CHEMISTRY LETTERS, pp. 1245-1248, 1978. Published by the Chemical Society of Japan

THE PREPARATION OF 4-METHYL-1,3,4,5-TETRAHYDROPYRROLO[4,3,2-de]ISOQUINOLINE AND ITS CONVERSION INTO 3,4-DISUBSTITUTED INDOLES[1]

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Various 3,4-disubstituted indoles were prepared from 4-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline which was obtained readily by the two novel synthetic routes starting from 2-methyl-5-nitroisoquinolinium iodide.

In our synthetic project for Ergot alkaloids, we have chosen 4-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinolines 1a-1c as suitable key compounds. Although several pyrrolo[4,3,2-de]isoquinolines have been prepared previously,[2] their syntheses utilized 4-substituted indoles as starting materials whose preparations were rather tedious.

Now, we wish to report the synthesis of 1a by the two novel synthetic routes from readily accessible 2-methyl-5-nitroisoquinolinium iodide 2 and its further conversion to indoles (e.g. 13) suitably functionalized both at the 3- and 4-positions to be a synthon for Ergot alkaloids.

I. Five step synthesis of 1a in the overall yield of 9% from 2

Reduction of 2 with 1.0 mol equiv of $NaBH_4$ in MeOH at room temperature afforded a 3 to 1 mixture of 1,2-dihydro-2-methyl-5-nitroisoquinoline 3 [NMR ($CDCl_3$, δ): 2.83 (3H,s,N-Me), 4.23 (2H,s,CH_2-N), 6.06 (1H,d,J=8 Hz), 6.26 (1H,d,J=8 Hz)] and 2-methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline [2.43 (3H,s,N-Me), 2.66 and 3.15 (each 2H, A_2B_2 triplet), 3.56 (2H,s,CH_2-N)] in 90% yield. The mixture was then subjected to Vilsmeyer reaction using $POCl_3$ and dimethylformamide (DMF) in refluxing $CHCl_3$ (3 hr) to give 4-formyl-1,2-dihydro-2-methyl-5-nitroisoquinoline 4 [mp 190-192° (dec.), IR (KBr): 1604, 1595 cm^{-1}, NMR (DMSO-d_6, δ): 3.13 (3H,s), 4.58 (2H,s), 7.00-7.51 (3H,m), 7.51 (1H,s), 8.71 (1H,s), Mass m/e: 218 (M^+)] in 48% overall yield from 2. 5-Nitroisocarbostyril was obtained as a by-product in 15% yield.

