Synthesis of Novel 8- and 10-Substituted Clavine Derivatives

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The hydrogen at C-10 of agroclavine was readily removed by butyl-lithium to give an ambident carbanion. The addition of a range of electrophiles produced 10-substituted agroclavines (**2a**—**l**), 8-substituted lysergines (**3e**—**i**), and isolysergic acid derivatives (**3c**, **d**). Catalytic reduction of 1-methyl-10-propylagroclavine (**2c**) yielded 1-methyl-10-propylpyroclavine (**5b**) as the major product. Oxidation of 8-methylthiolysergine (**3g**) followed by an elimination reaction produced the alkaloid lysergene (**7**).

The ergot alkaloids are naturally occurring derivatives of the tetracyclic ring system known as ergoline. They can be divided into two structural types depending on the oxidation state of the group at C-8.† Historically, the pharmacologically important group have been the lysergic acid derivatives.[1] The clavine alkaloids, having either methyl [*e.g.* agroclavine (**1a**), festuclavine (**6**), pyroclavine (**5a**), lysergine (**3a**), isolysergine (**4a**)] or hydroxymethyl (elymoclavine) at C-8, have been less extensively studied. One such alkaloid agroclavine (**1a**), can be readily obtained from fermentation procedures using *Claviceps purpurea* AA218. In common with the clavines generally, it affects the level and turnover rates of catecholamines in the central nervous system. In particular, it interacts postsynaptically with dopaminergic receptors,[2] thus disease states in which dopamine imbalance is implicated (*e.g.* schizophrenia, Parkinson's disease) may be amenable to treatment with an appropriately modified clavine agent. The initial aim of our work was to prepare 2-substituted derivatives of agroclavine. During the course of this work, we also obtained a novel entry into 10-substituted agroclavine and pyroclavine derivatives and also number of 8-substituted lysergines. One of this last group has been converted into the diene alkaloid lysergene.

Results and Discussion

Roussel and Shirley have shown that 1-methylindole on treatment with butyl-lithium followed by an alkyl halide produces 2-alkyl-substituted indoles.[3] Since agroclavine contains the indole moiety this appeared to give an entry into useful 1-methyl-2-substituted derivatives. Addition of butyl-lithium to 1-methylagroclavine (**1b**) in tetrahydrofuran (THF) produces a cherry red anionic solution. Addition of propyl iodide gave, in high yield, a new compound which proved to be 1-methyl-10-propylagroclavine (**2c**) (Scheme 1) rather than the expected 1-methyl-2-propylagroclavine.

The 80 MHz ^{1}H n.m.r. spectrum (Table 1) showed the presence of a propyl group but no significant perturbation of the 8,9-double bond or the aromatic system was observed. Direct evidence for the position of substitution was obtained from the ^{13}C n.m.r. data. Most of the peaks in the spectrum could be assigned by comparison with data on agroclavine (Table 2). Off-resonance decoupling confirmed the position of the 1-Me and of two of the additional peaks attributable to the propyl group (δ_C 14.6, q; δ_C 16.9, t). The three carbons resonating around δ_C 40 could also be differentiated leading to the assignment of the 6-Me (δ 41.8, q), the other propyl methylene (δ 39.9, t), and most importantly, the identity of C-10 as a quarternary centre by its observation as a singlet. The small change in chemical shift, compared with agroclavine, is consistent with introduction of an axial alkyl group at this site. Data on an example for an underivatised indole nitrogen (**2g**) confirm that the significant shielding of C-4 is due to the effect of the 10-alkyl substituent. Thus butyl-lithium removes the proton at C-10 rather than that at C-2 to give the C-10 carbanion. Clavines substituted at C-10 with methoxy and hydroxy groups are known in the literature[4] but derivatives having carbon attached directly at C-10 are novel. The scope of this unexpected reaction was therefore investigated. The same rapid reaction was observed on the addition of methyl, ethyl, isopropyl, and allyl iodides to the carbanion to give the appropriate 1-methyl-10-alkylagroclavine (**2a**), (**2b**), (**2d**), and (**2e**).

Catalytic reduction of (**2c**) with platinum(IV) oxide in ethanol produced 1-methyl-10-propylpyroclavine (**5b**) as the major isomer (Scheme 2). This contrasts with the reduction of agroclavine itself where festuclavine (**6**) is the major product.[5] The steric bulk of the 10-propyl group presumably determines the stereochemical outcome of the reduction.

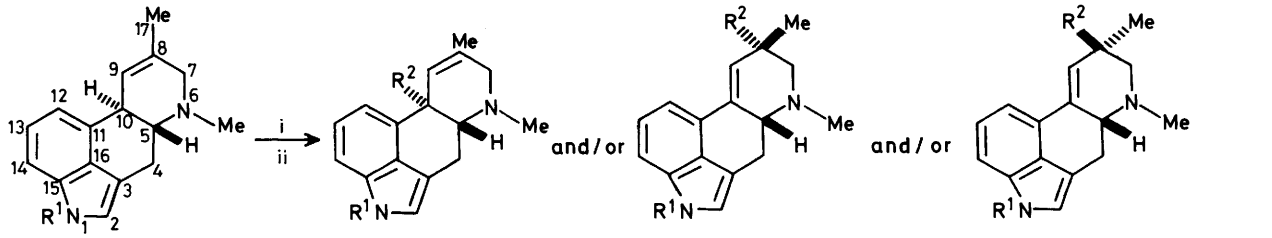
Since the C-10 carbanion may tautomerise to the C-8 carbanion, it was decided to investigate the addition of a range of electrophiles in the hope of obtaining 8-substituted clavines having a 9,10-double bond directly from agroclavine. The addition of ethyl chloroformate to the carbanion produced, in high yield, a mixture containing ethyl 1-methylagroclavine-10-carboxylate (**2i**) and ethyl 1,8-dimethylisolysergate (**3c**) in the ratio 2:3. The stereochemistry at the 8-position was determined using nuclear Overhauser effect (n.O.e.) difference spectroscopy.[6] Irradiation of the 8-methyl singlet showed a n.O.e. to the higher field of the two doublets assigned to the 7-H protons *via* the ^{1}H–^{13}C correlation spectrum. This doublet, in turn, exhibited an n.O.e. to the 5-H axial proton. Hence these three moieties are shown to be in close proximity above the plane of the tetracyclic system and indicate the structure shown in the Figure (one 7-H proton at δ 2.25 is 'pseudo' axial and 8-Me is 'pseudo' equatorial). A similar result was obtained with the addition of methyl isocyanate but the products (**2j**) and (**3d**) were found to be rather unstable during work-up.

