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Ergot Alkaloids. Synthesis of 6-Alkyl-8-ergolenes and 6-Methyl-8-aminoergolines as Potential Prolactin Inhibitors

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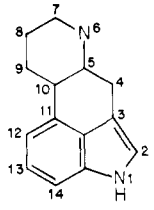
The synthesis of several N-6 derivatives of elymoclavine (**3**) and potential alkylating derivatives of 6-methyl-8-aminoergolines (**12**) is described. These compounds were screened for prolactin-inhibiting ability and 6-propyl-8-hydroxymethyl-8-ergolene (**9**) was found to be as active as the most potent prolactin inhibitors reported to date. The total synthesis of racemic methyl dihydrolysergate I (**23**), having a trans C,D ring fusion, from the tricyclic ketone **18** is also described.

A variety of compounds containing the ergoline (**1**) ring system has been shown to be effective inhibitors of prolactin release.[1-7] Two compounds developed by Semonsky and co-workers,[8,9] VUFB 6605 (**2a**) and VUFB 6683 (Deprenon, **2b**), are currently undergoing clinical trials in Europe. Compound **2c** which was developed by the group of Kornfeld and Clemens at Eli Lilly and Company is also undergoing clinical evaluation as a prolactin inhibitor and an anti-Parkinson agent.[4]



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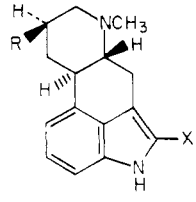


2a, X = H; R = CH_2CN; VUFB 6605
b, X = H; R = $CONH_2$; VUFB 6683
c, X = Cl; R = CH_2CN; lergotrile

Based on the work of several groups, a number of conclusions can be drawn about the relationship between the ergoline structure (**1**) and prolactin inhibitory activity.[1-7] Although Barfknecht and co-workers[10] have reported that an aminotetralin derivative exhibits prolactin inhibition, it seems that in order to produce significant inhibition the intact ergoline skeleton (**1**) is necessary. Reduction of the double bond at the 2,3 position to the corresponding indoline derivative decreases activity. Compounds with an 8,9 double bond are generally more active than the corresponding 9,10 isomers. However, several compounds in which the D ring is completely saturated are quite potent prolactin inhibitors. The ergoline nucleus (**1**) can accommodate substituents at the 1, 6, and 8 positions without a significant decrease in activity, but substitution at positions 7 or 9 is not tolerated.

Previously, elymoclavine (**3**) and several C-17 derivatives were shown to be potent prolactin inhibitors.[2,6] Our present investigation involved preparation of N-6 derivatives of elymoclavine in order to determine (a) if a basic nitrogen at the 6 position was necessary for activity and (b) if dopaminergic activity could be increased by changes in the alkyl substituent. Dopaminergic activity has been demonstrated for several ergoline compounds[11,12] and it appears that these compounds inhibit prolactin release by a dopaminergic mechanism.[13] The potency of dopaminergic agonists has been shown in some cases to depend on the length of the *N*-alkyl substituent.[14] Furthermore, in activation of reserpinized mice, an effect which is used as a criterion for dopaminergic activity, *n*-ethyl- and *n*-propylapomorphine were reported to be twice as potent as apomorphine in reversing reserpine depression.[15] Thus, introduction of the proper N-6 substituent could result in a compound with extremely potent prolactin inhibitory activity.

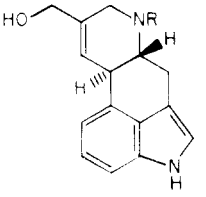
The second phase of our investigation was concerned with preparation of potential alkylating derivatives of 6-methyl-8-aminoergoline (**12**). Our choice of alkylating derivatives was based on the fact that compounds in the 8-aminoergoline series are generally good prolactin inhibitors.[8,9] The compounds designed contain alkylating groups ($NHCOCH_2Cl$, $NHCOCH_2Br$, NHCOCH=CHCOOH, and maleimide) that are capable of reacting with biological nucleophiles (SH, NH_2, ^-OH, or COO^-). Proper positioning of the alkylating group to a nucleophilic species at or near the active site of an enzyme or protein can result in a rapid neighboring group reaction with covalent bond formation.[16]

If an ergoline could first reversibly bind at the prolactin-inhibiting factor[1] (PIF) receptor, followed by alkylation of an appropriate nucleophile at or near the receptor, then covalent bond formation could result in irreversible prolactin inhibition. An ergoline capable of irreversibly inhibiting prolactin release could be useful in the treatment of prolactin-dependent tumors.

