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Technical Notes

Integration of a Highly Selective Demethylation of a Quaternized Ergoline into a One-Pot Synthesis of Pergolide

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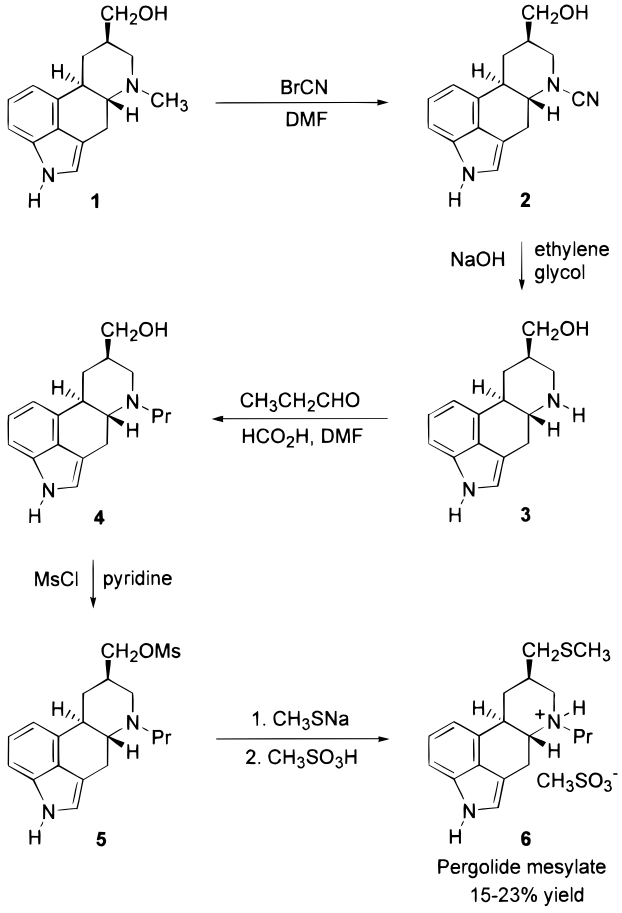
Abstract:

We have developed a high-yielding one-pot synthesis of pergolide (10) from dihydrolysergol (1), which was isolated as pergolide mesylate (6, Permax), a semisynthetic ergot alkaloid marketed for the adjunctive treatment of Parkinson's disease. The process involved the formation of quaternized amine intermediates, followed by a highly selective demethylation and thioether formation via thiomethoxide ion. A novel tandem chromatography procedure was used to remove closely related byproducts, which included an unexpected and unusual thiomethyl ether homologue of pergolide.

Pergolide mesylate (Permax, **6**) is an extremely potent dopamine receptor agonist marketed for the adjunctive treatment of the symptoms of Parkinson's disease. Variations of a multistep synthesis of pergolide from dihydrolysergol (dihydroelymoclavine, **1**) have been described previously.[1−3] Scheme 1 depicts the most developed version of this process. Dihydrolysergol, the starting material, is available in commercial quantities, but can also be accessed via reduction of elymoclavine with Raney nickel or from the reduction of dihydrolysergic acid. In manufacturing practice, campaigns to produce **6** by this process averaged 4−6 months and resulted in variable overall product yields of 15−23%. This was largely the result of having to isolate and evaluate the purity of each intermediate, including concomitant recrystallizations, prior to proceeding to the next step. Further, the need to handle dried solids on at least 18 occasions per campaign created potential exposure hazards from the dust of these potent compounds. Consequently, a shorter, more streamlined process became an important objective.

A communication by Hutchins and Dux[4] proved to be the key that led to the development of a much more satisfactory process. Their paper described an exceptionally selective but very specific procedure for the S_N2 demethylation of quaternary ammonium salts by lithium thiopropoxide in HMPA. Previous methods lacked the exquisite sensitivity, very high yields, and generally mild conditions of this lithium thiopropoxide/HMPA procedure. The best of the earlier procedures used thiophenoxide anion in 2-butanone to effect a ratio of demethylation to deethylation of only 3.5:1,[5] whereas Hutchins and Dux reported selectivities of 23−100:1. As the synthesis of pergolide already used thiomethoxide anion, we thought that it might prove to be a good surrogate nucleophile for thiopropoxide. Further, we

Scheme 1



(1) Kornfeld, E. C.; Bach, N. J. U.S. Patent 4 166 182, 1979; *Chem. Abstr.* **1980,** *92,* 181450q.
(2) Misner, J. W. U. S. Patent 4 782 152, 1988; *Chem. Abstr.* **1987,** *107,* 40177x.
(3) Sprankle, D. J.; Jensen, E. C. In *Analytical Profiles of Drug Substances*; Brittain, H. G., Ed.; Academic: New York, 1992; Vol. 21, pp 375−413.
(4) Hutchins, R. O.; Dux, F. J. *J. Org. Chem.* **1973**, *38*, 1961−2.