Because of the high reactivity of the C-10 and C-8 carbanions it was found unnecessary to protect the N-1 position of agroclavine. Thus, the addition of two mol equiv. of butyl-lithium to agroclavine itself followed by one mol equiv. of an alkyl iodide (R = Me, Pr, or Bu) produced selectively the appropriate 10-alkylagroclavine (**2f**), (**2g**), or (**2h**) in high yield. When propyl iodide was used, a small amount of 8-propyl-isolysergine (**4b**) was also isolated. In this case, signals at δ_H 2.37 and δ 2.58 were assigned to the two protons at position 7. N.O.e. difference experiments showed the proximity of the 8-methyl group to the proton at δ_H 2.58. However, an n.O.e. was observed between the proton at δ 2.37 and 5-H proton, indicating that the methyl is below the plane of the tetracyclic ring in this product. The isomeric lysergine derivative (**3b**) was not detected.

† The ergoline numbering system, shown in structure (**1**), is used throughout.

Table 1. ^{1}H N.m.r. (80 MHz in $CDCl_3$) data [δ_H and J(Hz)] of compounds (**2a**—**j**), (**3c**, **d**), (**3g**—**i**), (**4b**, **c**), (**8a**—**c**), and (**9**)

Protons:	1 (m)	3 (m)	1 (s)	1 (s)	3 (s)	3 (s)	5 (m)	3 (s)	
Position:	NH	12, 13, 14,	2	9	1-Me	6-Me	4, 5, 7	8-Me	Other functional groups
Compd.									
(**2a**)		6.9—7.2	6.75	6.20	3.74	2.42	2.5—3.5	1.73	1.22 (3 H, s, 10-Me)
(**2b**)		6.9—7.2	6.71	6.18	3.73	2.41	2.5—3.5	1.74	0.77 (3 H, t, *J* 7 Hz, 10-CH_2*Me*), 1.2—2.0 (2 H, m, 10-CH_2Me)
(**2c**)		6.9—7.2	6.75	6.20	3.75	2.43	2.5—3.5	1.74	0.78 (3 H, t, *J* 7 Hz, 10-CH_2CH_2*Me*), 1.0—2.0 (4 H, m, 10-C*H*$_2$C*H*$_2$Me).
(**2d**)		6.9—7.2	6.75	6.10	3.74	2.40	2.5—3.5	1.75	0.55 (3 H, d, *J* 7 Hz, 10-CHMe*Me*), 1.10 (3 H, d, *J* 7 Hz, 10-CH*Me*), 2.0 (1 H, m, 10-C*H*Me$_2$)
(**2e**)		6.9—7.2	6.75	6.10	3.74	2.42	2.5—3.5	1.72	4.6—5.0 (2 H, m, 10-CH_2CH=C*H*$_2$), 5.7 (1 H, m, 10-CH_2C*H*=CH_2), 2.5—3.0 (2 H, m, 10-C*H*$_2$CH=CH_2)
(**2f**)	7.9	6.9—7.2	6.88	6.20		2.43	2.5—3.5	1.73	1.24 (3 H, s, 10-Me)
(**2g**)	7.9	6.9—7.2	6.88	6.20		2.43	2.5—3.5	1.74	0.78 (3 H, t, *J* 7 Hz, 10-CH_2CH_2*Me*), 1.0—2.0 (4 H, m, 10-C*H*$_2$C*H*$_2$Me)
(**2h**)	7.9	6.9—7.2	6.89	6.20		2.43	2.5—3.5	1.74	0.8 (3 H, t, *J* 7 Hz, 10-[CH_2]$_3$*Me*), 1.0—2.0 (6 H, m, 10-[C*H*$_2$]$_3$Me)
(**2i**)		6.9—7.2	6.78	6.31	3.75	2.46	2.5—3.5	1.77	1.05 (3 H, t, *J* 6 Hz, 10-CO_2CH_2*Me*), 3.95 (2 H, q, *J* 6 Hz, 10-CO_2C*H*$_2$Me)
(**2j**)		6.9—7.2	6.75		3.77	2.48	2.5—3.5	1.77	2.73 (3 H, s, 10-CONH*Me*), 8.7 (1 H, ex, 10-CON*H*Me)
(**3c**)		7.1—7.2	6.73	6.39	3.75	2.51	2.5—3.5	1.31	1.17 (3 H, t, *J* 6 Hz, 8-CO_2CH_2*Me*), 4.15 (2 H, q, *J* 6 Hz, 8-CO_2C*H*$_2$Me)
(**3d**)		7.1—7.2	6.77	6.31	3.76	2.54	2.5—3.5	1.31	2.73 (3 H, s, 8-CONH*Me*), 8.7 (1 H, ex, 8-CON*H*Me)
(**3g**)	7.9	7.1—7.2	6.91	6.23		2.50	2.5—3.5	1.40	2.21 (3 H, s, 8-SMe)
(**3h**)	7.85	7.1—7.2	6.84	6.44		2.48	2.5—3.5	1.56	7.3—7.8 (5 H, m, 8-SPh)
(**3i**)	7.8	7.1—7.2	6.87	6.35		2.50	2.5—3.5	1.25	0.07 (9 H, s, 8-$SiMe_3$)
(**4b**)	7.9	7.1—7.2	6.87	6.25		2.53	2.3—3.5	1.22	0.78 (3 H, t, 8-CH_2CH_2*Me*), 1.0—2.0 (4 H, m, 8-C*H*$_2$C*H*$_2$Me)
(**4c**)	7.9	7.1—7.4	7.00	6.34		3.09	3.0—4.0	1.57	2.14 (3 H, s, 8-SMe)
(**8a**)		6.9—7.2		6.20	3.75	2.45	2.5—3.5	1.74	0.78 (3 H, t, *J* 7 Hz, 10-CH_2CH_2*Me*), 1.2—2.0 (4 H, m, 10-C*H*$_2$C*H*$_2$Me)
(**8b**)	8.4	6.9—7.2		6.41		3.05	3.0—4.5	1.85	0.75 (3 H, t, *J* 7 Hz, 10-CH_2CH_2*Me*), 0.9—2.0 (4 H, m, 10-C*H*$_2$C*H*$_2$Me)
(**8c**)	8.25	6.9—7.2		6.43		3.05	3.0—4.0	1.86	0.73 (3 H, t, *J* 7 Hz, 10-$CH_2CH_2CH_2$*Me*), 0.9—2.2 (6 H, m, 10-[C*H*$_2$]$_3$Me)
(**9**)	7.9	7.1—7.2	6.95	6.05		2.47	2.5—3.5	1.42	2.53 (3 H, s, MeS=O)
				6.20		2.41		1.46	2.75



