Photocyclisation of Enamides. Part 24.[1] Total Synthesis of (±)-Isofumigaclavine B and (±)-Lysergic Acid[2]

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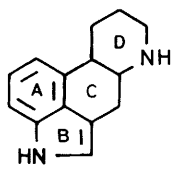
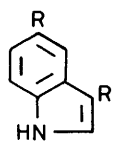
Total syntheses of two ergoline-types of alkaloids, (±)-isofumigaclavine B (**14**) (for the first time) and methyl (±)-lysergate (**21**) and methyl (±)-isolysergate (**22**), *via* a route involving reductive photocyclisation of the enamide (**2**) followed by glycol formation and oxidative cleavage of the dihydrofuran ring, are described.

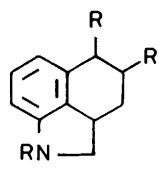
In Part 22[3] we have reported the establishment of a potential synthetic route to the despyrrole analogues of lysergic acid and isofumigaclavines, aiming at its application to the respective alkaloids. We now report novel total syntheses of isofumigaclavine B and lysergic acid according to the synthetic methodology involving reductive photocyclisation of the enamide (**2**) followed by ring opening of the dihydrofuran ring of the photocyclised lactam (**3**). Previously, lysergic acid has been regarded as a central target alkaloid not only from the synthetic viewpoint but also because of its remarkable pharmacological potential, and it has been synthesized by six different methodologies,[2,4] which are divided into two types depending upon the starting compounds used, *i.e.* route A from



Ergoline



(I)

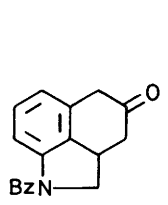


(II)

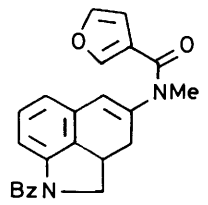
the indole derivatives (**I**) and the route B from the indoline derivatives (**II**). However, the synthesis of the alkaloid according to route A has only been successful when attempted by Oppolzer *et al.*[4d] but the method has achieved some success in the synthesis of D-saturated ergolines.[5] These results reflect that the high reactivity of the indole ring and the feasibility of aromatisation of ring C might have been the major problems to overcome in the case of the synthesis starting from the indole derivatives (**I**). Therefore, this suggests that a synthetic approach by route B would be advantageous, in the case of the synthesis of ergolenes having a double bond in ring D, compared with route A.

Therefore we chose our approach toward these ergolene alkaloids by starting from the enamide (**2**) which was prepared from the indoline derivative (**1**) and 3-furoic acid according to the methodology developed for the despyrrole analogues.[3]

Acylation of the enamine prepared from 1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-4(5*H*)-one (**1**)[6] and methylamine with furan-3-carbonyl chloride in the presence of triethylamine afforded the enamide (**2**) in 96% yield, which showed the n.m.r. peak for an olefinic proton at δ 6.45 as a broad singlet and broad and strong i.r. absorptions in the region of 1 640—1 620 cm^{-1}. Irradiation of the enamide (**2**) in benzene–methanol (5:1) in the presence of excess of sodium borohydride (10 mol equiv.) at 4—10 °C with a high-pressure mercury lamp afforded the crystalline products in 81% yield, which were found to be a mixture of three compounds (**3**), (**4**), and (**5**) in the proportions 10:4:1 by high-performance liquid chromatography (h.p.l.c.).†



(1)



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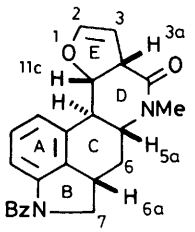

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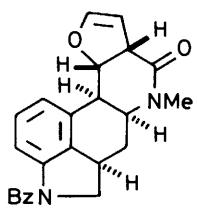

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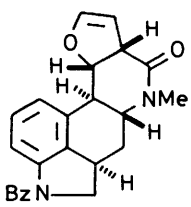

