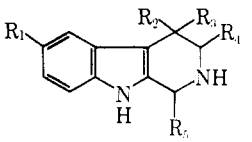
TABLE I
YIELDS, PHYSICAL CONSTANTS, AND ANALYTICAL RESULTS OF SUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLINES



R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_3O	H	H	H	CH_3	60	154–155	$C_{13}H_{16}N_2O$	72.2	7.46	13.0	72.4	7.48	13.2
CH_3O	H	H	H	C_6H_5	51	295–297 dec	$C_{18}H_{18}N_2O \cdot HCl$	68.7	6.08	8.90	69.0	6.13	9.06
CH_3O	H	H	CH_3	CH_3	48	211–213	$C_{14}H_{18}N_2O$	73.0	7.88	12.2	72.6	7.83	12.3
CH_3O	H	H	CH_3	C_6H_5	45[a]	281–284 dec	$C_{19}H_{20}N_2O \cdot HCl$	69.1	6.44	8.52	69.1	6.47	8.80
CH_3O	H	H	CH_3	$(CH_3O)_3C_6H_2$	33[a]	273–277 dec	$C_{22}H_{26}N_2O \cdot HCl \cdot 0.5H_2O$	61.7	6.59	6.55	61.3	6.78	6.70
CH_3S	H	H	H	CH_3	20	185–188	$C_{13}H_{16}N_2S$	67.2	6.94	12.1	67.4	6.81	11.8
CH_3S	H	H	H	C_6H_5	17[a]	268–273	$C_{18}H_{18}N_2S \cdot HCl$	65.3	5.79	8.47	64.8	5.80	8.58
CH_3S	H	H	CH_3	CH_3	36	235–240	$C_{14}H_{18}N_2S$	68.3	7.36	11.4	68.0	7.27	11.6
CH_3S	H	H	CH_3	C_6H_5	39	259–263 dec	$C_{19}H_{20}N_2S \cdot HCl$	66.2	6.14	8.12	66.0	6.12	8.02
CH_3S	H	H	CH_3	$(CH_3O)_3C_6H_2$	35	273–278 dec	$C_{22}H_{26}N_2O_3S \cdot HCl \cdot H_2O$	58.3	6.15	6.18	58.1	6.53	6.15
H	H	H	CH_3	CH_3	56	188–189	$C_{13}H_{16}N_2$	78.0	8.05	14.0	77.8	7.91	14.2
H	H	H	CH_3	C_6H_5	52	287–290 dec	$C_{18}H_{18}N_2 \cdot HCl$	72.4	6.11	9.38	72.2	6.18	9.18
H	H	H	CH_3	$(CH_3O)_3C_6H_2$	16	255–258 dec	$C_{22}H_{26}N_2O_3 \cdot HCl \cdot H_2O$	62.0	6.69	6.89	62.0	6.65	7.06
F	H	H	CH_3	CH_3	42	179–181	$C_{13}H_{15}FN_2$	71.5	6.93	12.8	71.7	6.96	12.8
F	H	H	CH_3	C_6H_5	45[a]	297–300 dec	$C_{18}H_{17}FN_2 \cdot HCl$	68.2	5.73	8.84	68.2	5.89	9.02
F	H	H	CH_3	$(CH_3O)_3C_6H_2$	50[a]	273–277 dec	$C_{22}H_{25}N_2O_3F \cdot HCl \cdot H_2O$	59.1	6.17	6.59	59.1	6.16	6.71
F	CH_3	H	H	C_6H_5	16[a]	296–300	$C_{18}H_{17}FN_2 \cdot HCl$	68.2	5.73	8.84	67.9	5.93	8.76
F	CH_3	H	H	$(CH_3O)_3C_6H_2$	30[a]	253–257	$C_{22}H_{25}N_2O_3F \cdot HCl$	62.0	5.95	6.89	61.7	6.33	7.13
F	CH_3	CH_3	H	CH_3	37	153–157	$C_{14}H_{17}FN_2$	72.4	7.38	12.1	72.1	7.63	12.2

[a] Hydrochloride isolated from 6 *N* HCl.

5-methoxy-, 5-methoxy-α-methyl-,[2] 5-methylthio-,[3] 5-methylthio-α-methyl-,[3] α-methyl-, 5-fluoro-α-methyl-, 5-fluoro-β-methyl-,[4] and 5-fluoro-β,β-dimethyltryptamine.[4]

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Some Reactions with 4-Cyano-4-phenyltetrahydropyran

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4-Cyano-4-phenyltetrahydropyran[1] has been used as a starting point for the synthesis of compounds of possible pharmacological interest, including imines, ketones, and alcohols derived from an initial reaction with an appropriate Grignard reagent.[2] New compounds prepared are listed in Table I (on next page).

Experimental Section[3]

4-Aminomethyl-4-phenyltetrahydropyran. Method A.—4-Cyano-4-phenyltetrahydropyran[1] (10 g) in benzene (125 ml) was added to $LiAlH_4$ (3 g) in ether (125 ml) and refluxed for 3.5 hr. Standard procedures afforded the desired product.