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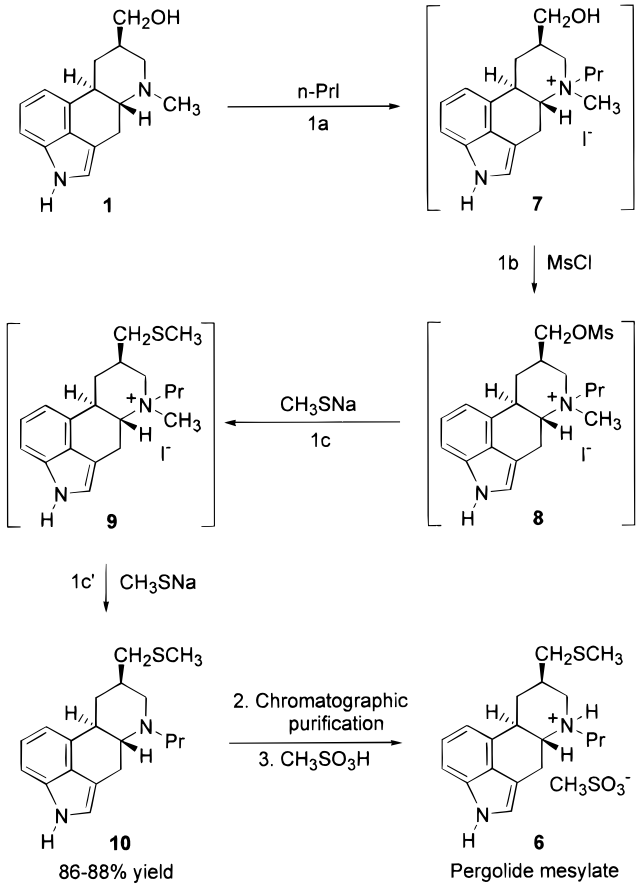
Scheme 2



rationalized that if **1** could be quantitatively quaternized to the propyl ammonium salt, it might then be mesylated, followed by simultaneous thiomethyl ether formation and selective demethylation, thereby rendering pergolide in a one-pot scheme.[6]

We found that complete quaternization of **1** to **7** (Scheme 2) was achievable by careful optimization of reaction conditions. The use of HMPA as a solvent was avoided from the outset due to its toxic properties. Quaternization in commonly used solvents, such as chloroform or DMF, typically achieved ≤75% conversion, even in the presence of an acid-scavenging base such as Na_2CO_3. Ultimately, only three solvents facilitated complete conversion to **7** as determined by HPLC: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMEU), and 1-methyl-2-pyrrolidinone (NMP). The combination of one of these solvents with Na_2CO_3 (or $NaHCO_3$) and **1** at 75−80 °C produced **7** in quantitative yield.

Intermediate **7** and all other quaternized ergolines that we have examined had physical properties that were very different from those of their parent compounds. These quaternized compounds were not hydrophobic and were only isolable via chromatography as amorphous solids. Without the ability to readily isolate these intermediates, the completion of a one-pot synthesis became not only desirable but essential.

The efficient mesylation of **7** to **8** required the use of pyridine (or related bases picoline or lutidine) as both base and primary solvent. In practice, the conversion approached but never reached completion, with 98% being typical for this transformation. A ratio of 5:1 pyridine/NMP and 2.5 equiv of methanesulfonyl chloride (MsCl) were required. Larger excesses of MsCl did not produce a better conversion. Unlike **7**, intermediate **8** proved to be somewhat unstable in solution, especially at temperatures >15 °C, so it was reacted with thiomethoxide anion in step 1c/c′ promptly after being made.

When an excess of sodium thiomethoxide was combined with a solution of **8** at 0 °C, rapid conversion to the quaternized thioether **9** occurred. Under the reaction conditions, the formation of **9** was accompanied by the simultaneous but slower demethylation of **9** to crude pergolide **10**. Since the latter would precipitate from solution on forming if water were present, the sodium thiomethoxide reagent was most advantageously made from a combination of methanethiol and aqueous NaOH.[7] Also, in contrast to the solvent and reagent restrictions of Hutchins and Dux,[4] the use of lithium, potassium, or sodium thiomethoxide provided equivalent results in step 1c/c′, and the various ratios and types of the solvents carried through the one-pot process had no effect on the outcome. The reaction was accelerated to completion by heating to 80 °C. When filtered and dried, the mass of **10** was typically 90−95% of the theoretical amount based on **1**. With a purity of 94−95% by HPLC, an overall yield of 86−88% for the one-pot synthesis was achieved.