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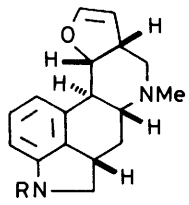
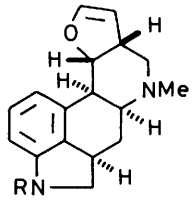
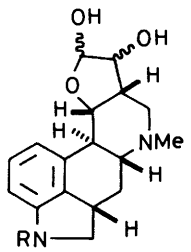


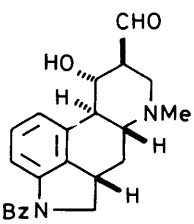
(6) R = H
(7) R = Bz



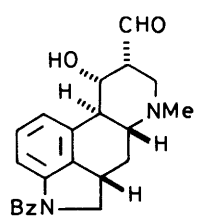
(8) R = H
(9) R = Bz



(10)



(11)



(12)

† Although only two photocyclised lactams (**3**) and (**4**) were reported in the preliminary communication (ref. 2), three isomers (**3**)—(**5**) have now been isolated by repeated column chromatography.

These three products (3)—(5) were separated by repeated recrystallisation and column chromatography and were established as the expected products by reductive photocyclisation, from their mass spectra which exhibited a molecular ion peak at *m/z* 386, and from their i.r. absorptions at 1 660—1 620 cm^{-1} (2NCO). Contrary to the cases of the model compounds[3] (the despyrrole analogues of the alkaloids) in which the stereochemistry of the products was influenced by the solvent used, the proportions of the lactams (3)—(5) were not influenced by the solvent, either by the amount of methanol or by the use of acetonitrile in place of benzene. Their stereochemistries were established from their n.m.r. spectra and by comparison of those of the model compounds.[3] The D/E-*cis* fusion of three lactams (3)—(5) was determined from the coupling constants between the respective 3a- and 11c-H [10—11 Hz in (3)—(5)] and from the conversion of compound (3) into the 8,9-*cis*-disubstituted ergoline derivative (16). The *trans* relationship between 11b- and 11c-H was deduced from their coupling constants of 10 Hz in (3)—(5) and by mechanistic considerations of enamide photocyclisation that have been well documented[1] as proceeding *via* conrotatory cyclisation of the 6 π-electron system in the enamide, thus forming a *trans* cyclic intermediate. The C/D-ring junctions were determined from the coupling constants between 5a- and 11b-H [10 Hz in (3) and (5)], thus suggesting their C/D-*trans* fusion, while the value of 6 Hz in (4) suggested a *cis* fusion. Furthermore, the relative configuration between 5a- and 6a-H as being *cis* was also deduced from the signal pattern of 6-H_{ax} which appeared as a sharp quartet with *J* 12 Hz at δ 1.68 in (3) and at δ 1.55 in (4), thus suggesting their *cis*-1,3-diaxial relationship where ring C would take a half-chair conformation as shown in Figure 1. This deduction coincides well with that

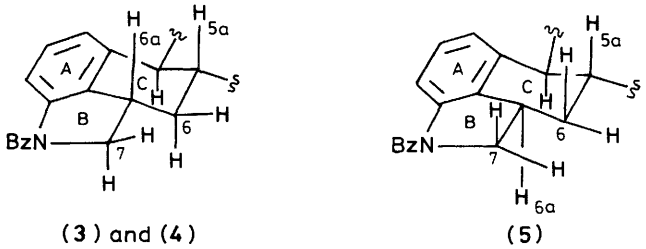


Figure 1.

reached by Rebek *et al.*[4e] for the analogous compounds. On the other hand, the n.m.r. signals of hydrogens on rings D and E in (5) closely resemble those of (3) but the signals for 6-H_2 overlap at δ *ca.* 2.38—2.02. This behaviour can be readily explained by assuming the conformation of ring C is a half-boat form which would have a *trans* relationship of two hydrogens at the 5a- and 6a-positions as shown in Figure 1. Previously,[4c,4e,7] only those compounds having these two hydrogens at the 5a- and 6a-position in a *cis*-1,3-diaxial orientation had been isolated and this is the first time that a compound having a *trans* configuration between hydrogens at positions 5a and 6a has been prepared.