Previously we reported the total synthesis[2] of DL-methyl dihydroisolysergate II (**24**). This paper reports the total synthesis of DL-methyl dihydrolysergate I (**23**), which serves as a precursor for entry into the 8-aminoergoline series.

Chemistry. Preparation of N-6 ergolenes (Table I) utilized elymoclavine (**3**), which is available from submerged cultures of *Claviceps* strain SD-58,[17] as the starting material. Reaction of **3** with cyanogen bromide gave **4** which was converted via a dissolving metal reduction[18] to 8-hydroxymethyl-8-ergolene (**5**). Selective acylation of **5** was carried out using acetic and propionic anhydrides in methanol to give the 6-acetyl and 6-propionyl derivatives

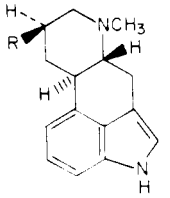
Table I. N-6-Substituted 8-Ergolenes[a]



Compd no.	R	Prolactin control value	Prolactin value after treatment	Inhibn, %	Level of significance[b]	Inhibn of ergoconine (or lergotrile), %
3	CH_3	32.54 ± 0.9	9.39 ± 0.3	71	$p < 0.001$	75
4	CN	29.1 ± 3.4	21.8 ± 1.8	25	NS	67
5	H	29.1 ± 3.4	12.1 ± 1.0	58	0.01	67
6	$COCH_3$	30.0 ± 4.4	46.9 ± 6.4	Stim	0.05	
7	$COCH_2CH_3$	52.9 ± 6.5	50.3 ± 6.0		NS	(77)
8	CH_2CH_3	52.9 ± 6.5	22.1 ± 3.3	63	<0.001	(77)
9	$CH_2CH_2CH_3$	52.9 ± 6.5	14.9 ± 1.4	72	<0.001	(77)
10	$CH_2CO_2C_2H_5$	52.9 ± 6.5	46.5 ± 4.3	14	NS	(77)
11	$CH_2C_6H_5$	24.6 ± 1.7	31.0 ± 4.1		NS	(60)

[a] All compounds were tested at 10 μg per animal. Values listed are means ± standard errors. [b] The level of significance was obtained according to Student's *t* test.

Table II. 8-Aminoergolines



Compd no.	R	Prolactin control value	Prolactin after treatment	Inhibn, %	Level of significance
12	NH_2	26.5 ± 3.6	11.3 ± 2.1	57	$p < 0.01$
13	$NHCOCH_3$	27.0 ± 3.3	27.0 ± 3.4		NS
14	$NHCOCH_2Cl$	27.3 ± 4.0	29.6 ± 3.4		NS
14a	$NHCOCH_2Cl$ (HCl salt)	27.3 ± 4.0	39.0 ± 3.4	Stim	$p < 0.05$
15	$NHCOCH_2Br$	27.3 ± 4.0	41.1 ± 3.4	Stim	$p < 0.05$
16	$NHCOC(H)=C(H)COOH$	27.0 ± 3.3	32.9 ± 4.3		NS
17	$NCOCH=CHCO$	27.3 ± 4.0	29.2 ± 3.6		NS

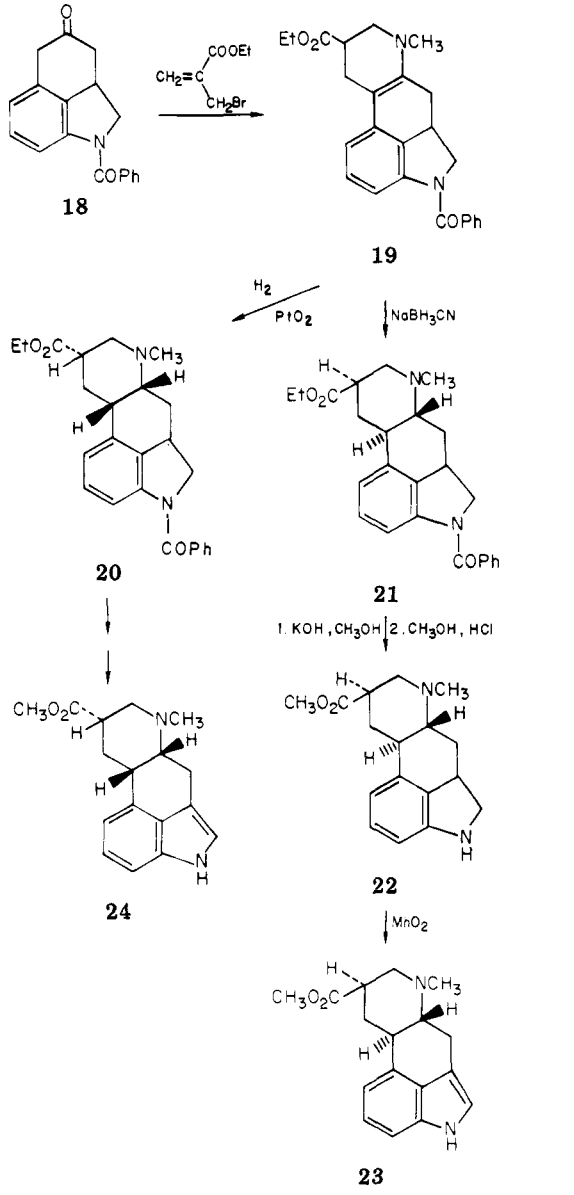
6 and 7, respectively. Reduction of the amides 6 and 7 with sodium bis(2-methoxyethoxy)aluminum hydride produced the 6-ethyl- and 6-propylergolenes 8 and 9 without difficulty. The 6-ethoxycarbonylmethyl derivative 10 was prepared by treatment of 5 with ethyl bromoacetate. The 6-benzylergolene 11 was prepared by reaction of 8-hydroxymethyl-8-ergolene (5) with benzyl bromide in dimethylformamide using sodium bicarbonate as the base.