(**1**) **a**; R^1 = H (agroclavine)
b; R^1 = Me

(**2**) **a**; R^1 = R^2 = Me
b; R^1 = Me, R^2 = Et
c; R^1 = Me, R^2 = Pr
d; R^1 = Me, R^2 = Pr^i
e; R^1 = Me, R^2 = Allyl
f; R^1 = H, R^2 = Me
g; R^1 = H, R^2 = Pr
h; R^1 = H, R^2 = Bu
i; R^1 = Me, R^2 = CO_2Et
j; R^1 = Me, R^2 = CONHMe
k; R^1 = R^2 = Ac
l; R^1 = H, R^2 = Ac

(**3**) **a**; R^1 = R^2 = H (lysergine)
b; R^1 = H, R^2 = Pr
c; R^1 = Me, R^2 = CO_2Et
d; R^1 = Me, R^2 = CONHMe
e; R^1 = R^2 = Ac
f; R^1 = H, R^2 = Ac
g; R^1 = H, R^2 = SMe
h; R^1 = H, R^2 = SPh
i; R^1 = H, R^2 = $SiMe_3$

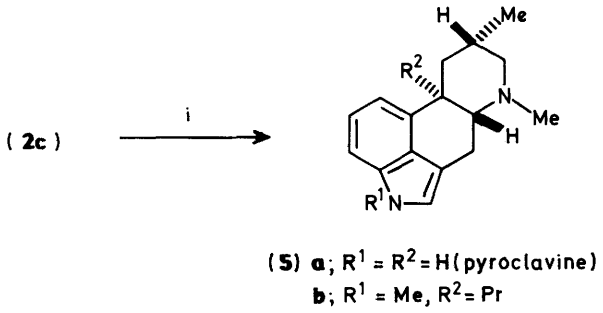
(**4**) **a**; R^1 = R^2 = H (isolysergine)
b; R^1 = H, R^2 = Pr
c; R^1 = H, R^2 = SMe

Scheme 1. *Reagents and conditions:* i, BuLi, THF; ii, R^2X, $ClCO_2Et$, MeNCO, $(MeCO)_2O$, or R^2SSR^2

Table 2. ^{13}C N.m.r. (300 MHz in $CDCl_3$ data [δ_C(p.p.m.)] for compounds (**1a**), (**2c**), (**2h**), (**2l**), (**3c**), (**3f**), and (**7**)