Three principal byproducts of 1−2% each were detected in **10**. We readily identified impurity **4**, as it is an intermediate in the multistep process. The presence of **4** had been anticipated due to the inability to completely mesylate **7** in step 1b. Likewise, a certain amount of **11** had been expected, depending upon the selectivity of demethylation vs depropylation. The fact that <2% was found showed that the degree of selectivity was similar to that found by Hutchins and Dux.[4] Impurity **11** was independently synthesized via the reaction of sodium thiomethoxide with the mesylate ester of **1**.

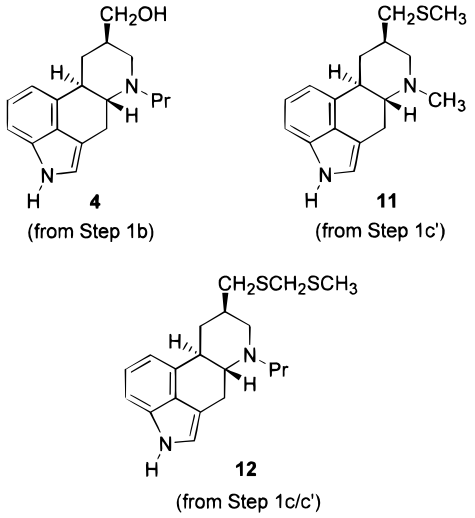
The third byproduct (**12**) was not anticipated. We have been unable to independently synthesize this homologated thiomethyl ether, but it has been isolated and characterized from a chromatography fraction. Mass spectrometry and HPLC analyses suggest that there is a much smaller amount of a double homologue also produced. The mechanism of the formation of **12** is not known, but we discovered that the use of less than 8 equiv of sodium thiomethoxide in the one-pot process would lead to a modest increase in its formation.

In the multistep synthesis of pergolide, crystallization of **10** as the mesylate salt (**6**) was extremely effective in removing impurities. In our new synthesis, closely related byproducts cocrystallized, making purification by this method

(5) Shamma, M.; Deno, N. C.; Remar, J. F. *Tetrahedron Lett.* **1966**, 1375−9.
(6) (a) Misner, J. W. U.S. Patent 5 463 060; 1995; *Chem. Abstr.* **1994**, *120*, 270946v. (b) Misner, J. W. Permax: A Level 3 Containment Challenge. Presented at the Midwest Pharmaceutical Process Chemistry Consortium, Abbott Park, IL, October 1994. (c) Misner, J. W. Genesis and Development of a One-Pot Synthesis of Pergolide. Presented as Paper 118 at the Technical Achievements in Organic Chemistry symposium at the 210th National Meeting of the American Chemical Society, Chicago, IL, August 1995.

(7) An excess of methanethiol must be used to ensure complete consumption of sodium hydroxide. Commercially available sodium thiomethoxide has not produced equivalent results (unless first treated with excess methanethiol).

Principal Byproducts



impractical. Since pergolide is such a potent pharmaceutical agent, its production volume on an industrial scale is modest. This modest volume allows chromatography to be a viable purification alternative. In practice, silica gel chromatography effectively separated impurities **4** and **11**, but not **12**.[8] However, the latter was strongly adsorbed on HP20ss resin, so a tandem chromatographic method was developed. Crude **10**, in the form of either dried solid or damp cake, was dissolved in a mobile phase of 17% acetonitrile and pH 3 phosphate buffer and eluted through a radial column packed with HP20ss resin to effect the removal of **12**. The acetonitrile was then removed by distillation, followed by a pH adjustment to 9. Extraction of the pergolide mixture with chloroform, followed by elution through a Prochrom column packed with high-performance silica gel (chloroform, methanol, and methanesulfonic acid as mobile phase), removed the remaining impurities. Pergolide mesylate was then crystallized from methanol/2-propanol in an overall yield of 71% from **1**.

The original objectives have been fully realized. One-pot chemistry is the ultimate in streamlining, and in this case, the only dried solids that must be handled, including handing during the chromatographies, are **1** and pergolide mesylate. The overall yield has been dramatically increased, and chemical processing time has been cut from months to less than 2 days. Finally, while the quaternization/demethylation methodology has been developed only for this process, the demonstrated performance suggests wide applicability. In particular, the two-step procedure of Madyastha and coworkers[9] for replacing *N*-methyl groups with different alkyl substituents can probably be shortened to a one-pot operation in many cases.