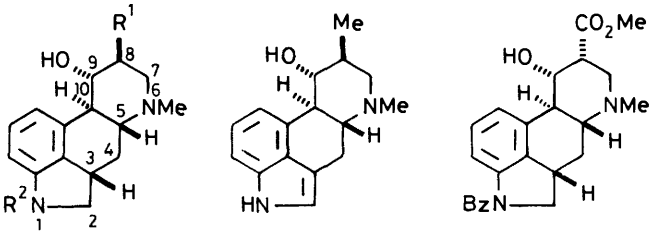
Of the photocyclised lactams (3)—(5), the C/D-*trans*-lactam (3), which was obtained predominantly, was used for the total syntheses of isofumigaclavine B and methyl lysergate.

Ring opening of the dihydrofuran ring of the photocyclised lactam (3) was accomplished according to the procedure described previously.[3] Lithium aluminium hydride reduction of the C/D-*trans*-lactam (3) afforded the diamine (6) as a result of accompanying debenzoylation. This diamine (6) was then re-benzoylated with benzoyl chloride to give the *N*-benzoate (7) in 74% yield. A similar reduction of a mixture of the C/D-*trans*-and -*cis*-lactams (3) and (4) (5:1) with lithium aluminium hydride gave a mixture of the corresponding *N*-debenzoylated amines (6) and (8) which were also rebenzoylated to yield a mixture of two benzoates (7) and (9) in 61 and 9% yield respectively; these benzoates were separated by column chromatography. Their n.m.r. spectra, which showed, for (7), δ 2.22 (td, *J* 10 and 2 Hz, 5a-H) and 1.43 (q, *J* 10 Hz, 6-H_{ax}), and for (9), δ 2.22 (br d, *J* 11 Hz, 5a-H) and 1.44 (q, *J* 11 Hz, 6-H_{ax}), established their structures. Hydroxylation of the dihydrofuran ring in the amine (7) was first carried out by using an equimolar amount of osmium tetraoxide followed by treatment with hydrogen sulphide gave the glycols (10) in 53% yield. The yield of the glycols (10) was improved to 83% by reaction with a catalytic amount of osmium tetraoxide and trimethylamine *N*-oxide as the oxidising agent.[8] The product (10) was found to be a mixture of two *cis*-glycols in the ratio 3:2 which was estimated from the peak area of the two alcoholic proton signals in the n.m.r. spectrum, though it remained to be determined which isomer was predominant.* This glycol mixture was also observed in the case of despyrrole derivatives.[3] The mixture of *cis*-glycols (10), without separation, was then treated with sodium metaperiodate in methanol–water (1:1) to cleave the glycol to afford the 9α-hydroxy-8β-aldehyde (11) as the sole unstable product upon work-up with sodium carbonate. This base treatment after the glycol cleavage brought about a complete isomerisation of the ring-opened 8-formyl group from the unstable 8α-orientation to the stable 8β-configuration. The structure of the 9α-hydroxy-8β-aldehyde (11) was established from its spectral data [$\nu_{max.}$ 3 500 (OH) and 1 720 cm^{-1} (CHO); δ 9.80 (br s, CHO) and 2.35 (s, NMe)]. On the other hand, similar glycol cleavage of a mixture of the glycols (10) but without the base treatment afforded a mixture of two epimeric aldehydes (11) and (12) with the ratio *ca.* 1:1, which was estimated from the peak area of the 8-formyl protons in the n.m.r. spectrum [(12); δ 9.93 (br s, CHO)]. The structures of these aldehydes (11) and (12) were later unambiguously established by their conversion into the stable synthetic intermediates (15) and (16). The aldehydes (11) and (12) bear all the functional groups required for the synthesis of ergot alkaloids having an ergoline nucleus.

