IMPROVEMENT OF THE SYNTHETIC METHOD OF ANTI-TUMOR BENZO[c]PHENANTHRIDINE ALKALOIDS

Hisashi Ishii, Takeo Deushi, Ken-Ichi Harada, Mitsugi Sakamoto, Keiko Watanabe (Née Nakajima), Etsuko Ueda, Toshiaki Ishida, and Tsutomu Ishikawa

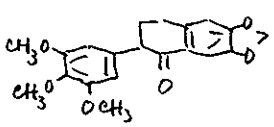
Faculty of Pharmaceutical Sciences, Chiba University

1-33, Yayoi-cho, Chiba, Japan

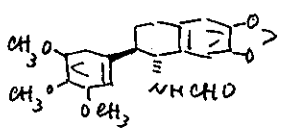
It is well known that some benzo[c]phenanthridine alkaloids naturally occurred in Rutaceous plants, nitidine and fagaronine, show the antitumor activity. In order to clarify the structure-antitumor activity relationship, we tried to improve the Robinson's reaction sequence for benzo[c]phenanthridine alkaloids as the model compound, 7,8,9-trimethoxy-2,3-methylenedioxybenzo[c]phenanthridinium salt.

Leuckart reaction of 2-phenyl-1-tetralone derivative (1) gave a mixture of trans- and cis-formamides (2a and 2b). The pure trans-formamide (2a) was obtained by treatment of the above mixture with HCOOH. On the other hand, pure cis-formamide (2b) was prepared *via* hydrogenation of the α-tetralone (1) hydrazone on Pt in AcOH or the tetralone oxime on Raney Ni in EtOH. Treatment of cis-formamide (2b) with HCOOH gave a stilbene product almost quantitatively but Bischler-Napieralski reaction of it afforded the dihydroisoquinoline compound without formation of the stilbene derivative. This fact indicates that the Leuckart mixture of cis- and trans-formamides could be available for Bischler-Napieralski reaction.

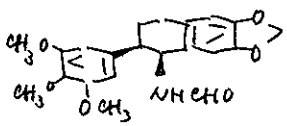
It is known that Bischler-Napieralski reaction could not take place with an -NHCO amide which has not an alkoxy group at the p-position to the cyclized point. In order to strengthen the electrophilicity of an amide group, Bishler-Napieralski reaction of an NMeCHO amide was examined. Quaternarization of a tertiary benzo[c]phenanthridine alkaloid, another defect of Robinson sequnece was overcome as follows. A solution of a tertiary base in HMPA was treated with Me_2SO_4 and $NaBH_4$ to give an N-methyl dihydrobenzo[c]phenanthridine derivative almost quantitatively. This was aromatized by treatment with DDQ to give a quaternary salt in good yield.



(1)



(2a)



(2b)