N-(Morpholinoethyl)tetrahydro-4-phenylpyran-4-methylamine. Method B.—4-Acetamidomethyl-4-phenyltetrahydropyran (7.6 g) in dioxane (50 ml) was treated with morpholinoethyl chloride (5.4 g) in the presence of sodamide (1.4 g) using a method previously described.[4] Hydrolysis of the acetyl derivative was effected by refluxing with 6 *N* HCl for 2 hr.

4-Amino-4-phenyltetrahydropyran. Method C.—4-Phenyltetrahydropyran-4-carboxylic acid[1] (5 g) was stirred with benzene (80 ml) and concentrated H_2SO_4 (40 ml) at 50–55°. Sodium azide (1.8 g) was added in small portions over a period of 30 min. The temperature was maintained at 50–55° for a further 5 hr. The mixture stood at room temperature overnight, was diluted with an equal volume of ice, and basified with 10 *N* NaOH. The mixture was extracted with ether, and the extracts were dried ($MgSO_4$). Addition of ethereal HCl afforded a crude hydrochloride (1.3 g). Acidification of the alkaline solution and extraction with ether gave unchanged carboxylic acid (3.3 g). The combined base hydrochlorides from three experiments (6.0 g) were dissolved in water (25 ml); the solution was basified with 2 *N* NaOH and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled. A fraction (2.1 g) of bp 80–82° (20 mm) proved to be aniline while 4-amino-4-phenyltetrahydropyran was obtained as a pale yellow oil (1.0 g), bp 158–160 (20 mm).

N-(2-Diethylaminoethyl)tetrahydro-4-phenylpyran-4-carboxamide. Method D.—4-Phenyl-4-tetrahydropyranoyl chloride[1] (9.2 g) was suspended in benzene (100 ml) and N,N-diethylethylenediamine (7.2 g) was added dropwise with stirring. When the exothermic reaction had subsided, the mixture was refluxed for 2 hr and allowed to stand overnight. The cooled mixture was shaken with 2 *N* NaOH and the benzene layer was removed. The aqueous solution was extracted with ether; the combined organic phases were dried (KOH) and evaporated, and the residue was distilled *in vacuo*. The diethylaminoethyl compound crystallized on cooling.

Ketimines. Method E.—4-Cyano-4-phenyltetrahydropyran (10 g, 1 molar equiv) in dry tetrahydrofuran (THF) (10 ml) was added slowly to a refluxing solution of the appropriate Grignard reagent (3 molar equiv) in dry THF (100 ml). The mixture was refluxed for 5 hr. The imine was obtained by normal work-up procedures and was purified by distillation. $LiAlH_4$ failed to reduce these imines.

Tetrahydro-4-phenyl-4-pyranyl Ketones. Method F.—The appropriate imine (10 g) was refluxed with 2 *N* HCl (170 ml) for 5 hr. The cooled mixture was extracted with ether, and the ether was dried ($MgSO_4$) and evaporated. The ketone was obtained by distillation. Attempts to convert the ketones to amines by reductive amination failed, as did an attempt to reduce the oxime of ethyl tetrahydro-4-phenyl-4-pyranyl ketone with $LiAlH_4$.

Secondary Alcohols. Method G.—The appropriate ketone (0.055 mole) in THF (50 ml) was added to $LiAlH_4$ (0.065 mole) in ether (150 ml) and the mixture refluxed with stirring for 7 hr. The alcohol was obtained by conventional procedures.

Acknowledgments.—The authors are grateful to Dr. R. E. Bowman for his advice and encouragement and Mr. F. H. Oliver for the microanalyses.

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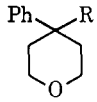
TABLE I

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
$CONH(CH_2)_3NEt_2$	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[c]	...	$C_{18}H_{19}NO$	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	$C_{20}H_{23}NO_2$	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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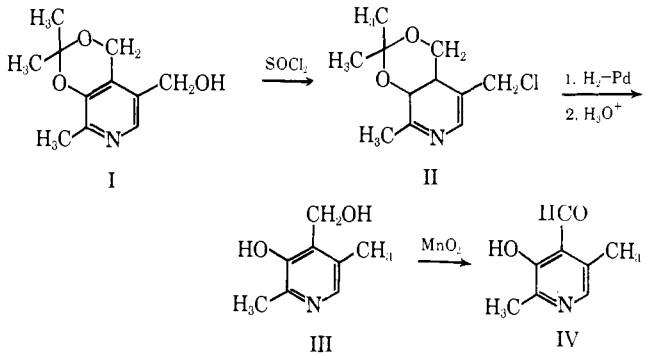
Unlike pyridoxal, 5-deoxypyridoxal (IV) cannot form an internal hemiacetal, but closely resembles instead in spectrum and reactivity the coenzyme form of vitamin B_6, pyridoxal 5′-phosphate.[2,3] For this and other reasons, this vitamin antagonist



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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