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Biochemical Studies on Drugs and the Central Nervous System. 1. Synthesis and Activity of Pyridoxal Derivatives (Studies on the Syntheses of Heterocyclic Compounds. 438¹)

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It is well known that vitamin B₆ has significant action on the CNS, and that it is of importance in the metabolism of brain cells. A number of studies on the pharmacological action of vitamin B₆ and its derivatives have been reported.^{2,3}

We had found a method of synthesizing the various 1,2,3,4-tetrahydroisoquinoline derivatives by cyclization of the corresponding carbonyl compounds with 3-hydroxyphenethylamine derivatives III-VI without acid⁴⁻⁷ as a catalyst. We wish to report the synthesis of 1,2,3,4-tetrahydro-1-pyridoxylisoquinoline derivatives (VIII-XI), 4-pyridoxyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (VII), and their Ac derivatives, by the application of this method using pyridoxal with several 3-hydroxyphenethylamines and histamine, respectively.

Chart I

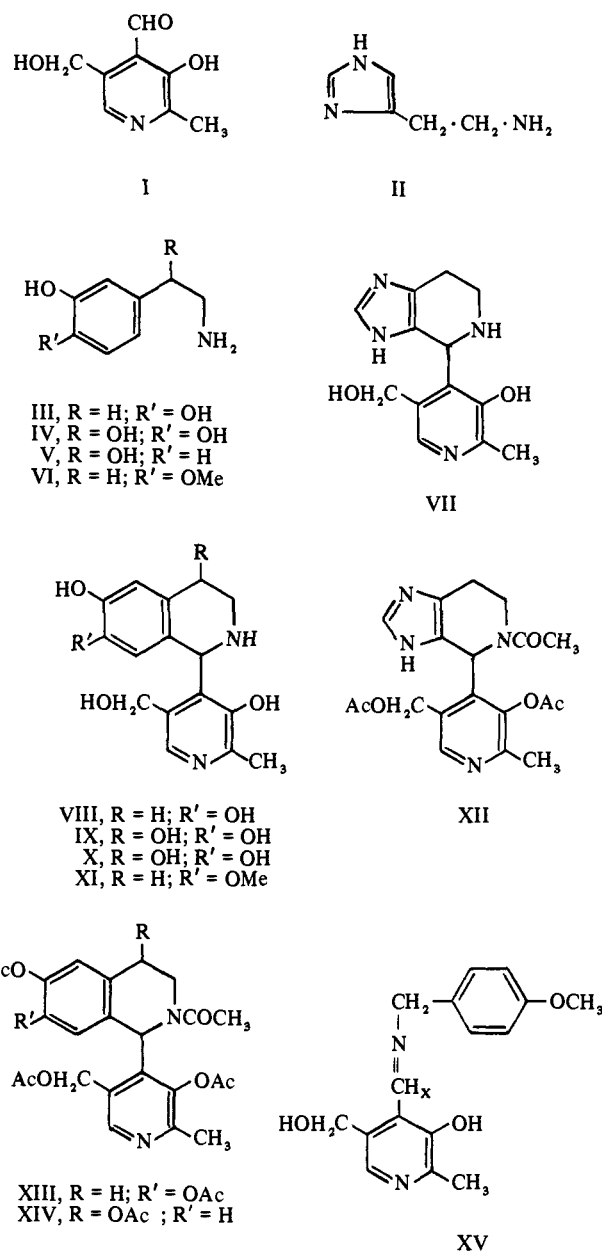


Table I. Products from Pyridoxal and 3-Hydroxyphenethylamines and with Histamine

Compd	Starting materials		Yield, mg (%)	Product			
	Pyridoxal, mg	Amine, mg		Mp, dec, °C	Appearance	Formula ^e	
VII	92	II	150	160 (82)	252-254 ^b	Colorless plates	C ₁₃ H ₁₅ N ₄ O ₂ ^f
VIII	420	III ^a -HCl	470	400 (53)	243-245 ^c	Colorless needles	C ₁₆ H ₁₈ N ₂ O ₄ ^f
IX	836	IV	845	810 (51)	270-273	Colorless needles	C ₁₆ H ₁₈ N ₂ O ₅
X	1050	V ^a -HCl	1020	630 (33)	243-245	Pale brown needles	C ₁₆ H ₁₈ N ₂ O ₄ · 0.5H ₂ O ^d
XI	410	VI ^a -HCl	500	120 (16)	198-200	Pale yellow needles	C ₁₇ H ₂₀ N ₂ O ₄ · 0.5H ₂ O ^d

^aThe free base was prepd as usual. ^bLit.¹⁰ mp 252-253° dec. ^cLit.¹¹ mp 242-244° dec. ^dDried over P₂O₅ at 120° (1 mm) for 24 hr. ^eC, H, N anal. ^fNot analyzed.