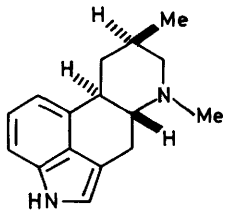
C	(1a)[a]	(1a)	(2c)[b]	(2h)	(2l)	(3c)	(3f)	(7)[c]
2	118.3	117.9	122.5 (d)	118.1	118.8	122.8	118.4	120.6
3	111.2	112.1	110.3 (s)	111.4	112.1	110.1	111.3	108.3
4	26.4	26.8	22.1 (t)	22.2	23.4	27.1	27.2	26.0
5	63.6	63.6	67.5 (d)	67.6	67.1	63.5	63.4	61.4
7	60.2	60.7	61.4 (t)	61.4	61.8	62.6	63.0	57.7
8	131.9	132.2	130.6 (s)	130.6	130.7	44.5	49.9	140.4
9	119.4	119.5	121.6 (d)	121.9	122.2	123.0	125.1	119.0
10	40.8	41.0	43.1 (s)	43.2	56.9	135.1	136.2	136.1
11	131.9	133.4	135.0 (s)	134.9	134.0	128.6	128.3	126.3
12	112.0	112.6	113.5 (d)	114.0	114.1	111.7	112.3	111.0
13	122.0	122.8	124.7 (d)	125.5	122.5	124.4	123.3	121.8
14	108.4	108.6	106.4 (d)	108.4	109.6	107.7	109.8	109.7
15	134.0	133.6	136.9 (s)	136.8	135.2	135.0	134.0	133.3
16	126.6	126.4	125.9 (s)	125.0	126.6	126.8	126.5	125.6
17	19.9	20.8	20.8 (q)	20.8	20.9	24.2	22.9	109.5
6-Me	40.2	41.0	41.8 (q)	41.8	41.4	43.8	43.7	42.1
1-Me			32.5 (q)			32.8		
10-Alkyl			14.6, 16.9, 39.9	14.1, 23.4, 26.8, 37.6				
10-Acyl					30.1, 189.7			
8-Ethyl						14.2, 60.6, 176.0		
8-Acyl						28.9, 185.3		

[a] In pyridine. [b] Multiplicity in off-resonance decoupled experiment. [c] In $(CD_3)_2SO$.



(5) a; $R^1 = R^2 = H$ (pyroclavine)
b; $R^1 = Me$, $R^2 = Pr$

Scheme 2. *Reagents and conditions:* i, H_2/PtO_2, EtOH



(6) (festuclavine)

When excess of acetic anhydride was added 1,8- and 1,10-diacetylation (**2k**) and (**3e**) occurred. The 1-acetyl group was readily cleaved by NaOH to give 10-acetylagroclavine (**2l**) and 8-acetyl-lysergine (**3f**). Using two-dimensional ^1H–^{13}C correlation spectroscopy, an unambiguous assignment of the aliphatic protons in both (**2l**) and (**3f**) was made (Table 3). For both isomers the multiplet pattern for 5-H was shown to be a double doublet, exhibiting couplings to the non-equivalent methylene protons C-4. This is in accordance with the absence of a proton in the 10-position, resulting from substitution by the acetyl group in (**2l**) and rearrangement of the double bond to C-9—C-10 in (**3f**).

Table 3. ^1H N.m.r. (300 MHz in $CDCl_3$) data [δ_H and J(Hz)] of compounds (**1a**), (**2l**), and (**3f**)

Compd.	(1a)		(2l)		(3f)	
Protons	δ	J	δ	J	δ	J
4α	2.78	15, 12	3.16	15, 12	2.66	15, 12
4β	3.31	15, 4	3.30	15, 5	3.51	15, 5.5
5	2.52	12, 4, 9.5	2.71	12, 5	3.08	12, 5.5
7α	3.24	16	3.35	17	3.30	11
7β	2.93	17, 4	2.80	17	2.26	11
9	6.18		6.34		6.43	
10	3.74					
17	1.77		1.81		1.20	
NMe	2.49		2.44		2.49	
Acetyl			2.19		2.27	

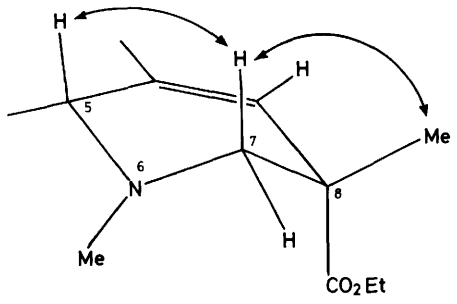
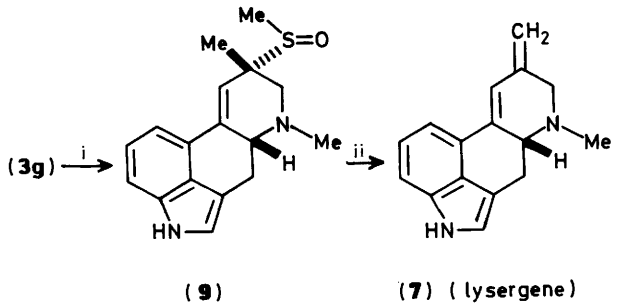


Figure.

High selectivity for the C-8 carbanion was achieved by the addition of dimethyl disulphide to produce 8-methylthiolysergine (**3g**), with only traces of 8-methylthioisolysergine (**4c**) being detected. Differentiation between these isomers at the 8-position can be made by comparison with data for festuclavine (**6**), pyroclavine (**5a**),[7] and the above compounds, the axial methyl being more deshielded. The same selectivity was also found when using diphenyl disulphide to give

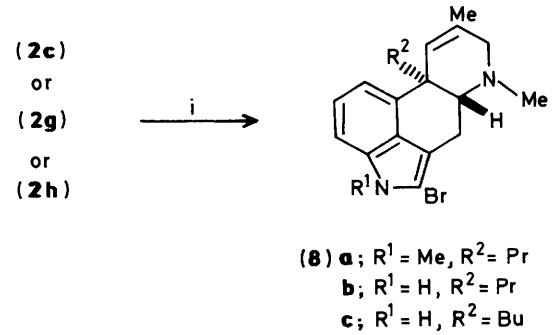
compound (**3h**), and hexamethyldisilane to give compound (**3i**). The methylthio group of compound (**3g**) was oxidised by $NaIO_4$ to the sulphoxide (**9**) which, in turn, was eliminated in 40% yield to the known alkaloid lysergene (**7**) (Scheme 3). Thus,



Scheme 3. *Reagents and conditions:* i, $NaIO_4$, aq. MeOH; ii, heat

by our route agroclavine can be readily converted into lysergene in three steps.