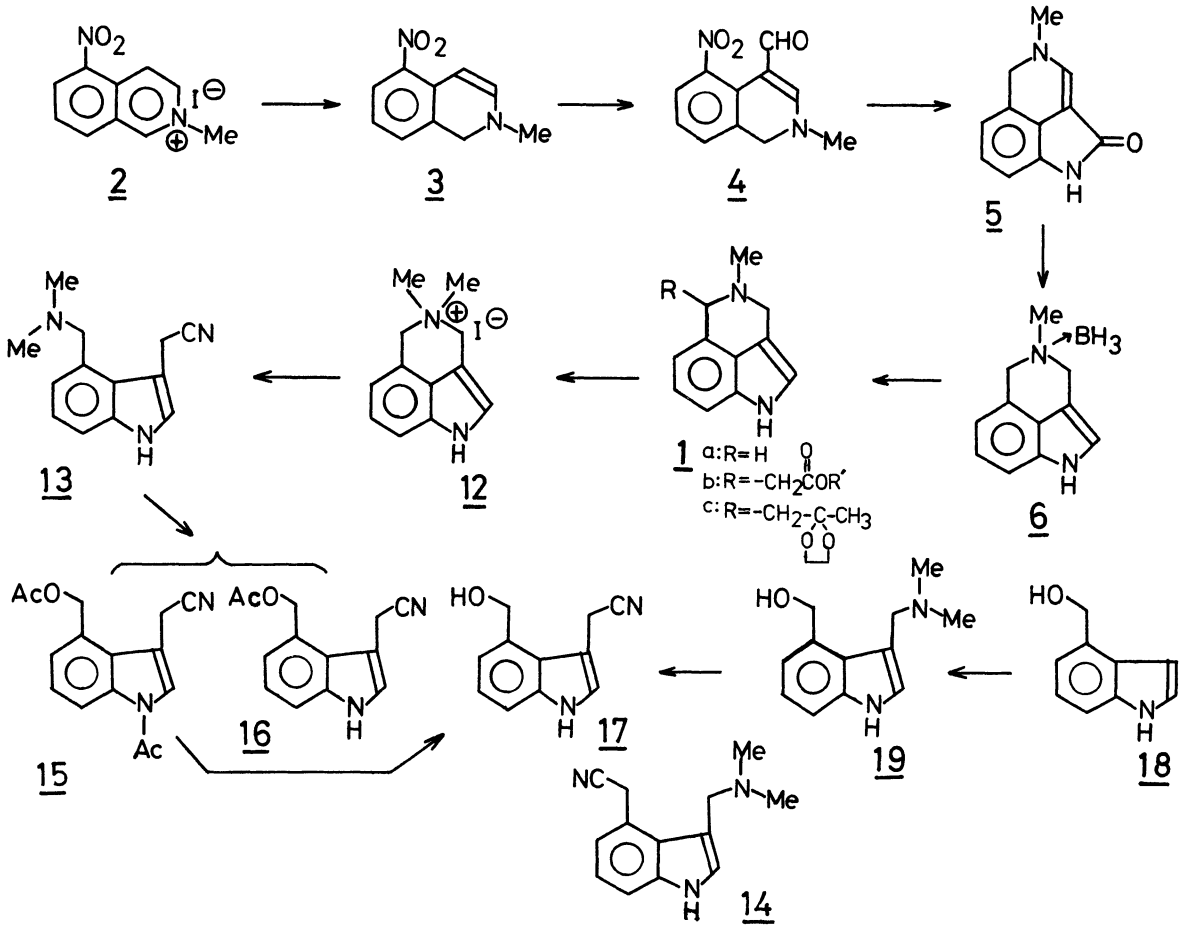
Treatment of 4 with refluxing triethylphosphite (TEP) under argon atmosphere for 4 hr gave a compound 5 as a major product, whose structure was established by nmr and mass data [NMR (20% CD_3OD in $CDCl_3$, δ): 3.03 (3H,s,N-Me), 4.76 (2H,s,N-CH_2-Ar), 6.50 (1H,d,J=7 Hz), 6.62 (1H,d,J=7 Hz), 6.93 (1H,t,J=7 Hz), 7.31 (1H,s,CH-N), Mass m/e: 186 (M^+)].

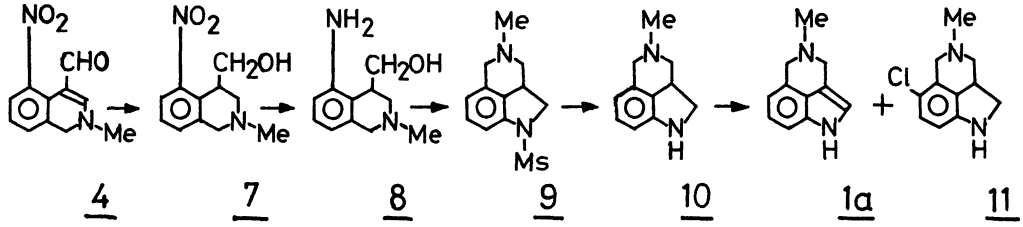
Since the compound 5 was rather unstable, the crude product obtained after evaporation of TEP in the above reaction was directly reduced with an excess of diborane in THF at reflux for 4 hr to give 4-methyl-1,3,4,5-tetrahydropyrrolo-[4,3,2-de]isoquinoline borane complex[3] 6 [mp $>$300°, IR (KBr): 3350, 2400-2250,

1613 cm^{-1}, Mass m/e: 186, 185 (M^+), NMR (25% CD_3OD in $CDCl_3$,δ): 2.42 (3H,s,N-Me), 4.04 (1H,d,J=17 Hz), 4.12 (1H,d,J=14 Hz), 4.42 (1H,d,J=14 Hz), 4.44 (1H,d,J=17 Hz), 6.82 (1H,d,J=7 Hz), 6.98 (1H,s), 7.12 (1H,t,J=7 Hz), 7.22 (1H,d,J=7 Hz)] in 28% overall yield from 4. The free base 1a [mp 188-189° (dec.), Mass m/e: 172 (M^+), IR (KBr): 3300-2250, 1623 cm^{-1}, NMR ($CDCl_3$,δ): 2.60 (3H,s,N-Me), 3.86 (4H,s,CH_2-N-CH_2), 6.76 (1H,br.s), 6.82 (1H,d.d,J=6 and 8 Hz), 7.11 (1H,d,J=6 Hz), 7.12 (1H, d,J=8 Hz), 8.20 (1H,br.s,NH)] was obtained from this complex in 65% yield by the treatment with 10% HCl in MeOH at room temperature for 1 week.