In an attempt to prepare potential irreversible prolactin inhibitors, several derivatives (Table II) of 6-methyl-8-aminoergoline (12) incorporating alkylating functions were synthesized. The amine 12, which served as the precursor, was prepared by a series of conversions starting from methyl dihydrolysergate I. Esterification of D-dihydrolysergic acid I gave the methyl ester which was smoothly converted to the hydrazide.[19] Diazotization of the hydrazide followed by treatment with dilute HCl gave the desired amine 12.[20] The 8-acetamido derivative 13, a nonalkylating compound, was formed in excellent yield by reaction of 6-methyl-8-aminoergoline (12) with acetic anhydride. Reaction of 12 with either chloroacetic or bromoacetic anhydride produced the corresponding α-haloamides 14 and 15. Two other potential alkylating derivatives were prepared by treating the amine 12 with maleic anhydride to yield the maleamic acid 16 which was dehydrated with anhydrous sodium acetate in acetic anhydride following Cava's procedure[21] to yield the maleimide 17.

The total synthesis of DL-methyl dihydrolysergate I (Scheme I) closely follows the route previously reported for the total synthesis[2] of DL-methyl dihydroisolysergate II (24). Reaction of the tricyclic ketone 18[22] with methylamine and ethyl α-(bromomethyl)acrylate[2,24] gave the tetracyclic ergoline ester 19 as reported earlier. Catalytic reduction of the enamine ester 19 with hydrogen over platinum had afforded the reduction product 20 having the cis–syn stereochemistry.[2]

Reduction of the enamine ester 19 with sodium cyanoborohydride gave as the predominant reduction product 21 with the trans–anti stereochemistry. TLC of this trans–anti product clearly distinguished it from the cis–syn product 20 previously obtained by catalytic reduction. The *N*-benzoyl group of compound 21 was readily removed in base to yield, after reesterification, methyl 2,3,9,10-tetrahydrolysergate I (22). The indoline ester 22 was oxidized with activated manganese dioxide to give the desired racemic methyl dihydrolysergate I (23). Compound 23 gave an identical IR spectrum with D-methyl dihydrolysergate I obtained by esterification of D-dihydrolysergic acid I. Further evidence of the trans–anti

Scheme I



D-ring stereochemistry was provided by cochromatography of **23** with authentic D-methyl dihydrolysergate I.

Biological Activity. The compounds listed in Tables I and II were evaluated for prolactin-inhibiting activity in the rat. The results of these tests are listed in the tables. In most runs ergocornine or lergotrile was included as a reference point and these values are given.

Examination of the data in Table I establishes that a basic nitrogen at the 6 position is necessary for activity since those derivatives, **4**, **6**, and **7**, which are nonbasic are inactive. Activity is increased by introduction of an alkyl group at N-6, since compounds **3**, **8**, and **9** are more potent than the *N*-nor compound **5**. Compounds **3**, **8**, and **9** appear to be equally potent; however, activity is abolished upon introduction of a benzyl group at the 6 position. This appears to be in accord with the findings of Neumeyer and co-workers[25] in evaluating dopaminergic activity of a series of *N*-noraporphines. Further refinement of the relative potency of **3**, **8**, and **9** would require testing at even lower doses.

