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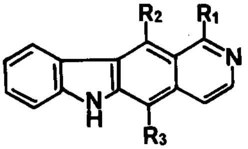
A NEW ROUTE TO THE OLIVACINE TYPE ALKALOID RING SYSTEM *via* THE FISCHER BASE INTERMEDIATE. A SIMPLE SYNTHESIS OF 6*H*-PYRIDO-[4,3-*b*]-CARBAZOLE

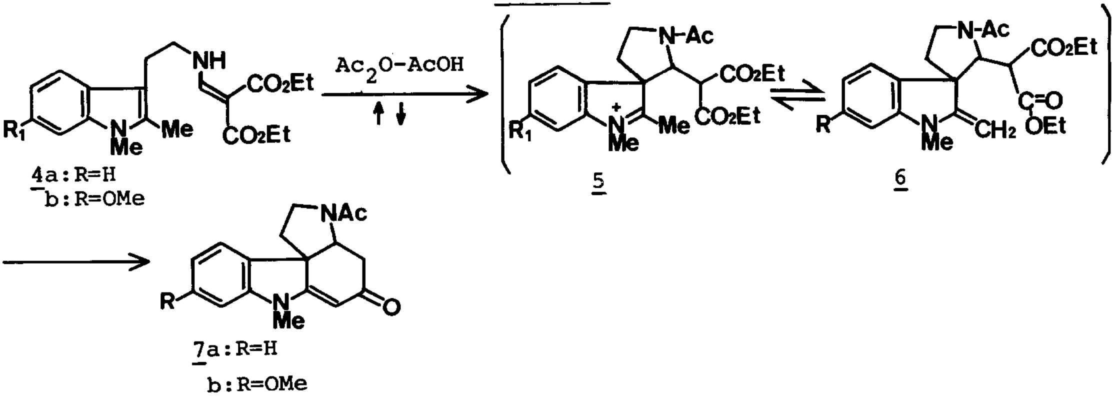
Seiichi Takano*, Kohtaro Yuta, Susumi Hatakeyama, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan 980.



1: $R_1=R_3=Me$, $R_2=H$
2: $R_2=R_3=Me$, $R_1=H$
3: $R_1=R_2=R_3=H$

The olivacine type indole alkaloids, olivacine(1)[1], ellipticine(2)[1], and their analogs[1] are of interest because of their antitumor and antileukemic activity[2]. The medicinal importance has stimulated a number of successful approaches to construction of these alkaloids and their derivatives[3]. We report here a novel method to the construction of the ring system of these alkaloids by a completely different approach utilizing the newly developed Fischer base intervening cyclization[4] which has allowed an efficient formation of the key intermediates(7a, b) of the functionalized aspidosperma indole alkaloids, vindorosine[5] and vindoline[6] (Scheme 1).

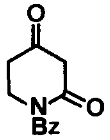
Scheme 1



Condensation of 1-benzylpiperidine-2,4-dione(8)[7], b.p. 143°(0.17 mmHg), m.p. 165-6°, prepared from ethyl 2-benzylaminopropionate and ethyl malonyl chloride through the two step sequence[8], with triethyl orthoformate and 2-nitroaniline at 140° for 10 min gave the vinylogous amide(9a)[9](83%), m.p. 163-4°, which upon treatment with 2-methyltryptamine[10] in refluxing ethanol induced the efficient amine exchange reaction to form the new vinylogous amide(9b)(90%), oil Refluxing 9b with acetic anhydride-acetic acid(5:3) for 48h afforded a mixture of carbazoles[11] (10a) and (10b)(11:6), which without separation was hydrolyzed with ethanolic sodium hydroxide to allow exclusive formation of the former(46% overall from 9b). Similarly the vinylogous amide(9c), oil, prepared from 9a and 1,2-dimethyltryptamine[10](91%), yielded the corresponding carbazole(10c)(49%), m.p. 182-3°.

The novel carbazole formation could be resulted by the intervention of the Fischer base intermediates(12) and (14), which could promote the critical cyclization(12→13) and the removal of the ethanamine moiety(14→15) as shown (Scheme 2).

Reduction of 10b with lithium aluminum hydride in boiling THF afforded the tertiary amine(10d), m.p. 210-11°, quantitatively, which upon heating with 5% palladized charcoal in decalin[12] at refluxing temperature underwent smooth dehydrogenation and spontaneous debenzylation to give 6*H*-pyrido[4,3-*b*]carbazole (3)(desmethylolivacine or desmethylellipticine), m.p. 285-7°(lit.[13] 286-9°) in 69% yield.



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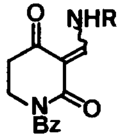
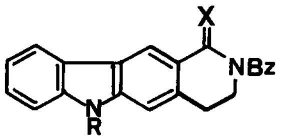
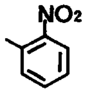
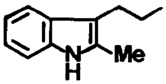




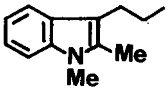
9a:R=



b:R=



c:R=



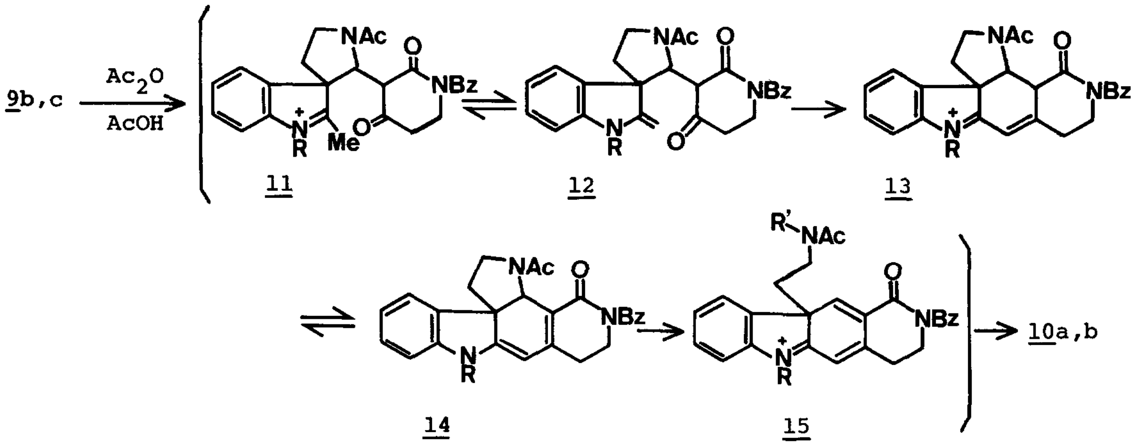
10a:R=H, X=O

b:R=Ac, X=O

c:R=Me, X=O

d:R=H, X=H$_2$

Scheme 2



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