Total Synthesis of (±)-*Isofumigaclavine B* (14).—Wolff–Kishner reduction of either the 9α-hydroxy-8β-aldehyde (11) or a mixture of the two epimeric aldehydes (11) and (12) gave the *N*-debenzoylated 8β-methyl-9α-ol (13) as the sole product in 40—47% yield, and which showed characteristic n.m.r. signals [δ 3.34 (t, *J* 10 Hz, 9-H) and 1.06 (d, *J* 7 Hz, 8-Me)], thus confirming its structure as 2,3-dihydroisofumigaclavine B (ergoline numbering). Dehydrogenation of the indoline (13) with manganese dioxide gave (±)-isofumigaclavine B (14) in 45% yield, which was identical with the natural alkaloid upon comparison of their i.r. and n.m.r. spectra and R_F values.[9] Alternatively, conversion of the indoline (13) into (±)-isofumigaclavine B (14) could be conveniently achieved by treatment with benzeneseleninic anhydride[10] in 50% yield. Thus, we succeeded in the first total synthesis of the alkaloid (±)-isofumigaclavine B.

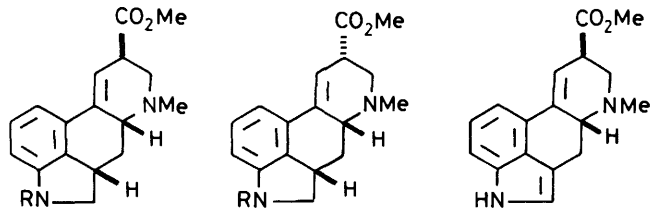
Novel Total Synthesis of Methyl (±)-*Lysergate* (21) *and Methyl* (±)-*Isolysergate* (22).—The conversion of the aldehydes (11) and (12) into the desired unsaturated esters (17) and (18) was accomplished according to the procedure established previously.[3] Oxidation of the 9α-hydroxy-8β-aldehyde (11) with chromium trioxide and sulphuric acid in methanol–acetone solution gave the 9α-hydroxy-8β-methyl

* Although we reported that the β-glycol was described as a major product in the preliminary communication (ref. 2), careful reinvestigation of the n.m.r. spectrum of a mixture of the glycols (10) showed the ambiguity of their assignment.



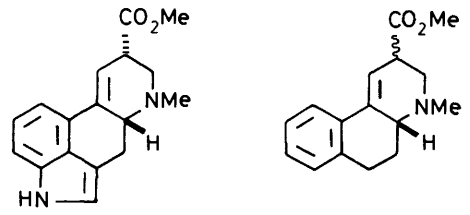
(13) R^1 = Me, R^2 = H (14) (16)

(15) R^1 = CO_2Me, R^2 = Bz



(17) R = Bz (18) R = Bz (21)

(19) R = H (20) R = H



(22) (23)

ester (**15**) in 38% yield. Similar oxidation of a mixture of the two epimeric aldehydes (**11**) and (**12**) (*ca.* 1:1) gave the 9α-hydroxy-8β-methyl ester (**15**) and 8α-methyl ester (**16**) in 11 and 14% yield respectively, which were separated by p.l.c. (preparative layer chromatography). The structures of these esters (**15**) and (**16**) were determined mainly from their n.m.r. spectra which suggested an equatorial orientation of the 8β-ester group in (**15**) [δ 4.04 (t, *J* 10 Hz, 9-H), 3.27 (dd, *J* 12 and 5 Hz, 7-H_{eq}), and 2.57 (t, *J* 12 Hz, 7-H_{ax})], and an axial configuration of the 8α-ester group in (**16**) [δ 3.86 (br dd, *J* 11 and 4 Hz, 9-H), 3.48 (dd, *J* 12 and 3 Hz, 7-H_{eq}), and 2.47 (dd, *J* 12 and 3 Hz, 7-H_{ax})].