In the 8-aminoergoline series (Table II) only the parent compound **12** showed any activity. Two alkylating derivatives **14a** and **15** elevate prolactin levels, a property shared by most antipsychotic agents.[26] Apparently, in the 8β-aminoergoline series bulky substituents sterically hinder binding at the PIF receptor. This seems to be in contrast to derivatives in the 8α-aminoergoline series, since several derivatives have good prolactin inhibitory activity.[27]

Experimental Section

General Procedures. UV spectra were recorded on a Perkin-Elmer Coleman 124 spectrophotometer and are reported in wavelength (nm) followed by molar extinction coefficient (ε). IR spectra were recorded as KBr pellets with a Beckman IR-33 spectrophotometer. Mass spectra (MS) were obtained on a Hitachi RMU-6 low-resolution or a CEC 21-110 high-resolution mass spectrometer; *m/e* values are reported with relative intensity. NMR spectra (60 or 100 MHz) were recorded in $CDCl_3$ unless otherwise specified with either a Varian Associates EM-360 or a JEOL-PFT-100 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) as the internal standard. Analytical data were obtained from the microanalysis laboratory, Department of Chemistry, Purdue University.

Determination of Prolactin-Inhibiting Ability. Adult male rats of the Sprague–Dawley strain (Harland Industries, Cumberland, Ind.) weighing about 200 g were used. All rats were housed in an air-conditioned room with controlled lighting (lights on 6 a.m. to 8 p.m.) and fed Purina lab chow and water ad libitum.

Every male rat received an intraperitoneal injection of 2.0 mg of reserpine in aqueous suspension 18 h before administration of the ergot derivatives. The purpose of the reserpine was to keep prolactin levels uniformly elevated.[2] All compounds to be tested were dissolved in 10% EtOH at a concentration of 10 μg/mL. The derivatives were injected intraperitoneally at a standard dose of 50 μg/kg. Each compound was administered to a group of ten rats, and a control group of ten intact males received an equivalent amount of 10% EtOH. One hour after treatment all rats were killed by decapitation, and 150-μL aliquots of serum were assayed for prolactin by radioimmunoassay using the NIAMD kit. Results were expressed as nanograms of NIAMD-prolactin-PR-1 per milliliter of serum. The results were evaluated statistically using the Student's *t* test.

6-Cyano-8-hydroxymethyl-8-ergolene (4). Compound **4** was prepared from elymoclavine (**3**) as described by Fehr in 70% yield: mp 239–241 °C (lit.[18] mp 240–241 °C).

8-Hydroxymethyl-8-ergolene (5). Compound **5** was prepared from **4** as described by Fehr in 83% yield: mp 148–150 °C (lit.[18] 151 °C).

6-Acetyl-8-hydroxymethyl-8-ergolene (6). 8-Hydroxymethyl-8-ergolene (157 mg, 0.655 mmol) was stirred with a premixed solution of Ac_2O (3 mL, 32.8 mmol) and CH_3OH (3 mL) under N_2 for 2 h. The reaction mixture was poured into 10% Na_2CO_3 solution, stirred for 1 h, and extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Recrystallization of the residue from CH_3OH gave 103 mg of **6**. Preparative layer chromatography of the mother liquor on a 20 × 20 cm × 2.0 mm Brinkmann silica gel plate, developing with $CHCl_3$–CH_3OH (9:1), afforded an additional 50 mg of **6** for a combined 77% yield: mp 221 °C dec; IR (KBr) 1610 cm^{-1} (C=O, amide); UV (CH_3OH) 293 (5570), 282 (6500), 277 (6150), and 221 nm (30400); NMR (Me_2SO-d_6) δ 2.11 (s, 3 H, $COCH_3$), 3.0–5.2 (m, 9 H), 6.48 (s, 1 H, vinyl), 6.8–7.3 (m, 4 H, Ar), and 10.77 (s, 1 H, NH); MS (low resolution) *m/e* 282 (M^+, 34), 239 (18), 223 (20), 205 (34), 193 (24), 192 (100), and 154 (33); MS (high resolution) calculated for $C_{17}H_{18}N_2O_2$, 282.137, found, 282.134. Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