Table II. The Properties of Acetyl Derivatives of 1,2,3,4-Tetrahydro-6-hydroxy-4-pyridoxylisoquinolines and 4-Pyridoxyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine

No.	Mp, °C	Recrystn solvent	Formula ^a
XII	181-183	MeOH-Et ₂ O ^b	C ₂₁ H ₂₄ N ₄ O ₆
XIII	204-206	MeOH-Et ₂ O ^c	C ₂₆ H ₂₈ N ₂ O ₉
XIV	241-243	MeOH ^b	C ₂₆ H ₂₈ N ₂ O ₉

^aC, H, N anal. ^bColorless prisms. ^cColorless needles.

mine, respectively. Their activity on the CNS has also been examined.

Chemistry. 3-Hydroxyphenethylamine derivatives (III-VI), prepared by the usual method, were cyclized with pyridoxal to give the cyclized compounds listed in Table I.

Although the structure of the above products could be thought to be that of Schiff bases, this was ruled out by the following evidence. Treatment of VII-XI with dil HCl led

Table III. Pharmacological Activities of Pyridoxal Derivatives^a

Comps	Behavioral observation	Barbiturate potentiating action		Traction test				Analgetic action		
		Relative activity	Judgement	30 min		90 min		45 min	90 min	Judgement
				TT ^b	FT ^c	TT ^b	FT ^c			
Aminophylline								1.63	1.25	++
VII	Pain response Flexor reflex	0.82	—	—	0	—	0	1.7	1.5	+++
VIII	No	0.90	—	—	0.07	—	0	1.0	0.9	—
IX	No	0.82	—	—	0	—	0	0.9	1.1	±
X	No	0.91	—	—	0	—	0	1.6	1.1	++
XI	No	1.46	±	—	0	—	0.07	1.6	1.4	++
XII	No	1.23	—	—	0	—	0	1.8	1.0	+++
XIII	No	1.13	—	—	0	—	0	1.0	0.8	—
XIV	No	1.36	±	—	0	—	0	0.9	0.7	—

^a[Each number shows the mean value for 5 mice (ddy strain, ♂, 23–28 g)]. ^bTT = tranquilizing tendency. ^cFT = fallen tendency.

to recovery of the starting material (VII–XI); the lack of absorption due to C=N was observed in the ir spectrum; and, although the H_x proton of XV was resonant at τ 1,⁸ there appeared no proton at a lower field than τ 2.1 in our product. Moreover, the uv spectrum showed the maximum characteristic of pyridoxal derivatives at 320 nm,⁹ and of tetrahydroisoquinoline derivatives of 280 nm.^{4–7} The compounds, VII, VIII, and X, were acetylated in the usual way to afford the Ac derivatives, which showed the absorption band attributable to NHC=O at around 1650 cm⁻¹ in the ir (KBr).⁸ Compounds VII and VIII were identical with the authentic sample prepared by Heyl and his coworkers.^{10,11} These facts are consistent with the cyclic structures presented here.

Pharmacology. The compounds so obtained were tested for analgetic effect, traction, and hypnotic action using mice as described later in the Experimental Section. The results are listed in Table III. Compounds VII and XII, which are derivatives of histamine, were found to have slightly more analgetic activity than aminophylline; X and XI have the same analgetic effects as aminophylline, used as a control.

Experimental Section†

Cyclization of Pyridoxal (1) with Amines (Table I). A mixt of 150 mg (0.9 mmole) of pyridoxal, 92 mg (0.9 mmole) of histamine, and 5 ml of EtOH was heated on a water bath for 7 hr. Evap of the solvent gave a pale yellow powder, which was dissolved in 5 ml of 5% NaOH. After filtration, followed by neutralization with 5% HCl, the sepd crystals were collected by filtration. Since the compd was insol in all the solvents, purification was done by repptn.

Acetylation of Pyridoxal Derivatives (Table II). A mixt of 100 mg (0.5 mmole) of 4-pyridoxyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine (VII), 2 ml of Ac₂O, and 1 ml of pyridine was heated on a water bath for 3 hr, and the excess reagents were distd off to leave the Ac derivative XII, recrystn of which from MeOH-Et₂O gave 120 mg (61%) of colorless prisms, mp 181–183°.

Pharmacological Tests (Table III). To male mice (ddy strain, 23–28 g), 100 mg/kg of each compd suspended in 1% arabic gum was administered per os. Barbiturate potentiating action, tractive action, and analgetic action were tested by the methods of Kuhn and coworkers,¹² Courvosier¹³ and Burn,¹⁴ respectively. After administration, general behavior was observed for 90 min and classified into 43 types.

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†Melting points were determined on a Yanagimoto microapparatus (MP-S2) and uncorrected.

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Antimalarial Compounds. † 12. ¹ Guanidine Derivatives of Diphenyl Sulfone and Related Compounds

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Continuing our research on potential antimalarial agents,² a series of biguanide and amidineurea derivatives of *p*-halo-diphenyl sulfones, *p*-nitrodiphenyl ether, *p*-nitrodiphenylmethane, and *p*-nitrodiphenylamine was prepared. In the present work we tried to investigate to what extent the nitro and sulfo group were responsible for the antimalarial activity of *p*-nitrodiphenyl sulfone derivatives.²

Chemistry. The starting amines I–VI were prepared according to the literature^{3–6} and subsequently caused to react

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