Communications to the Editor

[Chem. Pharm. Bull. 33(9)4088–4090(1985)]

N^3-BENZYLURIDINE EXERTS HYPNOTIC ACTIVITY IN MICE

Ikuo Yamamoto,* Toshiyuki Kimura, Yuji Tateoka, Kazuhito Watanabe [a] and Ing Kang Ho [b]

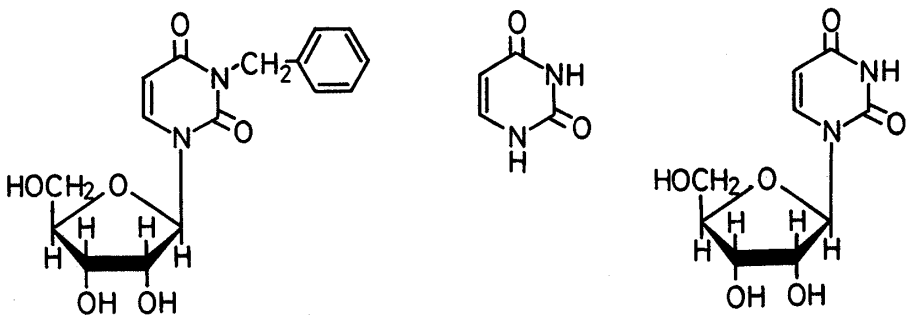
School of Pharmacy, Hokuriku University,[a] Ho-3, Kanagawa-machi, Kanazawa 920-11, Japan and University of Mississippi Medical Center,[b] 2500 North State Street, Jackson, Mississippi, 39216, U.S.A.

N^3-Benzyluridine (I), a derivative of uracil (II) or uridine (III), has hypnotic effect on mice.

The hypnotic effect of I was effected by intracerebroventricular injection. The response was dose-dependent with doses of 1.5-4.0 μmol/mouse. Further, I significantly prolonged pentobarbital-induced sleep in mice. In the same doses, II and III have no hypnotic or sleep-prolonging effects. These results suggest that III may be a sleep-promoting substance basically, as reported by Komoda et al.[1)]

KEYWORDS ——— N^3-benzyluridine; uracil; uridine; hypnotic activity; pentobarbital-induced sleep; sleep-promoting substance

Recently, Komoda et al.,[1)] Honda et al.[2)] and Inoue et al.[3,4)] reported that III is one of the active components of a sleep-promoting substance obtained from the brainstem of sleep-deprived rats. Wenzel and Keplinger[5,6)] reported that II extends the hexobarbital-induced sleeping time in mice, and Roberts[7)] described an anticonvulsant effect of III. We have also reported the effect of III and N^3-allyluridine on pentobarbital-induced sleep and diazepam-induced motor incoordination,[8)] although they had no hypnotic activity. In this paper, we wish to report the hypnotic activity of I by



I II III

Fig. 1. Chemical Structures of N^3-Benzyluridine (I), Uracil (II) and Uridine (III)

intracerebroventricular (i.c.v.) injection, and its synergism in pentobarbital-induced sleep.

The male mice used were of ddN strain and weighed 25 ± 3 g. II and III were purchased from Kohjin Co., Ltd. Sodium thiopental and sodium pentobarbital were obtained from Tanabe Seiyaku Co., Ltd. and Tokyo Kasei Kogyo Co., Ltd., respectively. I was prepared according to the method of Sasaki et al.[9] The analytical data of I were: mp 179.5 - 181.0°C (lit.[9] mp 181 - 182°C), yield 59.5%, ^{1}H-NMR (DMSO-d6) δ:3.68 (2H,m,5'-CH_2-), 3.96 (1H,m,4'-H), 4.08 (2H,m,2'-H + 3'-H), 5.08 (2H,s, N-CH_2-), 5.96 (2H,m,1'-H + 5-H), 7.38 (5H,m,Ph), 8.16 (1H,d,J=8Hz, 6-H). Anal.Calcd for $C_{16}H_{18}N_2O_6$: C,57.46; H,5.42; N,8.42. Found: C,57.46; H,5.43; N,8.40.

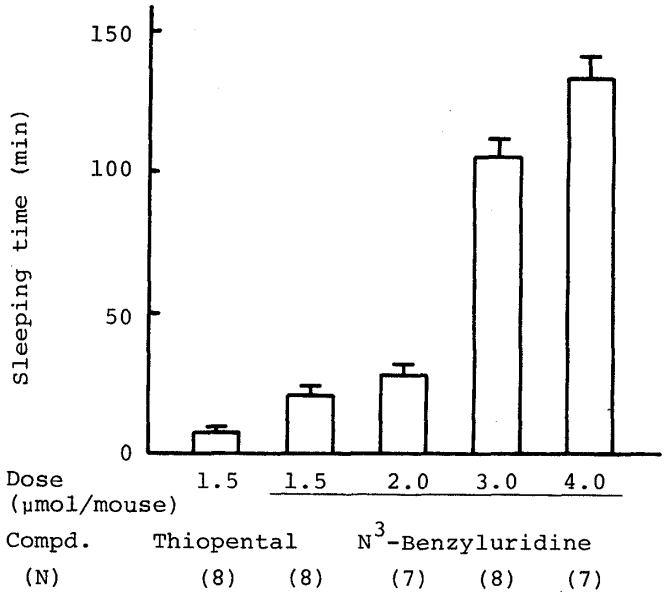


Fig. 2. Hypnotic Activity of N^3-Benzyluridine and Thiopental Injected i.c.v.
Results are expressed as the mean ± S.E.
The numbers of animals used are shown in parentheses.

