STUDY ON THE SYNTHESIS OF NEOSURUGATOXINE

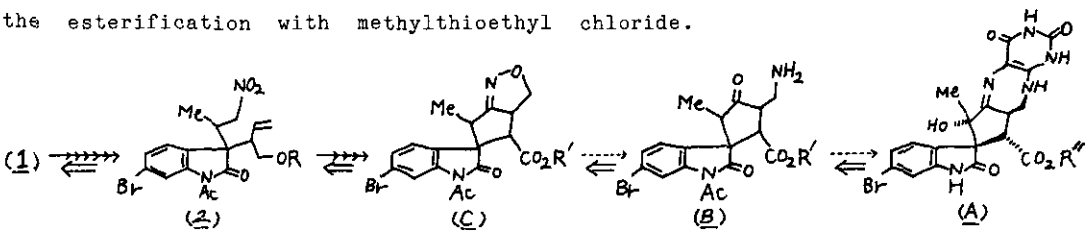
Hitoshi Ishida, Atsuhiro Inaba*, and Takuo Kosuge

Shizuoka College of Pharmacy

2-2-1 Oshika, Shizuoka-shi 422, Japan

In the course of our efforts for construction of neosurugatoxine(A), we were intriguted with the possibility of designing a spiro-(cyclopentane-1,3'-pseudo oxindole) derivative(B), which could be convertible into tricyclic compound(C) possessing suitably functionallized C-ring for elaborating the D-ring of (A). This notion, displayed in its retrosynthesis format(scheme 1), required that we be able to developed simple and efficient ways of preparing the new compound 6-bromo-2-oxindole(1), 3-(1-hydroxymetyl-2-propenyl)-derivative(2) from (1), and *isoxazoline(C) from* (2).

With regard to the first point, we discovered that general oxindole synthesis reported by Reisert and Sherck[1] be applicated to the preparation of (1) from commercially available 4-amino-2-nitrotoluene[2]. And then the efficient route from (1) to (C) was established as follows. After N-acylation, 1 was reacted with triethyl orthoacetate, and then the resulted compound was hydrolyzed by sodium hydroxide to yield 3-acetyl-6-bromo-2-oxindole[2]. Reaction of metal anion of this compound with 2-bromo-3-butene-1-ol gave the mixture of S_N2 and S_N2' substitution products. The S_N2 substituted compound was deacylated with sodium hydroxide, and subsequently protected the indole nitrogen by acylation and the hydroxyl group by t-butyldimethylsilylation. Reaction of 1-nitro-1-propene with the protected compound gave the nitro derivative (2). (2) was reacted with phenyl isocyanate to yield the isoxazoline in excellent yield. After desilylation of the isoxazoline, (C) was obtained by oxidation of hydroxy group with Sarret's reagent, followed by the esterification with methylthioethyl chloride.



⇐ : retrosynthetic analysis R'= methylthioethl R''=β-D-xylopyranosyl(1-5)myoinositol

References 1) A.Reissert and J.Scherk, Chem. Ber., 31, 387 (1955).

2) H.Ishida, A.Inaba and T.Kosuge, Chem. Pharm. Bull., 33, 1414 (1985).