Since no reaction had taken place at the 2-position of the indole ring under the above conditions a number of the 10-alkylagroclavine products (**2c**), (**2g**), and (**2h**) were brominated using trimethyl(phenyl)ammonium tribromide in refluxing methylene dichloride to give the appropriate 2-bromo-10-alkylagroclavine derivatives (**8a**—**c**) (Scheme 4).



Scheme 4. *Reagents and conditions:* i, $PhMe_3NBr_3$, CH_2Cl_2

Experimental

^1H and ^{13}C N.m.r. spectra were obtained on either a Varian FT 80A or a Bruker AM300 spectrometer with tetramethylsilane or solvent ($CDCl_3$ at δ_C 77.07) as internal reference. ^{13}C N.m.r. spectra were run with broadband proton decoupling except where indicated. For the two-dimensional ^1H–^{13}C shift-correlation spectra the parameters were: F_2 = 1 K data points zero-filled to 2 K; F_1 = 64 W zero-filled to 128 W; $SW2$ = 9 000 Hz; $SW1$ = 1 000 Hz; delays Δ_1 = 3 ms, Δ_2 = 1.5 ms, and 1 s relaxation delay. U.v. spectra were obtained in methanol on a Pye-Unicam SP800 or SP7500 spectrophotometer. I.r. spectra were recorded on a Perkin-Elmer 297 instrument as capillary films or potassium bromide discs. Mass spectra were recorded on a LKB 9000S spectrometer. Optical rotations were performed on a Bellingham and Stanley P.70-4 polarimeter, and m.p.s were measured on Kofler micro hot stage. Extracts were washed with water and dried ($MgSO_4$).

1-*Methyl*-10-*propylagroclavine* (**2c**).—Butyl-lithium in hexane (1.25 ml of a 1.6M solution, 2 mmol) was added dropwise at room temperature to a solution of 1-methylagroclavine (**1b**) (0.5 g, 2 mmol) in THF (10 ml) to give a red solution. After 5 min a solution of propyl iodide (1.7 g, 10 mmol) in THF (5 ml) was added dropwise to give a brown solution. After 1 h at room temperature, the mixture was treated with water and extracted with methylene dichloride three times. The extract was washed, dried, and evaporated to give a brown oil. The oil was dissolved in methylene dichloride and chromatographed on Florisil by elution with methylene dichloride then chloroform to give an oil which, on addition of acetonitrile, gave the *product* (**2c**) as white crystals (0.32 g, 50%), m.p. 112—114 °C (Found: C, 81.65; H, 8.8; N, 9.3. $C_{20}H_{26}N_2$ requires C, 81.6; H, 8.9; N, 9.5%); $\lambda_{max.}$ 293 nm (ε 7 630 dm^3 mol^{-1} cm^{-1}); *m/z* 294.

1,10-*Dimethylagroclavine* (**2a**).—Prepared from 1-methylagroclavine (**1b**) and methyl iodide using the above procedure (0.64 g, 60%), m.p. 122.5—124.5 °C (Found: C, 81.4; H, 8.6; N, 10.45. $C_{18}H_{22}N_2$ requires C, 81.2; H, 8.3; N, 10.5%); $\lambda_{max.}$ 293 nm (ε 7 610); *m/z* 266.

10-*Ethyl*-1-*methylagroclavine* (**2b**).—Butyl-lithium in hexane (2.6 ml of a 1.55M solution, 4 mmol) was added dropwise under nitrogen to a solution of 1-methylagroclavine (**1b**) (1 g, 4 mmol) in THF (25 ml) at −20 °C to give a red solution. After 15 min, the solution was cooled to −50 °C and a solution of ethyl iodide (0.65 g, 4.2 mmol) in THF (5 ml) was added dropwise. After the reaction mixture had reached room temperature (2 h) water was added and the mixture was extracted with ethyl acetate. The extract was washed, dried, and evaporated to give a brown oil (1.3 g), which was dissolved in methylene dichloride and chromatographed on Florisil by elution with methylene dichloride then chloroform to give an oil. On addition of acetonitrile the *product* (**2b**) was obtained as light brown crystals (0.49 g, 44%), m.p. 119—123 °C; $[\alpha]_D^{21}$ −178 °C (*c* 0.45 in pyridine) (Found: C, 81.1; H, 8.7; N, 9.7. $C_{19}H_{24}N_2$ requires C, 81.4; H, 8.6; N, 10.0%); $\lambda_{max.}$ 293 nm (ε 6 370); *m/z* 292.

10-*Isopropyl*-1-*methylagroclavine* (**2d**).—Prepared from 1-methylagroclavine (**1b**) and isopropyl iodide using the above procedure (0.41 g, 35%), m.p. 110—114 °C; $[\alpha]_D^{21}$ −159° (*c* 0.53 in pyridine) (Found: C, 81.3; H, 8.6; N, 9.3. $C_{20}H_{26}N_2$ requires C, 81.6; H, 8.9; N, 9.5%); $\lambda_{max.}$ 285 nm (ε 7 150); *m/z* 294.

10-*Allyl*-1-*methylagroclavine* (**2e**).—Prepared from 1-methylagroclavine (**1b**) and allyl iodide using the above procedure (0.6 g, 50%), m.p. 122—124 °C; $[\alpha]_D^{22}$ −153° (*c* 0.37 in pyridine) (Found: C, 82.15; H, 8.3; N, 9.6. $C_{20}H_{24}N_2$ requires C, 81.9; H, 8.5; N, 9.6%); $\lambda_{max.}$ 294 nm (ε 7 660); *m/z* 294.

