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DEHYDROGENATION WITH PHENYLSELENINIC ANHYDRIDE IN THE TOTAL SYNTHESIS OF ERGOT ALKALOIDS

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Abstract - The standardised procedure for dehydrogenation of indolines into indoles with phenylseleninic anhydride 1 was successfully applied to the final steps in the total synthesis of ergot alkaloids.

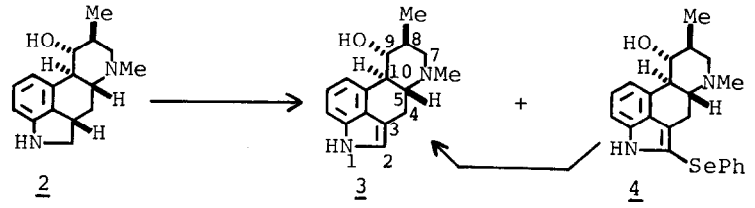
In some of previous total syntheses of ergot alkaloids, the conversion of the indoline nucleus into indoles by dehydrogenation (Na_2HAsO_4-Raney Nickel[1] and MnO_2[2]) was one of the key steps which however had never been accomplished with good results. Ninomiya et al.[3-5] had applied phenylseleninic anhydride[6] 1 to this dehydrogenation in their total synthetic work, but the yields obtained remained unsatisfactory.

In view of the necessity of establishing a practical procedure, extensive investigation has jointly been carried out with this reagent 1 and has resulted in the development of an efficient standardised procedure[7]. In the presence of indole as a scavenger

of the Se^{II} species formed during the course of reaction very good yields were obtained. This paper describes the successful application of this procedure to the total synthesis of ergot alkaloids as summarised in the Table. All the alkaloids synthesised were racemates.

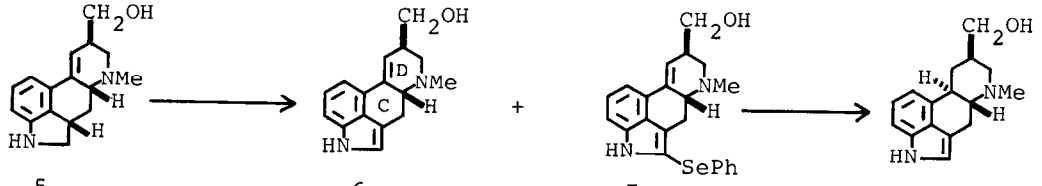
As reported previously,[3] treatment of dihydroisofumigaclavine 2 with 1 (40°C, THF, 2 hrs) afforded isofumigaclavine B 3 in 50% yield along with the 2-selenide[8] 4 in 25% yield. Similar dehydrogenation of dihydrolysergol[9] 5 yielded lysergol 6 in 47% yield and the corresponding 2-selenide[8] 7 in 29% yield. The structures of these selenides 4 and 7 were established from their MS and NMR spectra,[8] which showed the presence of a phenylselenyl group at 2-position, thereby suggesting their formation as a result of the secondary reaction[6b] of the alkaloids 3 and 6 with Se^{II} species. Deselenisation of these selenides was also investigated by the use of nickel borides,[10] thus giving isofumigaclavine B 3 and dihydrolysergol-I[11] 8, m.p. 248-250°C (MeOH), in 97 and 80% yields from the corresponding selenides 4 and 7 respectively. The formation of 8 shows the difficulty of selective removal of a selenenyl group when there also exists a double bond in the ring D.

Upon considering the above results, we carried out dehydrogenation with 1 under the condition developed in the previous paper.[7] Treatment of 2 and 5 with 1 (indole 3 equivs., 1 0.5 M equiv., 40°C, THF) afforded the corresponding alkaloids 3 and 6 in 84 and 97% yields respectively without forming any detectable amount of selenides. When dihydrofuran was added as scavenger instead of indole, the yield of 3 from 2 decreased to 50% with the formation of the selenide 4 (25%). Further applications of this standardised procedure to the total synthesis of ergot alkaloids are as summarised in the Table, which clearly shows the superiority of this newly developed procedure with phenylseleninic anhydride 1 for the conversion of the indoline nucleus into indoles irrespective of the presence of reactive functional group such as a double bond (Entries 4-9), hydroxyl group (Entries 1-4), and allylic hydroxyl group (Entry 5).



2 3 4

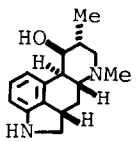
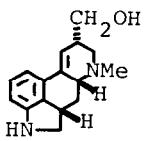
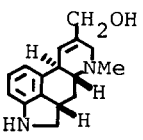
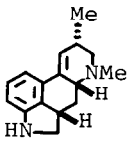
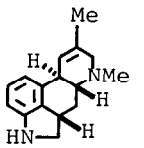
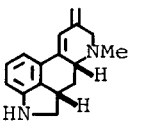
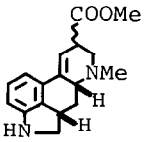
isofumigaclavine B



5 6 7 8

lysergol

Table

Entry	Indolines	(Isolated Yields) Indoles M.p. (Solvents)
1	2	(84%) isofumigaclavine B 3 271-273°C (dec.) (MeOH)
2	5	(97%) lysergol 6 220-224°C (dec.) (EtOH)
3		(89%) fumigaclavine B[12] 199-200°C (dec.) (EtOH)
4		(95%) isolysergol[5] 137-140°C (dec.) (MeOH)
5		(94%) elymoclavine[5] 207-210°C (dec.) ($CHCl_3$-MeOH)
6		(90%) isolysergine[12] 112-114°C (Me_2CO-n-C_6H_{14})
7		(84%) agroclavine[4] 182-184°C (Et_2O)
8		(81%) lysergene[4] 210-212°C (dec.) (Me_2CO)
9		(88%) methyl lysergates[3]

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8. Compound 4; m.p. 104-106°C (Et_2O), MS m/e 412 and 410 (M^+); NMR δ ($CDCl_3$, 200 MHz) 8.02 (1H, br s, NH), 7.73 (1H, br d, J=8 Hz, 12-H), 7.30-7.14 (7H, m, ArH), 3.62 (1H, t, J=10 Hz, 9-H), 2.46 (3H, s, NMe), and 1.14 (3H, d, J=7 Hz, CMe). Compound 7; m.p. 184-186°C (dec.)(CH_2Cl_2), MS m/e 410 and 408 (M^+); NMR δ ($CDCl_3$, 200 MHz) 8.08 (1H, br s, NH), 7.36-7.13 (8H, m, ArH), 6.45 (1H, br s, 9-H), 3.79 (2H, m, 8-CH_2), and 2.60 (3H, s, NMe).
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