References

(1) Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2150 (1962).
(2) Y. F. Shealy, *J. Pharm. Sci.*, **59**, 1533 (1970).
(3) J. K. Luce, W. G. Thurman, B. L. Issacs, and R. W. Talley, *Cancer Chemother. Rep.*, **54**, 119 (1970).
(4) J. L. Skibba, G. Ramirez, D. D. Beal, and G. T. Bryan, *Biochem. Pharmacol.*, **19**, 2043 (1970).
(5) G. E. Housholder and T. L. Loo, *J. Pharmacol. Exp. Ther.*, in press.
(6) R. Preussmann, A. von Hodenberg, and H. Hengy, *Biochem. Pharmacol.*, **18**, 1 (1969).
(7) Y. F. Shealy, J. A. Montgomery, and W. R. Laster, Jr., *ibid.*, **11**, 674 (1962).
(8) J. H. Burchenal, M. K. Dagg, M. Beyer, and C. C. Stock, *Proc. Soc. Exp. Biol. Med.*, **91**, 398 (1956).
(9) J. Elks and D. H. Hey, *J. Chem. Soc.*, 441 (1943).
(10) C. W. Noell and C. C. Cheng, *J. Med. Chem.*, **12**, 545 (1969).
(11) Y. F. Shealy and C. A. O'Dell, *J. Pharm. Sci.*, **60**, 554 (1971).

Biochemical Studies on Drugs and the Central Nervous System. 1. Synthesis and Activity of Pyridoxal Derivatives (Studies on the Syntheses of Heterocyclic Compounds. 438[1])

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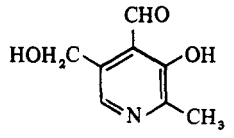
It is well known that vitamin B_6 has significant action on the CNS, and that it is of importance in the metabolism of brain cells. A number of studies on the pharmacological action of vitamin B_6 and its derivatives have been reported.[2,3]

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 acid[4–7] 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-3*H*-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. Their activity on the CNS has also been examined.

Chart I



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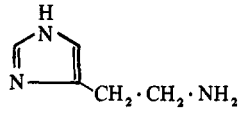
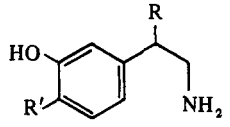
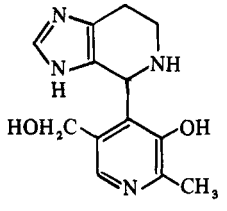


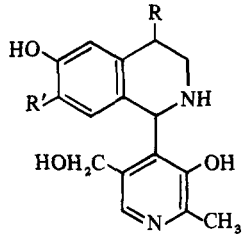
II



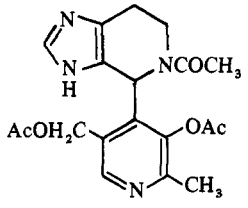
III, R = H; R′ = OH
IV, R = OH; R′ = OH
V, R = OH; R′ = H
VI, R = H; R′ = OMe



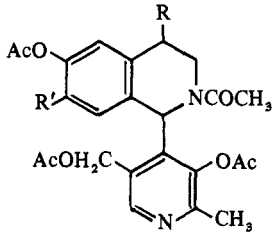
VII



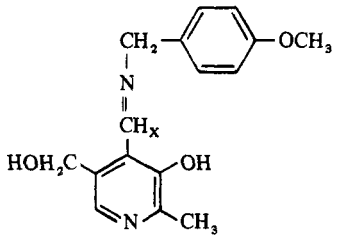
VIII, R = H; R′ = OH
IX, R = OH; R′ = OH
X, R = OH; R′ = OH
XI, R = H; R′ = OMe