II. Seven step synthesis of 1a in the overall yield of 19% from 2

Reduction of 4 with $NaBH_4$ in MeOH gave 7 [mp 121-122°, Mass m/e: 222 (M^+), IR (KBr): 3176, 1608, 1532, 1348 cm^{-1}, NMR ($CDCl_3$,δ): 2.49 (3H,s), 2.67 (1H,br.d, J=12 Hz), 3.20 (1H,br.d,J=12 Hz), 3.37 (1H,d,J=16 Hz), 3.80 (1H,br.s), 3.93-4.21 (3H,m), 7.36 (1H,d,J=4 Hz), 7.37 (1H,d,J=5.5 Hz), 7.86 (1H,q,J=5.5 and 4 Hz)] in





93% yield. Catalytic hydrogenation of 7 over 5% Pd/C in MeOH at room temperature afforded 8 [mp 145-146°, Mass m/e: 192 (M^+), IR (KBr): 3380-3100, 1640, 1592 cm^{-1}, NMR ($CDCl_3$,δ): 2.42 (3H,s), 2.56 (1H,d.d,J=11 and 3.5 Hz), 2.81 (1H,q,J=3.5 Hz), 3.16 (1H,d,J=11 Hz), 3.24 (1H,d,J=16 Hz), 3.92 (1H,d,J=16 Hz), 4.03 (2H,d,J=3.5 Hz), 6.52 (1H,d,J=8 Hz), 6.57 (1H,d,J=8 Hz), 7.03 (1H,t,J=8 Hz)] in 94% yield.

It is noteworthy that reduction of 4 with $NaBH_4$ in MeOH in the presence of 5% Pd/C gave 8 in quantitative yield and this procedure seems to constitute a convenient catalytic hydrogenation without using hydrogenation apparatus.

Treatment of 8 with 2 mol equiv of mesyl chloride in abs. pyridine afforded 1-mesyl-4-methyl-1,2,2a,3,4,5-hexahydropyrrolo[4,3,2-de]isoquinoline 9 [mp 136-137°, IR (KBr): 3400, 1624, 1598, 1345, 1156 cm^{-1}, Mass m/e: 252 (M^+), NMR ($CDCl_3$, δ): 2.17 (1H,t,J=10 Hz), 2.53 (3H,s), 2.83 (3H,s), 3.24 (1H,d,J=16 Hz), 3.12-3.64 (3H,m), 4.02 (1H,d,J=16 Hz), 4.24 (1H,t,J=8 Hz), 6.77 (1H,t,J=5 Hz), 7.13 (2H,d, J=5 Hz)] in 94% yield. The removal of mesyl group of 9 by the reduction with sodium naphthalene in THF resulted in the formation of 10 in 82% yield [oil, IR (film): 3360-3220, 1633, 1606, 1477, 1455 cm^{-1}, NMR ($CDCl_3$,δ): 2.19 (1H,t,J=9 Hz), 2.55 (3H,s), 2.96-3.72 (4H,m), 3.65 (1H,t,J=6 Hz), 3.98 (1H,d,J=15 Hz), 6.49 (2H,d,J=8 Hz), 7.00 (1H,t,J=8 Hz), Mass m/e: 174 (M^+)]. Oxidation of 10 with N-chlorosuccinimide[4] in CH_2Cl_2 at room temperature afforded 1a in 51% yield together with 24% yield of monochlorinated compound, tentatively assigned as 11[5] [mp 137-138°, Mass m/e: 210 and 208 (M^+), IR (KBr): 3275, 3144, 1631, 1607 cm^{-1}, NMR ($CDCl_3$,δ): 2.16 (1H,t,J=9 Hz), 2.52 (3H,s), 3.16 (1H,d,J=15 Hz), 3.72 (1H,t,J=6 Hz), 3.94 (1H,d,J=15 Hz), 3.04-4.00 (3H,m), 6.40 (1H,d,J=8 Hz), 6.94 (1H,d,J=8 Hz)]. Oxidation of 10 with active MnO_2[6] gave 1a in overall yield of 23% from 9.