6-Propionyl-8-hydroxymethyl-8-ergolene (7). 8-Hydroxymethyl-8-ergolene (102 mg, 0.425 mmol) was stirred with a premixed solution of propionic anhydride (2 mL, 15.5 mmol) and CH_3OH (2 mL) under argon for 2 h, then poured into 10% Na_2CO_3 solution (100 mL), and stirred vigorously for 1 h. The mixture was extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a solid residue. Recrystallization of the residue from MeOH–EtOAc–petroleum ether yielded 79 mg (65%) of **7**: mp 202–203 °C dec; IR (KBr) 1610 cm^{-1} (C=O, amide); UV (MeOH) 292 (5360), 282 (6280), 276 (5950), and 220 nm (28500); NMR (Me_2SO-d_6) δ 0.92 (t, J = 7 Hz, 3 H, CH_3), 2.41 (q, J = 7 Hz, 2 H, CH_2), 3.0–5.2 (m, 9 H), 6.50 (s, 1 H, vinyl),

6.8–7.3 (m, 4 H, Ar), and 10.73 (s, 1 H, NH); MS (low resolution) m/e 296 (M^+, 0.4), 239 (2), 219 (13), 205 (13), 192 (29), 165 (20), 154 (33) 127 (26), and 57 (100); MS (high resolution) calculated for $C_{18}H_{20}N_2O_2$, 296.154, found, 296.153. Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

6-Ethoxycarbonylmethyl-8-hydroxymethyl-8-ergolene (10). 8-Hydroxymethyl-8-ergolene (180 mg, 0.75 mol) was stirred in absolute EtOH (25 mL) with Et_3N (0.5 mL, 3.6 mmol) and $BrCH_2CO_2Et$ (0.5 mL, 4.5 mmol) was added via syringe under N_2. After stirring for 20 h under N_2, the reaction was poured into 1 N HCl solution (150 mL) and washed with $CHCl_3$ which was discarded. The aqueous layer was then made basic with Na_2CO_3 and extracted with EtOAc (3 × 75 mL). The combined EtOAc extracts were dried (Na_2SO_4) and evaporated to afford a solid. Recrystallization of the residue from C_6H_6 gave in several crops 187 mg (77%) of **10**: mp 132.5–133.5 °C; IR (KBr) 1705 cm^{-1} (C=O, ester); UV (MeOH) 292 (6000), 282 (7070), 276 (6680), and 224 nm (28 500); NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H, CH_3), 1.9–4.15 (m, 11 H), 4.20 (d, J = 7 Hz, 2 H, CH_2), 6.50 (s, 1 H, vinyl), 6.75–7.50 (m, 4 H, Ar), and 8.07 (s, 1 H, NH); MS m/e 326 (M^+, 67), 325 (83), 253 (86), 167 (38), 154 (45), and 153 (100). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

6-Ethyl-8-hydroxymethyl-8-ergolene (8). 6-Acetyl-8-hydroxymethyl-8-ergolene (126 mg, 0.45 mmol) was stirred in THF (35 mL) under argon and $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, 0.6 mL, 2.1 mmol) was injected via syringe. After stirring for 2 h the mixture was poured into H_2O (150 mL) and extracted with EtOAc (4 × 100 mL). The combined EtOAc extract was dried (Na_2SO_4) and concentrated in vacuo. The residual oil was recrystallized from MeOH–$CHCl_3$–petroleum ether to give 65 mg (58%) of **8**: mp 209–211 °C dec; IR (KBr) 3380 (OH), 2790, 1595, 1435, 1365, 1005, and 730 cm^{-1}; UV (MeOH) 292 (5690), 282 (6730), 276 (6380), and 224 nm (26 900); NMR (100 MHz, $CDCl_3$) δ 1.24 (t, J = 7 Hz, 3 H, CH_3), 2.33 (s, 1 H, OH), 2.6–4.1 (m, 8 H), 4.18 (s, 2 H, OCH_2), 6.48 (s, 1 H, vinyl), 6.8–7.4 (m, 4 H, Ar), and 8.04 (s, 1 H, NH); MS m/e 268 (56), 267 (M^+, 100), 237 (13), 167 (9), 154 (11), and 138 (7). Anal. ($C_{17}H_{20}N_2O$) C, H, N.

6-Propyl-8-hydroxymethyl-8-ergolene (9). This compound was prepared from **7** (133 mg, 0.45 mmol) and $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, 1.4 mL, 5.0 mmol) in the same manner as described for the synthesis of **8**. Similar work-up gave a solid. Preparative layer chromatography of this residue on a silica gel plate, developing with EtOAc–MeOH (8:2), gave after recrystallization from C_6H_6 82 mg (65%) of analytically pure **9**: mp 133–135 °C dec; IR (KBr) 3360 cm^{-1} (OH); UV (MeOH) 292 (5480), 282 (6490), 276 (6160), and 224 nm (25 700); NMR ($CDCl_3$) δ 0.92 (t, J = 7 Hz, 3 H, CH_3), 1.1–2.1 (m, 3 H), 2.3–4.0 (m, 8 H), 4.12 (s, 2 H, OCH_2), 6.47 (s, 1 H, vinyl), 6.75–7.50 (m, 8 H, Ar), and 8.00 (s, 1 H, NH); MS m/e 283 (14), 282 (M^+, 73), 281 (100), 251 (11), 239 (8), 167 (10), and 154 (12). Anal. ($C_{18}H_{22}N_2O$) C, H, N.

