A FACILE AND CONVENIENT SYNTHETIC ROUTE TO 4-SUBSTITUTED INDOLES

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I. 4-Methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline **1**, a suitable intermediate for the syntheses of both 3,4-disubstituted indoles and Ergot alkaloids, was prepared by the following two methods.

a) *Five step synthesis of 1 with the overall yield of 8.9% from 2-methyl-5-nitroisoquinolinium iodide 2*: Reduction of **2** to 1,2-dihydro-2-methyl-5-nitroisoquinoline and subsequent Vilsmeyer reaction afforded 1,2-dihydro-4-formyl-2-methyl-5-nitroisoquinoline **3**. Treatment of **3** with refluxing triethylphosphite (TEP), followed by the reduction with B_2H_6 gave borane complex of **1**. By the action of 10% HCl, **1** was liberated from this complex.

b) *Seven step synthesis of 1 with the overall yield of 19.2% from 2*: The compound **3** was reduced to 5-amino-4-hydroxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline **4** with $NaBH_4$ in the presence of 5% Pd/C in quantitative yield. Treatment of **4** with MsCl-Py afforded 1,2,2a,3,4,5-hexahydro-1-mesyl-4-methylpyrrolo[4,3,2-de]isoquinoline **5**. Removal of mesyl group of **5** and subsequent oxidation with NCS gave **1**.

II. Various 4-substituted indoles such as 4-dimethylamino-, 4-acetoxymethyl-1-acetyl-, 4-acetoxymethyl, and 4-hydroxymethyl-3-cyanomethylindole **6** were prepared from **1**. The structures of these compounds were established unequivocally by the preparation of **6** from the authentic 4-hydroxymethylindole.

III. Hofmann degradation reaction of 2-allyl, 2-benzyl, 2-methyl, and 2-propargyl-2-methyl-5-nitroisoquinolinium salts was found to give the corresponding *o*-nitrostyrene derivatives, which were converted to 4-[N,N-disubstitutedaminomethyl]indoles by the treatment with refluxing TEP.

IV. 5-Substituted pyrrolo[4,3,2-de]isoquinoline derivatives, 5-(2-acetoxypropyl)-, 5-(2-ethylenedioxypropyl)-, and 5-(2-ethylenedithiopropyl)-4-methyl-2-oxo-1,2,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline, were obtained by the introduction of acetonyl group into the 1-position of **2**, followed by the series of reaction as described in **Ia**.

V. A further attempt to introduce carbon side chains into the 5-position and also Meisenheimer rearrangement of **5** were studied.