Experimental Section

General. Dihydrolysergol supplied from Gedeon Richter, Kawaken Fine Chemicals, Boehringer Ingelheim, United Pharmaceutical Works, and Indena gave comparable results in this process. All other chemicals and reagents are commercially available and were used as received. In-process analytical HPLC for step 1a was done with a 25 cm YMC basic column and a mobile phase of 25% acetonitrile in 0.1 M phosphate buffer (2.0 mL/min, 266 nm). The ratio of acetonitrile in the mobile phase was increased to 35% for step 1b and to 40% for step 1c/c′. Elemental analyses (all samples were block dried at 120 °C) were performed by the Microanalytical Laboratory of the Lilly Research Laboratories.

Step 1a: (8*β*)-8-(Hydroxymethyl)-6-methyl-6-propylergolin-6-ium Iodide (7). A mixture of **1** (76.9 g, 0.30 mol), 1-iodopropane (63.8 g, 0.38 mol), sodium bicarbonate (2.5 g, 0.03 mol), and NMP (154 mL) was heated to 75 °C under a nitrogen atmosphere, becoming a dark solution within 0.5 h. Heating was continued until **1** (t_R = 3.3 min) could no longer be detected by HPLC (3−5 h). This solution of **7** was then used directly in step 1b. To obtain a sample free of solvent and reagents for characterization, a solution of 0.04 mol of **7** was chromatographed on neutral alumina (activity 1, 80−200 mesh), with an eluent of dichloromethane/methanol (9:1). The "center cut" as determined by HPLC (t_R = 4.0 min) was vacuum evaporated to 7.7 g of a light brown foam. This was dissolved in methanol (50 mL) and stirred with decolorizing carbon (Calgon ADP, 1.0 g). Following filtration to remove the carbon, the filtrate was vacuum evaporated to give **7** (6.8 g, 39.7%) as a beige foam: mp 155−200 °C; HPLC 99.15%; MS (FD) *m/z* 300 $(MH - I)^+$. Anal. Calcd for $C_{19}H_{27}IN_2O$: C, 53.53; H, 6.38; I, 29.77; N, 6.57. Found: C, 53.79; H, 6.39; I, 29.58; N, 6.49.

Step 1b: (8*β*)-8-(Hydroxymethyl)-6-methyl-6-propylergolin-6-ium Iodide, Methanesulfonate (Ester) (8). The solution of **7** from step 1a was diluted with pyridine (770 mL, 5 volumes vs NMP) and chilled to −10 °C under a nitrogen atmosphere. Methanesulfonyl chloride (85.9 g, 0.75 mol) was added dropwise at such a rate as to maintain the temperature <0 °C (50 min). The conversion was determined by HPLC to have reached its maximum (98% **3**, t_R = 4.9 min) in <0.5 h. This mixture was then taken directly to step 1c/c′. For characterization, a solution of 13.5 mmol of **8** was chromatographed on neutral alumina (activity 1, 80−200 mesh) with an eluent of dichloromethane/methanol (20:1) to give **8** (5.2 g, 76.6%) as a light orange foam: mp 155−65 °C. Anal. Calcd for $C_{20}H_{29}IN_2O_3S$: C, 47.62; H, 5.80; I, 25.16; N, 5.55; S, 6.36. Found: C, 47.88; H, 5.81; I, 25.32; N, 5.73; S, 6.33.

Step 1c/c′: (8*β*)-8-[(Methylthio)methyl]-6-propylergoline (Pergolide, 10). A mixture of sodium thiomethoxide was made by adding methanethiol (136 mL, 117.9 g, 2.45 mol) subsurface to NMP (750 mL) at −10 °C, followed by the addition of 50% aqueous sodium hydroxide solution (192.0 g, 125.5 mL, 2.40 mol) at such a rate that the temperature did not exceed 0 °C. The chilled mixture of **8** from step 1b and the sodium thiomethoxide suspension were combined. The mixture was then heated to 80 °C until **8** (t_R = 4.7 min) and **9** (t_R = 8.4/8.7 min) were no longer detected by HPLC (2 h). Complete precipitation of the crude **10** was ensured by the addition of water (1.25 L), which also facilitated ease of stirring. The slurry was chilled to 0

(8) Kennedy, J. H. Silica Gel Column Purification of Pergolide. Presented at the Midwest Pharmaceutical Process Chemistry Consortium, Indianapolis, IN, October 1993.
(9) Madyastha, K. M.; Manoharan, T. S.; Singh, B. B.; Bhatnagar, S. P.; Weiss, U. *Synthesis* **1983**, 809−12.

