STUDIES ON THE SYNTHESES OF HETEROCYCLIC AND NATURAL PRODUCTS. PART 968.[1] RACEMIZATION REACTION IN BISCHLER-NAPIERALSKI CYCLIZATION : SYNTHESIS OF β-CARBOLINE AND ISOQUINOLINE NUCLEI FROM L-TRYPTOPHAN AND L-PHENYLALANINE DERIVATIVE

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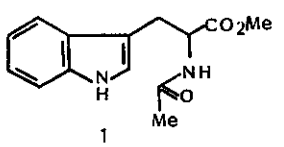
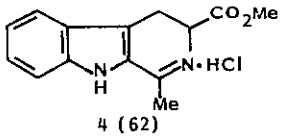
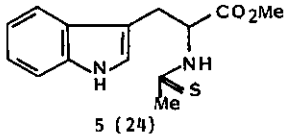
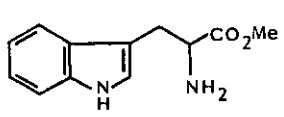
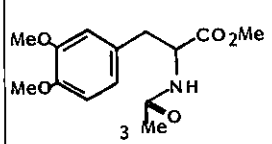
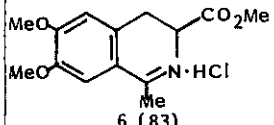
Abstract —— The Bischler-Napieralski type of cyclization of L-N-acetyltryptophan methyl ester and L-N-acetyl-3,4-dimethoxyphenylalanine methyl ester in order to obtain 3,4-dihydro-9H-pyrido[3,4-b]indole and 3,4-dihydroisoquinoline derivatives has been investigated.

In a previous paper[2], we have demonstrated the asymmetric synthesis of protoberberine alkaloids, (-)-xylopinine, by photocyclization of enamide derived from L-dopa, as a key reaction. In extension of our work on the synthesis of yohimbane alkaloids by the application of the above strategy, we investigated the synthesis of 3,4-dihydro-9H-pyrido[3,4-b]indole nucleus from L-tryptophan in an optically active form by Bischler-Napieralski cyclization of the corresponding N-acetyl derivatives. With regard to the synthesis of β-carboline derivatives bearing alkoxycarbonyl group at the 3-position by Bischler-Napieralski reaction, many papers[3-13] have been published up to date, however, none of which has made mention of optical activity for the products except Previero's report[14]. Here we wish to report some aspects on the synthesis of β-carboline and 3,4-dihydroisoquinoline derivatives using L-tryptophan and L-phenylalanine derivatives as starting materials, respectively. The results are summerized in Table, which indicated that phosphorous pentoxide in refluxing xylene for the conversion of 1 and 3 to 4 and 6, was the best in terms of cyclization yield. However, the products (4 and 6) obtained by the reaction condition in Table showed no optical rotation, the fact of which suggested that the racemization has occurred in some stage of cyclization. When tryptophan methyl ester (2) and N-acetyltryptophan methyl ester (1) were heated at 140°C without phosphorous pentoxide, no racemization had been observed. Whereas polyphosphate ester (PPE) was used as a cyclizaing agent, a partial racemization was observed. Even in the formation of the thio-amide (5)[15,16] which may lead to the desired compound 4 under mild reaction condition, the racemic thio-amide (5), was only isolated. On the contrary, the cyclization of 3 with phosphoryl chloride in acetonitrile afforded the desired compound 6 without racemization.

The above results demonstrated that the racemization of 3,4-dihydro-9H-pyrido[3,4-b]indole (4) occurred much faster than that of 3,4-dihydroisoquinoline (6). Moreover the cyclization of the amide with phosphorous pentoxide in refluxing xylene or polyphosphate ester (PPE) afforded the desired products in moderate yields, but in racemic form. Finally, treatment of L-tryptophan methyl ester with trifluoroacetic acid and acetyl chloride, followed by the esterification with thionyl chloride in methanol according to Previero's procedure afforded compound 4 with $[\alpha]_D$ + 260°.

Substances	Reagent	Solvent	Temp./Time	Product Yield (%)	$[\alpha]_D^{20}$
 a 1	$POCl_3$ PCl_5	MeCN $CHCl_3$	r.t./3.5h	———	———
1	P_2O_5	Xylene	140°/2h	 4 (62)	+ 3° b (c=1, $CHCl_3$)
1	PPE	———	80°/0.5h	4 (48)	+33° (c=0.2, $CHCl_3$)
1	P_2S_5	Benzene	60°/40h	 5 (24)	0° (c=1.5, $CHCl_3$)
 c 2	P_2O_5	Xylene	140°/2h	2 (90)	+19° (c=2.2, MeOH)
 d 3	$POCl_3$	MeCN	r.t./2h	 6 (83)	+160° (c=3, MeOH)
3	P_2O_5	Xylene	140°/2h	6 (85)	+25° (c=0.2, $CHCl_3$)
3	P_2O_5	Xylene	140°/4h	6 (81)	0° (c=1, $CHCl_3$)

a $[\alpha]_D$ + 24° (c=0.2, MeOH)

b Lit.,[13] + 227° (HCl salt)

c $[\alpha]_D$ + 19.0° (c=2.2, MeOH)

d $[\alpha]_D$ + 19.9° (c=1.3, MeOH)

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