6-Benzyl-8-hydroxymethyl-8-ergolene (11). 8-Hydroxymethyl-8-ergolene (92 mg, 0.384 mmol) was dissolved in DMF (20 mL) and $NaHCO_3$ (32 mg, 0.384 mmol) was added. To the solution was added $PhCH_2Br$ (72 mg, 0.422 mmol) as a 5% solution in DMF via syringe while the reaction mixture was kept under an N_2 atmosphere. The reaction mixture was stirred for 18 h at room temperature and then heated at 50 °C for 6 h. The solution was cooled, poured into H_2O (150 mL), and extracted with $CHCl_3$ (2 × 50 mL) and EtOAc (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated to give a solid foam. Recrystallization of the solid from $CHCl_3$–hexane gave in two crops 56 mg (43%) of **11**: mp 128–130 °C dec; IR (KBr) 3400 (NH), 3280 cm^{-1} (OH); NMR (100 MHz, $CDCl_3$) δ 2.94–4.17 (m, 8 H), 4.05 (s, 2 H, NCH_2Ph), 6.49 (s, 1 H, vinyl), 6.90–7.43 (m, 9 H, Ar), 7.95 (br s, 1 H, NH); MS m/e 330 (M^+, 54), 299 (7) 239 (15), 208 (14), 91 (100); MS (high resolution) calculated for $C_{22}H_{22}N_2O$, 330.173, found, 330.171.

6-Methyl-8-acetamidoergoline (13). A mixture of 6-methyl-8-aminoergoline (**12**)[19,20] (155 mg, 0.64 mmol) and Ac_2O (73 mg, 0.71 mmol) in THF (15 mL) was refluxed for 1 h and then stirred overnight at room temperature. The reaction mixture was poured into a saturated solution of $NaHCO_3$ (150 mL) and the entire mixture was extracted with $CHCl_3$ (3 × 50 mL) and EtOAc (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated to yield 146 mg (81%) of **13**. Recrystallization from CH_3COCH_3 afforded analytically pure 6-methyl-8-acetamidoergoline: mp 276–278 °C dec; IR (KBr) 1650 cm^{-1} (C=O, amide); NMR (Me_2SO-d_6) δ 0.90–4.07 (m, including s at 1.87, $COCH_3$ and s at 2.37, NCH_3, 18 H), 6.67–7.30 (m, 4 H, Ar), 7.90 (d, 1 H, NHCO); MS m/e 283 (M^+, 51), 224 (100), 209 (15), 168 (32), 154 (66), 127 (23), 43 (30). Anal. ($C_{17}H_{21}N_3O$) C, H, N.

6-Methyl-8-chloroacetamidoergoline (14). 6-Methyl-8-aminoergoline (**12**) (122 mg, 0.51 mmol) was dissolved in dry THF (25 mL) and chloroacetic anhydride (87 mg, 0.51 mmol) was added to the solution. The reaction mixture was refluxed for 2 h and cooled to room temperature, and the solvent was evaporated. Trituration of the oily residue with 5% $NaHCO_3$ solution (50 mL) gave a solid which was collected by filtration and washed repeatedly with small portions of H_2O. Recrystallization of the solid from THF–hexane gave 83 mg (51%) of analytically pure **14**: mp 343–345 °C dec; IR (KBr) 1655 cm^{-1} (C=O, amide); NMR (100 MHz, $CDCl_3$) δ 1.80–4.30 (m, including s at 2.49, NCH_3 and s at 4.10, $COCH_2$, 14 H), 6.44 (d, 1 H, NHCO), 6.91–7.21 (m, 4 H, Ar), 7.94 (br s, 1 H, indole NH); MS (low resolution) m/e 319 (M + 2, 28), 317 (M^+, 82), 225 (100), 92 (71); MS (high resolution) calculated for $C_{17}H_{20}ClN_3O$, 319.127, found, 319.127. Anal. ($C_{17}H_{20}ClN_3O$) C, H, N. The HCl salt **14a** had mp 325 °C dec; IR (KBr) 1675 cm^{-1} (C=O, amide); NMR [100 MHz, D_2O $(CH_3)_3Si(CH_2)_3SO_3Na$ reference] δ 2.8–4.0 (m, 12 H), 4.19 (s, 2 H, $COCH_2$), 6.95–7.37 (m, 5 H).