10-*Propylagroclavine* (**2g**) *and* 8-*Propylisolysergine* (**4b**).—Butyl-lithium (30.8 ml of a 1.55M solution in hexane, 40 mmol) was added dropwise under nitrogen to a solution of agroclavine (**1a**) (4.8 g, 20 mmol) in THF (60 ml), with the temperature maintained between −25 and −50 °C. After the mixture had been stirred for 15 min, a solution of propyl iodide (3.4 g, 20 mmol) in THF was added and the mixture was allowed to reach room temperature. Water was added to the ice-cooled mixture, which was then extracted three times with ethyl acetate; the extract was washed, dried, and evaporated to give a brown oil. The oil was dissolved in methylene dichloride and chromatographed on Florisil by elution with methylene dichloride then ethyl acetate to give two pure products. The major one was 10-*propylagroclavine* (**2g**) (3.7 g, 70%) and a sample was recrystallised from acetonitrile, m.p. 164—168 °C; $[\alpha]_D^{24}$ −107° (*c* 0.83 in pyridine); *m/z* 280 (Found: C, 81.3; H, 8.8; N, 9.7. $C_{19}H_{24}N_2$ requires C, 81.4; H, 8.6; N, 10.0%); $\lambda_{max.}$ 283 nm (ε 7 060); $\nu_{max.}$ 3 420 cm^{-1} (NH). The minor product was 8-*propylisolysergine* (**4b**) (0.08 g, 1.5%) and was crystallised from acetonitrile (0.04 g, 0.8%), m.p. 123—126 °C; $[\alpha]_D^{25}$ +53° (*c* 0.045 in pyridine) (Found: C, 81.3; H, 8.6; N, 9.7%); $\lambda_{max.}$ 310 nm (ε 9 840); *m/z* 280.

10-*Butylagroclavine* (**2h**).—Prepared from agroclavine (**1a**) and butyl iodide using the above procedure (3.4 g, 61%), m.p. 169—172 °C; $[\alpha]_D^{20.5}$ −30.6° (*c* 0.98 in pyridine) (Found: C, 81.7; H, 8.6; N, 9.3. $C_{20}H_{26}N_2$ requires, C, 81.6; H, 8.9; N, 9.5%); $\lambda_{max.}$ 282 nm; $\nu_{max.}$ 3 400 cm^{-1} (NH); *m/z* 294.

10-*Methylagroclavine* (**2f**).—Prepared from agroclavine (**1a**) and methyl iodide using the above procedure (0.45 g, 14%), m.p. 169—174 °C; $[\alpha]_D^{29.5}$ −29.5° (*c* 0.34 in pyridine) (Found: C, 80.7; H, 8.2; N, 11.0. $C_{17}H_{20}N_2$ requires C, 80.9; H, 8.0; N, 11.1%); $\lambda_{max.}$ 286 nm (ε 7 890); $\nu_{max.}$ 3 470 cm^{-1} (NH); *m/z* 252. A by-product (0.75 g, 27%) in this reaction was found to be 10-butylagroclavine (**2h**) due to an exchange reaction between methyl iodide and butyl-lithium.

1-*Methyl*-10-*propylpyroclavine* (**5b**).—A mixture of 1-methyl-10-propylagroclavine (**2c**) (1.6 g), platinum(IV) oxide (0.35 g), and ethanol was hydrogenated at 60 lb in^{-2} for two days. The catalyst was filtered off and the filtrate was evaporated to give an oil. This was dissolved in methylene dichloride and chromatographed on Florisil by elution with methylene dichloride then ethyl acetate to give the *product* (**5b**) (0.7 g, 43.9%), m.p. 114—116 °C (from acetonitrile); $[\alpha]_D^{23.5}$ +28.7° (*c* 0.40 in pyridine) (Found for HCl salt [ethanol–ether, m.p. 238—242 °C]: C, 72.3; H, 8.7; N, 8.5; Cl, 10.5. $C_{20}H_{29}ClN_2$ requires C, 72.15; H, 8.8; N, 8.4; Cl, 10.65%); $\lambda_{max.}$ 292 nm (ε 7 400); δ_H(80 MHz; $CDCl_3$) 7.1—7.2 (3 H, m, 12-, 13-, and 14-H), 6.72 (1 H, s, 2-H), 3.75 (3 H, s, 1-Me), 2.37 (3 H, s, 6-Me), 2.0—3.5 (5 H, m, 4-H_2, 5-H, and 7-H_2), 1.35 (3 H, s, 8-Me), 1.0—2.5 (3 H, m, 8-H and 9-H_2), 1.0—2.0 (4 H, m, $MeCH_2CH_2$), and 0.7 (3 H, t, $MeCH_2CH_2$); *m/z* 296.

2-*Bromo*-10-*propylagroclavine* (**8b**).—Trimethyl(phenyl)-ammonium tribromide (1.48 g, 4 mmol) in methylene dichloride (20 ml) was added dropwise during 25 min under nitrogen to a solution of 10-propylagroclavine (**2g**) (1 g, 3.6 mmol) in methylene dichloride (30 ml). After 1 h, water was added followed by conc. ammonia (*d* 0.88) and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a brown oil (1 g), which was chromatographed on neutral alumina by elution with methylene dichloride then ethyl acetate. Fractions containing pure product were evaporated to give an oil, which on addition of acetonitrile gave the *product* (**8b**) (0.6 g, 28%), m.p. 191—192 °C; $[\alpha]_D^{23.5}$ −46.8° (*c* 0.36 in pyridine) (Found on maleate salt: C, 58.4; H, 6.0; N, 5.7. $C_{23}H_{27}BrN_2O_4$ requires C, 58.1; H, 5.7; N, 5.9%); $\lambda_{max.}$ 282 nm; *m/z* 358/80.

