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# ONE-STEP CONSTRUCTION OF 2,3,3a,8a-TETRAHYDROFURO[2,3-b]INDOLE SYSTEM: AN APPLICATION TO PHYSOVENINE SYNTHESIS

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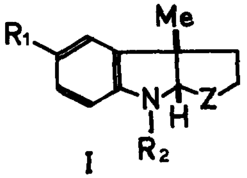
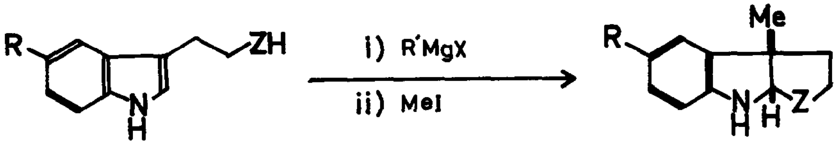
The alkaloidal constituents of Calabar beans belong to a small group of indole alkaloids whose structure consists of tryptamine and one extra carbon unit. These alkaloids, represented by the general formula I, has been comprehensively studied and there are excellent reviews[1,2] including synthetic investigations.



I

|  | $R_1$ | $R_2$ | Z | Alkaloid |
|---|---|---|---|---|
| Ia | MeNHCOO- | Me | O | physovenine |
| Ib | MeNHCOO- | Me | NMe | eserine |
| Ic | MeO- | Me | O | - |



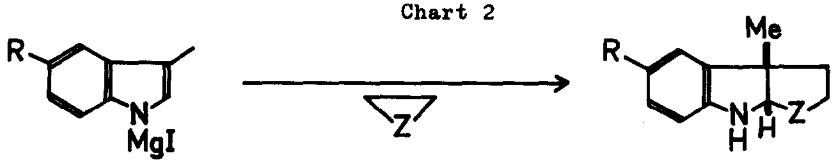
II

Chart 1

Among many solution for the synthesis of these systems, the one proposed by Hoshino and his co-workers[3,4] seems to be an excellent biogenetic approach toward these skeletons (Chart 1), but has a rather complicated step in preparing the appropriately arranged tryptophol or tryptamine derivatives (e.g. II) as the starting material. If, however, we could introduce a β-hydroxyethyl group into 3-substituted indoles, we should be able to develop not only a new process for these alkaloids from much simpler starting material, but also a general entry to the synthesis of indole alkaloids with 3-spiro structure. This communication give some new results on this possibility.

The reaction indicated in Chart 2 will be the most rational approach to realize the crucial step proposed above. Treatment of skatolylmagnesium iodide (IIIa) with an excess of anhydrous ethylene oxide (IVa) in absolute ether afforded the desired cyclic product (Va) directly which was accompanied by a small amount of dialkylated product. The successful result of this model reaction stimulated us to attempt the synthesis of physovenine (Ia), which had

Chart 2



IIIa: R=H
IIIb: R=OMe

IVa: Z=O
(IVb: Z=NMe)

Va: R=H, Z=O
Vb: R=OMe, Z=O

already been accomplished by 8 stages of reactions in overall yield of 0.16%.5)

5-Methoxyskatole, the starting material of our synthesis, was obtained as crystals after a chromatographic purification of the crude material prepared according to Späth's literature.6) To 5-methoxyskatolylmagnesium iodide (IIIb), derived from 5-methoxyskatole and methylmagnesium iodide in absolute ether, an excess of ether solution of anhydrous ethylene oxide (IVa) was added and reacted for 4 hr at room temperature with stirring. Extraction of basic part and purification over alumina column gave 2,3,3a,8a-tetrahydro-5-methoxy-3a-methylfuro[2,3-b]indole (Vb) as colorless oil in 13% yield. Methylation of Vb with NaH-DMF-MeI furnished 2,3,3a,8a-tetrahydro-5-methoxy-3a,8-dimethylfuro[2,3-b]indole (Ic) in 36% yield. The NMR spectrum of Ic thus synthesized was superimposable with the reported one.5) It formed a picrate of mp 143-145° which also agreed with the recorded value (mp 136-139°).

As Ic has already been converted to natural physovenine by demethylation and the succeeding methylcarbamoylation,5) our synthesis constitutes a convenient synthesis of physovenine (Ia) in a shorter reaction sequence.

The use of N-methylaziridine7) (IVb) in place of ethylene oxide ($IV_a$) in this reaction and the application of this reaction to a more complicated system will be subjects of considerable interest and further studies are awaited.

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