

Synthesis and hypnotic-sedative activities of N-substituted uracil on mice

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ABSTRACT

*N*³-Phenacyl-*N*¹-substituted uracils **3a-q** were synthesized by introduction of substituents at the *N*¹-position of *N*³-phenacyluracil **2**, and their hypnotic and sedative activities were evaluated. Pharmacological activities of these *N*³-phenacyl-*N*¹-substituted uracils were examined using hypnotic activity and synergistic effects with pentobarbital or diazepam for the hypnotic and sedative activities.

INTRODUCTION

Uridine is a pyrimidine nucleoside, which has a uracil ring in the structure, displaying sleep-promoting effect in rats (1) and *N*³-benzyl substituted uridine was discovered to show hypnotic action on mice by intracerebroventricular (i.c.v.) administration (2). The structure-activity relationships of oxypyrimidines for CNS depressant effects including sedative and hypnotic activity were investigated and *N*³-phenacyluridine exhibited the strongest hypnotic activity. In addition, Wenzel and Keplinger (3) revealed CNS depressant properties of uracil and oxypyrimidines as barbiturate-induced sleep-prolonging effect in mice. These evidences suggest that oxypyrimidines basically had

CNS depressant activity. We thus investigated whether the introduction of a substituent group at the *N*¹-position of *N*³-phenacyluracil leads to CNS depressant effects or not. The present paper describes CNS depressant activity of *N*¹-substituted *N*³-phenacyluracil in mice.

SYNTHESIS

To obtain a series of *N*¹-substituted congeners **3a-q**, *N*³-phenacyluracil **2** was chosen as a key compound. Thus, *N*¹-(tetrahydrofuran-2-yl)uracil **1** (4) was condensed with 2-chloroacetophenone to afford *N*³-phenacyl-*N*¹-(tetrahydrofuran-2-yl)uracil. Then, the product was treated with 1M HCl to give **2** in 69% yield. This *N*³-substituted uracil was examined to introduce various alkyl groups at *N*¹ as follows: Compound **2** was subjected to nucleophilic substitution with allyl, ethoxymethyl, substituted benzyl or picolyl halides in the presence of K₂CO₃ in DMF to give their *N*¹-substituted analogues **3a-c, i-1, n-q**. In the case that the halides are not commercially available, alcohols were employed as reagents. Therefore, 2-(methylthio)ethanol, 2,2-diphenylethanol, furanylmethanols and thiophenemethanols were condensed with **2** using the Mitsunobu reaction (5,6) to give the *N*¹-substituted congeners **3d-h, m**.

HMBC spectrum of the typical products **3b, j** prepared by method 1 or 2 showed correlation between the methylene protons of the phenacyl group and C2 and C4 of the uracil ring indicating *N*³-phenacyl structure (Fig. 1). Also, the *N*³-alkylated structure was confirmed by correlation between the methylene protons of the allyl or (thiophen-2-yl)methyl group and C2 and C6 of the uracil ring.

PHARMACOLOGICAL EFFECTS

Compounds *N*¹-(2-methylthioethyl)- **3d**, *N*¹-(2-chlorobenzyl)- **3i**, and *N*¹-(3-chlorobenzyl)-*N*³-phenacyluracil **3j** exhibited hypnotic activity in mice by i.c.v. injection at a dose of 2.0 μmol/mouse, whereas other *N*-substituted compounds did not possess the hypnotic activity. *N*¹-(2-Thiophenyl)-*N*³-phenacyluracil **3g** displayed significant potentiation of pentobarbital by i.c.v. injection to mice. On the other hand, certain derivatives such as *N*¹-(2-methylthioethyl)- **3d** and *N*¹-(4-*tert*-butylbenzyl)uracil **3l** significantly prolonged the diazepam-induced sleeping time compared to control. In particular, *N*¹-(4-picolyl)-*N*³-phenacyluracil **3q** strongly potentiated diazepam-induced sleep, indicating that there may be existence

of the regioselective interaction at the benzodiazepine receptor. The present study suggested that oxypyrimidines such as *N*¹-substituted *N*³-phenacyluracil basically produced CNS depressant effects.

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