XII



XIII, R = H; R′ = OAc
XIV, R = OAc ; R′ = H



XV

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

	Starting materials			Product			
Compd	Pyridoxal, mg	Amine, mg		Yield, mg (%)	Mp, dec, °C	Appearance	Formula[e]
VII	92	II	150	160 (82)	252–254[b]	Colorless plates	$C_{13}H_{15}N_4O_2$[f]
VIII	420	III[a]-HCl	470	400 (53)	243–245[c]	Colorless needles	$C_{16}H_{18}N_2O_4$[f]
IX	836	IV	845	810 (51)	270–273	Colorless needles	$C_{16}H_{18}N_2O_5$
X	1050	V[a]-HCl	1020	630 (33)	243–245	Pale brown needles	$C_{16}H_{18}N_2O_4 \cdot 0.5H_2O$[d]
XI	410	VI[a]-HCl	500	120 (16)	198–200	Pale yellow needles	$C_{17}H_{20}N_2O_4 \cdot 0.5H_2O$[d]

[a]The free base was prepd as usual. [b]Lit.[10] mp 252–253° dec. [c]Lit.[11] mp 242–244° dec. [d]Dried over P_2O_5 at 120° (1 mm) for 24 hr. [e]C, H, N anal. [f]Not 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-3*H*-imidazo[4,5-*c*]pyridine

No.	Mp, °C	Recrystn solvent	Formula[a]
XII	181–183	MeOH-Et_2O[b]	$C_{21}H_{24}N_4O_6$
XIII	204–206	MeOH-Et_2O[c]	$C_{26}H_{28}N_2O_9$
XIV	241–243	MeOH[b]	$C_{26}H_{28}N_2O_9$

[a]C, H, N anal. [b]Colorless prisms. [c]Colorless needles.

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]

Compds	Behavioral observation	Barbiturate potentiating action: Relative activity	Barbiturate potentiating action: Judgement	Traction test: 30 min: TT[b]	Traction test: 30 min: FT[c]	Traction test: 90 min: TT[b]	Traction test: 90 min: FT[c]	Analgetic action: 45 min	Analgetic action: 90 min	Analgetic action: Judgement
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)]. [b] TT = tranquilizing tendency. [c] FT = 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-3*H*-imidazo[4,5-*c*]pyridine (VII), 2 ml of Ac_2O, 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–Et_2O 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] Courvosier[13] and Burn,[14] respectively. After administration, general behavior was observed for 90 min and classified into 43 types.

Acknowledgments. The authors are indebted to the Psychopharmacology Division of Research Laboratories, Chugai Pharmaceutical Co. Ltd., for the pharmacological data presented.

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

References

(1) T. Kametani, K. Kigasawa, M. Hiragi, and T. Aoyama, *J. Med. Chem.*, **14**, 1235 (1971).
(2) P. A. G. Dereymaeker, *Med. Pharmacol. Exp.*, **17**, 333 (1967).
(3) R. Koch, *Strahlentherapie*, **113**, 89 (1960).
(4) T. Kametani, K. Fukumoto, H. Yagi, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc. C*, 112 (1968).
(5) T. Kametani, S. Shibuya, and M. Satoh, *Chem. Pharm. Bull.*, **16**, 953 (1968).
(6) T. Kametani, H. Yagi, and K. Fukumoto, *ibid.*, **16**, 1285 (1968).
(7) T. Kametani, S. Takano, and S. Hibino, *Yakugaku Zasshi*, **88**, 1123 (1968).
(8) W. Kuryinyk, H. Ahrens, and N. Angelino, *Tetrahedron*, **26**, 5445 (1970).
(9) S. F. Mason, *J. Chem. Soc.*, 1253 (1959).
(10) D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **70**, 3669 (1948).
(11) D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *ibid.*, **74**, 414 (1952).
(12) W. L. Kuhn and E. F. Van Marren, *J. Pharmacol. Exp. Ther.*, **134**, 60 (1961).
(13) S. Courvosier, "Psychotropic Drugs," Garanttini and Ghetti, Ed., Elsevier Publishing Co., Amsterdam, p 373.
(14) J. H. Burn, "Biological Standardization," Oxford University Press, London, 1950.

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*-halodiphenyl 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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