°C, filtered, and washed with water. When the materials was dried, the yield of **10** as a white to pale brown solid was 88.2 g (93.5%), with an HPLC t_R of 9.0 min (94%), for an overall yield of 87.8%.

(8*β*)-8-[(Methylthio)methyl]-6-propylergoline Monomethanesulfonate (Pergolide Mesylate, Permax, 6). Following chromatography and crystallization of **10** as the methanesulfonate salt from methanol/2-propanol, **6** (87.5 g, 71% from **1**) was obtained as an off-white crystalline solid, identical in all respects with authentic material.

(8*β*)-8-[(Methylthio)methyl]-6-methylergoline (11). A suspension of sodium thiomethoxide was prepared from a −10 °C solution of methanethiol (4.2 mL, 3.6 g, 75 mmol) in DMF (90 mL) and sodium methoxide (3.9 g, 72 mmol). To this was added the methanesulfonate ester of **1**[10] (9.6 g, 28.8 mmol), followed by heating to 80 °C for 1 h. The product was precipitated by the addition of water (90 mL), cooled to 10 °C, filtered, and dried to give crude **11** (6.6 g, 80%). This was dissolved in refluxing methanol (120 mL) and stirred with decolorizing carbon (2 g, Calgon ADP). The carbon was removed by filtration, leaving a clear yellow filtrate. Upon reheating to reflux, methanesulfonic acid (2.9 g, 30 mmol) was added. Methanol was distilled until crystals were observed. After the mixture was slowly cooled to 5 °C, the crystalline solid was filtered and dried to give **11** as its methanesulfonate salt (7.0 g, 63.5%), an off-white solid with a light purple tint: mp 273−5 °C; HPLC t_R = 5.6 min (99.3%); MS (FAB) *m/z* 287 $(MH - CH_3SO_3)^+$. Anal. Calcd for $C_{18}H_{26}N_2O_3S_2$: C, 56.52; H, 6.85; N, 7.32; S, 16.76. Found: C, 56.76; H, 7.09; N, 7.32; S, 17.02.

(8*β*)-8-{{[(Methylthio)methyl]thio}methyl}-6-propylergoline (12). Impurity **12** was eluted from HP20ss resin by increasing acetonitrile from 17% to 60% of the mobile phase and then distilling off the acetonitrile, causing it to precipitate. After filtration and drying in vacuo at 50 °C, **12** was obtained as an off-white solid: mp 205−6 °C; HPLC t_R = 12.6 min (98.6%); ^{13}C NMR (300 MHz, pyridine-d_5)[11] δ 134.7, 134.1, 127.4, 123.1, 119.0, 113.1, 112.0, 109.3, 64.8, 59.4, 55.5, 41.7, 38.6, 36.1, 35.9, 35.0, 27.7, 18.5, 14.5, 12.1.; HRMS (EI) calcd for $C_{20}H_{28}N_2S_2$ 360.1694, found 360.1693.

(10) The methanesulfonate ester of **1** was made by the treatment of a solution of **1** in pyridine with methanesulfonyl chloride. Precipitation was effected by dilution of the solution with water and adjustment of the pH to >9 with ammonium hydroxide.

(11) The NMR spectra of **12** and **10** are virtually identical throughout the ring systems and N-6 propyl side chain, leaving the thiomethyl ether at C-17 as the only point of attachment for a new methylene moiety [^{1}H δ 3.86 (s, 2H) and ^{13}C δ 36.1]. While an acceptable elemental analysis has not been obtained, the parent ion and fragments seen by mass spectrometry clearly support the assigned structure.

Acknowledgment

Helpful discussions with Mary K. Peters and Leland O. Weigel, and also Prof. David A. Evans, Harvard University, are gratefully acknowledged. Insightful interpretation of ^{1}H and ^{13}C NMR spectra by Jonathan W. Paschal and Thomas Elzey in conjunction with mass spectral evidence generated by John Occolowitz and Gary G. Cooke proved invaluable in the characterization of byproduct **12**. Patrick J. Baker's expertise with HP20ss resin was most helpful in the development of the chromatographic purification.

Supporting Information Available

NMR (^{1}H and ^{13}C) and mass spectra for compounds **4**, **10**, and **12** (9 pages). See any current masthead page for ordering and Internet access instructions.

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