Dehydration of the epimeric esters (**15**) and (**16**) was performed by heating with phosphoryl trichloride and 85% phosphoric acid in pyridine[11] to afford a mixture of the two epimeric unsaturated esters (**17**) and (**18**)* in identical ratios (3:1), with the 8β-ester (**17**) as the major product in 44—55% yield from the respective esters (**15**) and (**16**). Recrystallisation of the above mixture afforded the homogeneous 8β-ester (**17**), the n.m.r. and i.r. spectra of which were completely identical with those of the *N*-benzoate of methyl 2,3-dihydrolysergate presented by Ramage.[4c] However, attempts to isolate the 8α-ester (**18**) on h.p.l.c. was unsuccessful due to ready isomerisation to the 8β-ester (**17**) during the course of purification. Furthermore, the facts that the homogeneous 8β-ester (**17**) yielded a 3:1 mixture of two epimeric esters (**17**) and (**18**) upon being heated in methanol and that the same 3:1 mixture was formed during the course of purification of compound (**17**) supported the isomerisability of the respective esters (**17**) and (**18**) to afford the equilibrium mixture as reported by Rebek *et al.*[4e],† Furthermore, the n.m.r. peaks ascribable to the minor component (**18**) present in the 3:1 mixture completely correlate with those of the *N*-benzoate of methyl 2,3-dihydroisolysergate reported by Rebek *et al.*[4e],†

Since the 8β-ester (**17**) had already been converted into (±)-lysergic acid by Woodward *et al.*[4a] and Ramage *et al.*,[4c] the present work formally completed the synthesis of (±)-lysergic acid.

Selective removal of the *N*-benzoyl group from the 3:1 mixture of the two epimeric esters (**17**) and (**18**) was achieved by alkylation with triethyloxonium tetrafluoroborate[4e] followed by hydrolysis under mild acidic conditions to afford the indolines (**19**) and (**20**) in the ratio 5:2 in 55% combined yield. The n.m.r. spectra and the ratio of two isomers (**19**) and (**20**) were found to be identical with those of authentic samples reported by Ramage *et al.*[4c] Dehydrogenation of the above mixture of indolines (**19**) and (**20**) with benzene seleninic anhydride[10] furnished methyl (±)-lysergate (**21**) and methyl (±)-isolysergate (**22**), in the ratio 3:2 in 60% yield, which were separated by h.p.l.c. The respective isomers (**21**) and (**22**) were identical with natural alkaloids‡ on comparison of their n.m.r. spectra and R_F values; thus we had completed a novel total synthesis of (±)-lysergic acid.

Equilibrium and Stereochemical Study of the Unsaturated Esters (**17**)—(**22**).—Through our results in the synthesis of lysergic acid and its derivatives based on the synthetic route developed for their despyrrole analogues,[3] we have succeeded in the synthesis of eight compounds having analogous structures, *i.e.* a 9-ergolene-8-methyl ester and its despyrrole analogues, and this offers us a good opportunity of establishing their stereochemistry and of analysing the relationship between the isomerisation between respective epimers and their conformation, details of which have not been fully clarified even though a couple of syntheses of lysergic acid have been achieved.

By taking advantage of the fact that we possessed two pairs of epimers, we investigated the isomerisation of these 9-ergolene-8-carboxylates (**17**) and (**18**), and (**21**) and (**22**), and their despyrrole analogues (**23**) once we had isolated the respective epimers and had measured their n.m.r. spectra at 200 MHz.

As described above, the 8β-ester (**17**) and 8α-ester (**18**) underwent isomerisation in methanol to yield identical equilibrium (3:1) mixtures, with epimer (**17**) as the major component, which were detected by h.p.l.c. (Microporasil; 5% MeOH–CH_2Cl_2). This isomerisation mixture ratio coincided with that reported by Rebek *et al.*[4e], though Ramage *et al.*[4c] stated that the isomerisation only occurred with pure compound (**18**).†

Attempts to isolate a pair of epimers of the *N*-nor derivatives were unsuccessful due to their instability, though it has previously been recognised[4c,4e] that compounds (**19**) and (**20**) exist as an equilibrium mixture.

Methyl (±)-lysergate (**21**) and methyl (±)-isolysergate (**22**) were separated by h.p.l.c. using Microporasil in 3% MeOH–$CHCl_3$ and their structures were completely assigned by ^1H n.m.r. spectroscopy for the first time as described later in this

* Although the 8β-ester (**17**) was described as the sole product in the preliminary communication (ref. 2), the epimeric 8α-ester (**18**) was also detected by n.m.r. spectroscopy and h.p.l.c.