2-*Bromo*-10-*butylagroclavine* (**8c**).—Prepared from 10-butylagroclavine (**2h**) using the above procedure (0.8 g, 87%), m.p. 190—193 °C; $[\alpha]_D^{23.5}$ −22.0° (*c* 1.03 in pyridine) (Found on maleate salt: C, 59.2; H, 5.9; Br, 15.9; N, 5.3; O, 13.2. $C_{24}H_{29}BrN_2O_4$ requires C, 58.9; H, 6.0; Br, 16.3; N, 5.7; O, 13.1%); $\lambda_{max.}$ 281 nm; *m/z* 372/374.

2-*Bromo*-1-*methyl*-10-*propylagroclavine* (**8a**).—Prepared from 1-methyl-10-propylagroclavine (**2c**) using the above procedure (0.5 g, 56%), m.p. 116—118 °C; $[\alpha]_D^{22}$ −158° (*c* 0.40 in pyridine) (Found: C, 64.15; H, 7.0; N, 7.41. $C_{20}H_{25}BrN_2$ requires C, 64.3; H, 6.75; N, 7.4%); $\lambda_{max.}$ 287 nm (ε 8 950); *m/z* 372/374.

1,8-*Diacetyl-lysergine* (**3e**) *and* 1,10-*Diacetylagroclavine* (**2k**).—Butyl-lithium (1.6M solution in hexane; 13.1 ml, 21 mmol) was added dropwise under nitrogen to a rapidly stirred solution of agroclavine (**1a**) (2.38 g, 10 mmol) in THF (50 ml), whilst the temperature was kept between −50 and −70 °C. After 30 min at −50 °C, the red solution was cooled to −70 °C and a solution of acetic anhydride (10 ml) in THF (30 ml) was added dropwise. The solution was allowed to reach room temperature during 1.5 h, when water was added followed by evaporation to give a black residue. Excess of conc. ammonia (*d* 0.88) and water were added followed by extraction with methylene dichloride. The extract was washed dried, and evaporated to give a black residue (2.5 g). This was purified by column chromatography using Florisil (150 g), with methylene dichloride then with increasing amounts of methanol in methylene dichloride as eluant, to give two major products. The first product was 1,8-diacetyl-lysergine (**3e**) (1.18 g, 37%); *m/z* 323 (*M* + 1). The second product was 1,10-diacetylagroclavine (**2k**) (1.1 g, 34%); *m/z* 323 (*M* + 1).

8-*Acetyl-lysergine* (**3f**).—A mixture of 1M sodium carbonate (40 ml), water (20 ml), ethanol (50 ml), and 1,8-diacetyl-lysergine (**3e**) (1.13 g, 3.5 mmol) was stirred at room temperature for 4 h. The mixture was diluted with water and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give an oil. This was purified on a column of neutral alumina, with methylene dichloride, then increasing amounts of methanol in methylene dichloride as eluant, to give the *product* (**3f**) as a solid (0.5 g, 51%), m.p. 154—155 °C (from acetonitrile); $[\alpha]_D^{28.5}$ +183° (*c* 0.455 in pyridine) (Found: C, 77.1; H, 7.3; N, 9.9. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.2; N, 10.0%); $\lambda_{max.}$ 331 nm (ε 10 800); $\nu_{max.}$ 3 340 (NH) and 1 685 cm (CO); *m/z* 281 (*M* + 1).

10-*Acetylagroclavine* (**2l**).—Prepared from 1,10-diacetyl-agroclavine (**2k**) using the above procedure (0.4 g, 41% [from acetonitrile]), m.p. 177—181 °C (decomp.); $[\alpha]_D^{28.5}$ −18.4 °C (*c* 0.435 in pyridine) (Found: C, 76.9; H, 7.05; N, 10.1%); $\lambda_{max.}$ 287 nm (ε 8 120); $\nu_{max.}$ 1 700 cm^{-1} (CO); *m/z* 281 (*M* + 1).

Ethyl 1-*Methylagroclavine*-10-*carboxylate* (**2i**) *and Ethyl* 1,8-*Dimethylisolysergate* (**3c**).—Butyl-lithium (4.1 ml of a 1.55M solution in hexane, 6.3 mmol) was added dropwise under nitrogen to a solution of 1-methylagroclavine (**1b**) (1.4 g, 5.6 mmol) in THF (25 ml) at −20 °C to produce a red solution. After 5 min at −10 °C the mixture was cooled to −70 °C, treated with a solution of ethyl chloroformate (0.64 g, 6.4 mmol) in THF (25 ml) and allowed to reach room temperature during 2 h. Water was added followed by extraction with methylene dichloride and the extracts were washed, dried, and evaporated to give a black oil, which was purified on a column of Florisil by elution with methylene dichloride then ethyl acetate to give isomer A (**3c**) (0.8 g, 45%) and isomer B (**2i**) (0.25 g, 14%). A sample of A was recrystallised from ethanol to give pale yellow crystals of *ethyl* 1,8-*dimethylisolysergate* (**3c**), m.p. 95—96.5 °C; $[\alpha]_D^{20.5}$ +108° (*c* 0.35 in pyridine) (Found: C, 73.85; H, 7.6; N, 8.4. $C_{20}H_{24}N_2O_2$ requires C, 74.05; H, 7.5; N, 8.6%); $\lambda_{max.}$ 319 nm (ε 9 100); $\nu_{max.}$ 1 715 cm^{-1} (CO); *m/z* 324. A sample of isomer B was recrystallised from ethanol to give pale yellow crystals of *ethyl* 1-*methylagroclavine*-10-*carboxylate* (**2i**), m.p. 125—130 °C; $[\alpha]_D^{20.5}$ +65° (*c* 0.35 in pyridine) (Found: C, 73.8; H, 7.3; N, 8.4%); $\lambda_{max.}$ 303 nm (ε 7 820); $\nu_{max.}$ 1 705 cm^{-1} (CO); *m/z* 324.