6-Methyl-8-bromoacetamidoergoline (15). Compound **15** was prepared from **12** (100 mg, 0.41 mmol) and bromoacetic anhydride (107 mg, 0.41 mmol) in the same manner as described for the synthesis of **14**. Similar work-up followed by recrystallization from THF–hexane gave 37 mg (25%) of analytically pure **15**: mp 330 °C dec; IR (KBr) 1650 cm^{-1} (C=O, amide); NMR (100 MHz, $CDCl_3$) δ 2.06–4.36 (m, including s at 2.54, NCH_3 and s at 3.92, $COCH_2$, 14 H), 6.35 (d, 1 H, NHCO), 6.91–7.21 (m, 4 H), 7.94 (br s, 1 H, indole NH). Anal. ($C_{17}H_{20}BrN_3O$) C, H, N.

6-Methyl-8-maleamylergoline (16). 6-Methyl-8-aminoergoline (**12**) (200 mg, 0.829 mmol) was dissolved in $CHCl_3$ (50 mL) and maleic anhydride (81 mg, 0.829 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and then refluxed for 7 h. The mixture was cooled and the solvent evaporated to give a white solid. Recrystallization of the solid from CH_3CN–EtOH gave in two crops 179 mg (65%) of **16**: mp 210–212 °C; IR (KBr) 1710 (C=O, acid) and 1650 cm^{-1} (C=O, amide); NMR (Me_2SO-d_6) δ 1.00–4.24 (m, including s at 2.14, NCH_3, 12 H), 6.37 (s, 2 H, CH=CH), 6.63–7.57 (m, 5 H), 9.74 (d, 1 H, NHCO), 10.37 (s, 1 H, COOH). Anal. ($C_{19}H_{21}N_3O_3$) H, N; C: calcd, 67.22; found, 65.61.

6-Methyl-8-maleimidoergoline (17). A mixture of 6-methyl-8-maleamylergoline (139 mg, 0.41 mmol), anhydrous NaOAc (18 mg, 0.21 mmol), and 0.5 mL of Ac_2O was heated on a steam bath for 1 h. The dark yellow solution was poured into a 5% solution of $NaHCO_3$ (50 mL) and the entire mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extracts were washed with H_2O (25 mL), dried (Na_2SO_4), and filtered, and the solvent was evaporated to give a yellow oil which upon trituration with hexane produced a yellow solid. Preparative layer chromatography on a 20 × 20 cm × 2.0 mm Brinkmann silica gel plate, developing with $CHCl_3$–MeOH (9:1), extracting the desired band with $CHCl_3$–MeOH (8:2), and evaporating the solvents, afforded a light yellow solid. Recrystallization of the solid from C_6H_6–hexane gave 57 mg (43%) of **17**: mp 118–120 °C dec; IR (KBr) 1745 and 1700 cm^{-1} (C=O, imide); NMR (100 MHz, $CDCl_3$) δ 2.18–4.56 (m, including s at 2.50, NCH_3, 12 H) 6.69 (s, 2 H, CH=CH), 6.81–7.36 (m, 4 H, Ar), 7.93 (br s, 1 H, NH); MS (high resolution) calculated for $C_{19}H_{19}N_3O_2$, 321.149, found, 321.146. Anal. ($C_{19}H_{19}N_3O_2$) H; C: calcd, 71.00; found, 70.22.

Ethyl 1-Benzoyl-2,3,9,10-tetrahydrolysergate I (21). 1-Benzoyl-2,3-dihydro-6-methyl-8-carbethoxy-5,10-ergolene (**19**)[2] (428 mg, 1.06 mmol) was dissolved in THF (12 mL) and MeOH (4 mL) under N_2 and a trace of bromocresol green indicator was added. $NaCNBH_3$ (131 mg, 2.08 mmol) was added followed by dropwise addition of 1 N methanolic HCl solution until the yellow color just persisted. After stirring 1 h, the reaction mixture was poured into H_2O and basified with Na_2CO_3. The solution was extracted with $CHCl_3$ (3 × 75 mL). The combined $CHCl_3$ extracts

were washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated to an oil. EtOAc (3 mL) was introduced and stirred briefly. The solution was then allowed to crystallize, affording 237 mg of **21**. Preparative layer chromatography of the mother liquor on a silica gel plate (20 × 20 cm × 2 mm) using EtOAc–NH_4OH (98:2) afforded an additional 118 mg (total 355 mg, 83%): mp 192.5–193.5 °C. TLC of **21** using EtOAc–NH_4OH (98:2) easily distinguished this trans-anti product, R_f 0.27, from the cis-syn product **20**, R_f 0.36, previously obtained by catalytic reduction. Ethyl 1-benzoyl-2,3,9,10-tetrahydrolysergate I exhibited the following spectral characteristics: IR (KBr) 1730 (C=O, ester), 1650 (C=O, amide), 1455, 1385, 1250, 1170, 775, and 695 cm^{-1}; UV (MeOH) 289 (9540) and 264 nm (12280); NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H, CH_3), 2.34 (s, 3 H, NCH_3), 4.20 (q, J = 7 Hz, 2 H, CH_2), 1.5–4.6 (m, 12 H), and 6.65–7.8 (m, 8 H, Ar); MS m/e 405 (19), 404 (M^+, 89), 359 (5), 154 (7), and 105 (100); MS (high resolution) calculated for $C_{25}H_{28}N_2O_3$, 404.210, found, 404.211. Anal. ($C_{25}H_{28}N_2O_3$) C, H, N.

Methyl 2,3,9,10-Tetrahydrolysergate I (22). Ethyl 1-benzoyl-2,3,9,10-tetrahydrolysergate I (201 mg, 0.496 mmol) was refluxed under N_2 with KOH (2.05 g, 36.6 mmol) in H_2O (12 mL) and MeOH (12 mL) for 24 h. The reaction mixture was carefully concentrated to dryness in vacuo. The residue was suspended in MeOH (40 mL), chilled in a dry ice–acetone bath, and slowly saturated with dry HCl. The mixture was allowed to stir under N_2 at 25 °C for 60 h. Concentration in vacuo removed the volatile components. The residue was suspended in 10% Na_2CO_3 solution (100 mL) and extracted several times with $CHCl_3$ and then EtOAc. The organic extracts were dried (Na_2SO_4), combined, and concentrated. Trituration with ether–petroleum ether afforded 110 mg (78%) of **22**: mp 167.5–168.5 °C; IR (KBr) 3300 (NH), 2950, 2840, 1730 (C=O), 1625, 1600, 1455, 1440, 1245, 1160, and 710 cm^{-1}; UV (MeOH) 289 (2055) and 241 nm (6120); NMR (100 HMz, $CDCl_3$) δ 1.45–3.6 (m, including s at 2.41, NCH_3, 15 H), 3.74 (s, 3 H, OCH_3), 3.88 (t, J = 7 Hz, 1 H), 6.48 (d, J = 7.5 Hz, 1 H, Ar), 6.52 (d, J = 7.5 Hz, 1 H, Ar), and 7.04 (d, J = 7.5 Hz, 1 H, Ar); MS m/e 287 (20), 286 (M^+, 100), 285 (16), 271 (16), 255 (7), 157 (15), 144 (15), and 130 (17); MS (high resolution) calculated for $C_{17}H_{22}N_2O_2$, 286.168, found, 286.166. An analytical sample was obtained by recrystallization of 35.5 mg. The sample was dissolved in $CHCl_3$ (0.5 mL), diluted with hexane (3.5 mL), and filtered through Celite. Seeding the filtrate and chilling afforded 24.4 mg of the pure compound as orange needles. Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

Methyl Dihydrolysergate I (23). The total synthetic methyl 2,3,9,10-tetrahydrolysergate I (55 mg, 0.191 mmol) was stirred with MnO_2 ("Manganese Hydrate No. 37", General Metallic Oxides Co., Jersey City, N.J.) (530 mg, ca. 6.1 mmol) in $CHCl_3$ (10 mL) for 70 h under N_2. The mixture was filtered through Celite and washed well with $CHCl_3$. Concentration in vacuo gave 45 mg (83%) of crude **23**. Repetitive preparative layer chromatography on silica gel (20 × 10 cm × 2 mm) using EtOAc–MeOH–NH_4OH (92:5:3) afforded pure product, 10 mg (18%). The IR and mass spectra were identical with those of authentic methyl dihydrolysergate I. TLC on silica gel in EtOAc–NH_4OH (98:2) and three other systems further corroborated the trans-anti D-ring stereochemistry of this product (R_f 0.37, identical with authentic material) by comparison to methyl dihydroisolysergate I (trans-syn) and II (cis-syn) (R_f 0.46 and 0.41, respectively).

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