The hypnotic activity in mice was determined by measuring sleeping time, the time between loss of righting reflex and recovery. All compounds (I, II and III) were suspended in 3% Tween-80 saline for injection. The i.c.v. injection was performed according to the method of Haley and McCormick.[10] Eight mice were used in each group.

Table I. Effect of Uracil (II), Uridine (III) and N^3-Benzyluridine (I) on Pentobarbital-Induced Sleep

Compd.	Dose (μmol/mouse)	Sleeping time (min)	(N)
Control	——	68 ± 4	(8)
(II)	0.5	71 ± 2	(8)
	1.0	67 ± 4	(8)
	1.5	61 ± 6	(7)
(III)	0.5	66 ± 4	(8)
	1.0	63 ± 3	(8)
	1.5	69 ± 3	(8)
(I)	0.5	103 ± 7 **	(8)
	1.0	105 ± 3 **	(8)
	1.5	125 ± 5 **	(8)

Results are expressed as the mean ± S.E.
**, significantly different from the control, $p<0.01$.
(N), number of animals used.

The hypnotic activity of I was examined by i.c.v. administration (1.5 - 4.0 μmol/mouse). These results are summarized in Fig. 2. Administration of I (≥1.5 μmol/mouse) caused sleep, although a dose of 1.0 μmol/mouse had no hypnotic effect. The sleeping time of I administered at 1.5, 2.0, 3.0 and 4.0 μmol/mouse was 22, 28, 106 and 134 min, respectively. In contrast, when mice were injected i.c.v. with 1.5 μmol/mouse of thiopental, the sleeping time was 8 min. At the same dosage, I had stronger hypnotic activity than thiopental.

The effect of I, II and III on the sleeping time induced by pentobarbital was tested (Table I). The compounds (0.5, 1.0 and 1.5 μmol/mouse, respectively) and 3% Tween-80 saline as control were injected i.c.v. into mice. Fifteen min later, 40 mg/kg of sodium pentobarbital was given intraperitoneally, and the pentobarbital-induced sleep was measured. The administration of I resulted in significantly prolonged sleeping time at all doses. I at doses of 0.5, 1.0 and 1.5 μmol/mouse prolonged sleeping time by 51%, 54% and 83%, respectively, compared with the control. II and III did not prolong sleep at these doses, although we previously reported that III and N^3-allyluridine significantly prolonged pentobarbital-induced sleep at higher doses.[8)]

From these results, it is apparent that I, a derivative of III, has hypnotic activity and prolongs pentobarbital-induced sleep. It is thus interesting to note that not only I is a hypnotic, but also the structures of I, II and III are very similar to barbiturates. Further research is now in progress on the synthesis of N^3-substituted compounds of III and the elucidation of the action mechanism of I.

REFERENCES AND NOTES

1) Y. Komoda, M. Ishikawa, H. Nagasaki, M. Iriki, K. Honda, S. Inoue, A. Higashi and K. Uchizono, Biomed. Res., 4, 223 (1983).
2) K. Honda, Y. Komoda, S. Nishida, H. Nagasaki, A. Higashi, K. Uchizono and S. Inoue, Neurosci. Res., 1, 243 (1984).
3) S. Inoue, K. Honda, Y. Komoda, K. Uchizono, R. Ueno and O. Hayaishi, Proc. Natl. Acad. Sci. U.S.A., 81, 6240 (1984).
4) S. Inoue, K. Honda, Y. Komoda, K. Uchizono, R. Ueno and O. Hayaishi, Neuroscience Letters, 49, 207 (1984).
5) D. G. Wenzel and M. L. Keplinder, J. Am. Pharm. Assoc., 44, 56 (1955).
6) D. G. Wenzel, J. Am. Pharm. Assoc., 44, 550 (1955).
7) C. L. Roberts, Brain Res., 55, 291 (1973).
8) Part of this work was presented at the 62nd Meeting of the Hokuriku Branch and the 105th Annual Meeting of the Pharmaceutical Society of Japan, Abstracts p.16 and p.174, Toyama and Kanazawa, June 1984 and April 1985, respectively.
9) T. Sasaki, K. Minamoto and H. Suzuki, J. Org. Chem., 38, 598 (1973).
10) T. J. Haley and W. G. McCormick, Brit. J. Pharmacol., 12, 12 (1957).

(Received July 8, 1985)