated through the use of cordycepin 1-oxide. The slow enzymatic reduction back to cordycepin in the tumor cell provided a means of continuous administration of cordycepin to the tumor. In an attempt to provide, similarly, a therapeutically better form of the adenine β-arabinoside and β-xyloside, their 1-oxides were prepared by the methods described in this paper.

Experimental Section[4]

9-(β-D-Xylofuranosyl)adenine 1-Oxide.—A solution of 2.20 g (8.24 mmoles) of 9-β-D-xylofuranosyladenine in 125 ml of glacial acetic acid which contained 11 ml of 30% aqueous H_2O_2 was stored at room temperature for 6 days,[5] then was cooled to 0° and the excess peroxide was decomposed by the cautious addition of 5% Pd–C. The mixture was filtered through Celite, and the filtrate was evaporated to dryness *in vacuo* to give a pale orange solid which was a 3:1 mixture of product and starting material as shown by paper chromatography in solvents A and B. Trituration with several portions of warm methanol removed the starting material to leave 1.0 g (43%) of oxide that was homogeneous on paper chromatography in solvents A and B and had mp 249–250° dec. The analytical sample was obtained by recrystallization from methanol: mp 244–246° dec; $[\alpha]^{26.5}D$ −32° (*c* 1, water); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε11,700); $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 9160); $\lambda_{max}^{pH\ 13}$ 307 mμ (ε 5050), 268 mμ (ε 9400).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.4; H, 4.62; N, 24.7. Found: C, 42.2; H, 4.81; N, 24.6.

The product had R_{sl} values of 0.24 and 2.0 on paper chromatography in solvents A and B, respectively, as compared with xylofuranosyladenine which had R_{sl} values of 0.66 and 1.3, respectively.

9-(β-D-Arabinofuranosyl)adenine 1-Oxide.—A solution of 0.50 g (1.87 mmoles) of 9-(β-D-arabinofuranosyl)adenine with 3 ml of 30% H_2O_2 in 25 ml of glacial acetic acid was stored for 10 days at room temperature, then worked up as described for the preparation of 9-(β-D-xylofuranosyl)adenine 1-oxide to give a mixture of product and starting material. Trituration with refluxing 95% ethanol dissolved the bulk of the starting material to yield 0.39 g (74%) of product. Recrystallization from water gave the analytical sample: mp 245–252° dec; $[\alpha]^{28}D$ +15° (*c* 0.5, water); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 12,200); $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 8650); $\lambda_{max}^{pH\ 13}$ 305 mμ (ε 3790), 267 mμ (ε 8750).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.4; H, 4.62; N, 24.7. Found: C, 42.4; H, 4.91; N, 24.5.

Paper chromatography in solvents A and B showed spots at R_{sl} 0.52 and 1.3, respectively, compared to starting material which had R_{sl} 0.22 and 1.9, respectively, and adenine 1-oxide which had R_{sl} 0.41 and 1.4, respectively.

(4) Melting points were taken on a Thomas–Hoover apparatus and are corrected. Paper chromatograms were run by the descending method with adenine used for a standard. Solvent systems were water-saturated butanol (solvent A) and 5% aqueous Na_2HPO_4 (solvent B).

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Esters and Amides from Mannich Ketones

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Reduction of Mannich ketones to the alcohols followed by benzoylation has been reported to give esters possessing local anesthetic action.[2] Some new esters of this type have been synthesized from 2-(*t*-amino)methylcyclohexanol and various acyl chlorides. When the 2-(*t*-amino)methylcyclohexanone was reductively aminated by a modification of the method of Smith and Day[3] and the resulting cyclohexylamine derivative was treated with an acyl chloride, amides corresponding to the esters were formed. All the compounds were isolated as their hydrochlorides and are listed in Table I.

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