1,N-*Dimethylagroclavine*-10-*carboxamide* (**2j**) *and* 1,8,N-*Trimethylisolysergamide* (**3d**).—Prepared from 1-methyl-agroclavine (**1b**) and methyl isocyanate using the above procedure. The first *product* was found to be compound (**3d**) (40 mg, 0.5%) (Found: C, 73.8; H, 7.2; N, 13.2. $C_{19}H_{23}N_3O$ requires C, 73.75; H, 7.5; N, 13.6%); $\lambda_{max.}$ 319 nm (ε 9 000); $\nu_{max.}$ 3 400 (NH) and 1 658 cm^{-1} (CO); *m/z* 309. The second *product* was found to be compound (**2j**) (40 mg, 0.5%), m.p. 226—229 °C (Found: C, 73.95; H, 7.6; N, 13.3%); $\lambda_{max.}$ 285 nm (ε 5 360); $\nu_{max.}$ 3 400 and 3 200 (NH) and 1 640 cm^{-1} (CO); *m/z* 309.

8-*Methylthiolysergine* (**3g**) *and* 8-*Methylthioisolysergine* (**4c**).—Butyl-lithium (35 ml of a 1.55M solution in hexane, 50 mmol) was added dropwise under nitrogen to a solution of agroclavine (**1a**) (6.0 g, 25 mmol) in THF (125 ml) at −70 °C. After 5 min, the temperature was allowed to reach −20 °C during 10 min then the mixture was recooled to −70 °C and a solution of dimethyl disulphide (2.6 g, 27.6 mmol) in THF (10 ml) was added dropwise. After being stirred for 15 min, the mixture was allowed to reach room temperature during 90 min. Water and 5M HCl were added followed by extraction with ethyl acetate. The aqueous phase was basified with conc. ammonia (*d* 0.88) and extracted with methylene dichloride. The latter extract was washed, dried, and evaporated to give an unstable white solid (6.5 g), which was purified on a column of neutral alumina by elution with methylene dichloride then 10% methanol in methylene dichloride to give the *major product* (**3g**) (4.7 g, 66%); $[\alpha]_D^{25}$ +369° (*c* 0.4 in pyridine) (Found: C, 71.6; H, 7.2; N, 10.1; S, 11.0. $C_{17}H_{20}N_2S$ requires C, 71.8; H, 7.1; N, 9.85; S, 11.3%). A sample was converted into the maleate salt [m.p. 155—157 °C (decomp.)]; $\lambda_{max.}$ 313 nm; $\nu_{max.}$ 3 150s cm^{-1} (NH); *m/z* 284. The minor product (**4c**) was obtained as an oil (5 mg); $\lambda_{max.}$ 313 nm; *m/z* 284.

8-*Phenylthiolysergine* (**3h**).—Prepared from agroclavine and diphenyl disulphide using the above procedure (66%); *m/z* 252.

8-*Trimethylsilyl-lysergine* (**3i**).—Prepared from agroclavine and bis(trimethylsilyl) disulphide using the above procedure (100%); *m/z* 310.

Conversion of Sulphide (**3g**) *into Lysergene* (**7**).—(A): 8-*Methylsulphinyl-lysergine* (**9**). A solution of sodium periodiate (2.2 g, 21.6 mmol) in water (20 ml) was added dropwise to a solution of the sulphide (**3g**) (2.2 g, 17 mmol) in methanol (200 ml at 55 °C). After 30 min water was added followed by conc. ammonia (*d* 0.88) and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give the product (**9**) as a glassy solid (2.2 g); $\lambda_{max.}$ 325 nm; $\nu_{max.}$ 3 200 cm^{-1} (NH); *m/z* 245 (*M* − CH_2=S).

(B): *Lysergene*. Compound (**9**) (2 g) was heated in toluene (150 ml) at 100 °C for 30 min to give a black solution, which was evaporated to dryness. The product was dissolved in methylene dichloride and chromatographed on Florisil by elution with 5% methanol in methylene dichloride to give lysergene (**7**) as a pure solid (0.62 g, 40%), m.p. (from EtOH) 243—244 °C (lit.,[8] 244—245 °C); $\lambda_{max.}$ 341 nm; $\nu_{max.}$ 3 150 cm^{-1} (NH); δ_H[300 MHz; $(CD_3)_2SO$] 10.75 (1 H, ex, NH), 7.21 and 7.17 (2 H, 2 d, 12- and 14-H), 7.08 (1 H, t, 13-H), 7.07 (1 H, br s, 9-H), 6.93 (1 H, s, 2-H), 5.00 and 4.90 (2 H, 2 s, C=CH_2), 3.43 and 304 (2 H, 2 d, 7-H_2), 3.10 (1 H, dd, 5-H), 3.45 and 2.50 (2 H, 2 dd, 4-H_2), and 2.44 (3 H, s, NMe) (confirmation of proton and carbon chemical-shift assignments was obtained from the ^1H–^{13}C correlation spectrum); *m/z* 236.

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