III. Preparation of various 3,4-disubstituted indoles

3,4-Disubstituted indoles were easily prepared from 1a. Thus, for example, the iodomethylate 12 was treated with KCN in refluxing DMF for 2 hr to afford 3-cyanomethyl-4-dimethylaminomethylindole 13 [oil, Mass m/e: 213 (M^+), IR (film): 3400, 2230, 1613 cm^{-1}, NMR ($CDCl_3$,δ): 2.20 (6H,s,N-Me_2), 3.64 (2H,s,CH_2-CN), 4.35 (2H,s,CH_2-N), 6.90 (1H, d.d,J=7 and 1 Hz), 7.08 (1H,d.d,J=7 and 8 Hz), 7.13-7.19 (1H,br.s), 7.28 (1H,d.d,J=8 and 1 Hz), 8.24 (1H,br.s,NH)] in 73% yield. The other possible structure 14 for 13 was excluded by the following experiments. The compound 13 was led to 4-acetoxymethyl-1-acetyl-3-cyanomethylindole 15 [mp 165-166°, NMR ($CDCl_3$,δ): 2.08 (3H,s), 2.63 (3H,s), 4.01 (2H,d,J=1.5 Hz), 5.32 (2H,s), 7.20-7.44 (2H,m), 7.55 (1H,t,J=1.5 Hz), 8.50 (1H,d.d,J=6.5 and 3.0 Hz), IR (KBr): 3400, 2235, 1740-1730, 1703 cm^{-1}, Mass m/e: 270 (M^+)] with refluxing Ac_2O for 6 hr in 92% yield, together with 5% yield of 4-acetoxymethyl-3-cyanomethylindole 16 [mp 152-154°, Mass m/e: 228 (M^+), IR (KBr): 3348, 2230, 1728 cm^{-1}, NMR ($CDCl_3$, δ): 2.12 (3H,s), 4.04 (2H,d,J=1 Hz,CH_2-CN), 5.41 (2H,s,CH_2-O), 7.12-7.48 (4H,m), 8.36 (1H,br.s,NH)]. Hydrolysis of 15 with 2% aqueous NaOH in MeOH at reflux for 40 min yielded 3-cyanomethyl-4-hydroxymethylindole 17 [mp 166-167°, IR (KBr): 2230, 1620 cm^{-1}, Mass m/e: 186 (M^+), NMR (50% CD_3OD in $CDCl_3$,δ): 4.17 (2H,d,J=1 Hz,CH_2-CN), 4.91 (2H,s,Ar-CH_2-O), 6.99 (1H,d.d,J=7 and 2 Hz), 7.11 (1H,t,J=7 Hz), 7.24 (1H,s), 7.35 (1H,d.d,J=7 and 2 Hz)] in 90% yield.

On the other hand, 4-hydroxymethylindole 18[7] was led to 4-hydroxymethyl-3-dimethylaminomethylindole 19 [mp 157-158°, IR (KBr): 3500-2250, 1618 cm^{-1}, NMR (20% CD_3OD in $CDCl_3$, δ): 2.26 (6H,s,N-Me_2), 3.79 (2H,s,CH_2-N), 4.84 (2H,s,CH_2-OH), 6.93 (1H,d.d,J=7 and 1.5 Hz), 7.08 (1H,d.d,J=8 and 7 Hz), 7.08 (1H,s), 7.30 (1H,d.d,J=8 and 1.5 Hz), Mass m/e: 204 (M^+)] under usual Mannich reaction conditions (Me_2NH, HCHO, and AcOH) in 79% yield. Treatment of 19 with KCN in refluxing DMF afforded 3-cyanomethyl-4-hydroxymethylindole in 72% yield, which was identical in every respect with the compound 17 derived from 13.

Since the introduction of various carbon side chains into the C_1 position of isoquinoline is possible,[8] our approach seems to provide a useful and convenient method for the preparation of 3,4-disubstituted indoles. We are currently investigating to convert these indoles to Ergot alkaloids.

References and Notes

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(Received August 26, 1978)