† Although the 8α-methyl ester (**18**) had been already synthesized both by Ramage *et al.*[4c] and Rebek *et al.*,[4e] their respective n.m.r. spectra and the equilibrium experiment results did not coincide. Comparison of the n.m.r. spectrum of an equilibrium mixture (3:1) of (**17**) and (**18**), which we prepared, with those reported by Professors Ramage and Rebek clearly established that the n.m.r. spectrum of compound (**18**) quoted by the latter should be correct.

‡ The samples were gifts from Dr. P. A. Stadler, Sandoz Ltd.

Table 1. ^{1}H N.m.r. data for methyl (±)-lysergate (**21**) in $CDCl_3$ (200 MHz)

	δ (*J* in Hz)	δ on irradiation (observation)
NH	7.95 (br)	
2-H	6.95 (t, *J* 2)	7.95 (lose *J* 2) 2.74 (lose *J* 2)
4-H_{eq}	3.55 (dd, *J* 14, 6)	3.24 (lose *J* 6) 2.74 (lose *J* 14)
4-H_{ax}	2.74 (ddd, *J* 14, 12, 2)	6.95 (lose *J* 2) 3.55 (lose *J* 14) 3.24 (lose *J* 12)
5-H	3.24 (m)	6.64, 3.77, 3.55, 2.74 (sharpening of peaks)
7-H_{eq}	3.31 (br dd, *J* 11, 5)	6.64 (sharpening of peaks; *J* 11, 5 apparent) 3.77 (lose *J* 5) 2.74 (change)[a]
7-H_{ax}	2.72 (t, *J* 11)	3.77 (lose *J* 11) 3.31 (lose *J* 11)
8-H	3.77 (m)	6.64, 3.31, 3.24 (sharpening of peaks) 2.74 (change)[a]
9-H	6.64 (br s)	3.77, 3.31, 3.24 (sharpening of peaks)
CO_2Me	3.80 (s)	
NMe	2.64 (s)	

[a] Irradiation at δ 2.74 (4-H_{ax}) changed the signal patterns of 8-H and 7-H_{eq} in addition to that of 4-H_{eq} as a result of double irradiations both at 4-H_{ax} and 7-H_{ax} (δ 2.72).

Table 2. ^{1}H N.m.r. data for methyl (±)-isolysergate (**22**) in $CDCl_3$ (200 MHz)

	δ (*J* in Hz)	δ on irradiation (observation)
NH	7.96 (br)	
2-H	6.92 (t, *J* 2)	7.96 (lose *J* 2) 2.75 (lose *J* 2)
4-H_{eq}	3.44 (dd, *J* 14, 5)	3.22 (lose *J* 5) 2.75 (lose *J* 14)[a]
4-H_{ax}	2.75 (ddd, *J* 14, 11, 2)	6.92 (lose *J* 2) 3.44 (lose *J* 14) 3.22 (lose *J* 11)
5-H	3.22 (m)	6.58, 3.44, 2.75 (sharpening of peaks)
7-H_{eq}	3.37 (m)[b]	6.58 (sharpening of peaks) 2.75 (change)[a]
7-H_{ax}	2.74 (m)	
8-H	3.32 (m)	6.58 (sharpening of peaks) 2.75 (change)[a]
9-H	6.58 (br, d, *J* 4)	3.22 (sharpening of peaks; *J* 4 apparent)
CO_2Me	3.74 (s)	
NMe	2.59 (s)	

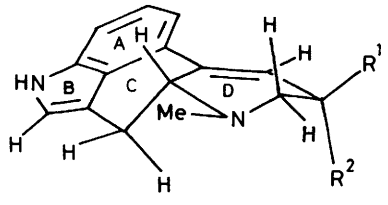
[a] Irradiation at δ 2.75 (4-H_{ax}) changed the signal patterns of 8-H and 7-H_{eq} in addition to that of 4-H_{eq} as a result of double irradiations both at 4-H_{ax} and 7-H_{ax} (δ 2.74). [b] The signal pattern of 7-H_{eq} was described as a broad doublet (*J* 12 Hz) in our recent paper (ref. 13).

paper. The respective epimers were each found to give an equilibrium mixture (3:2), with epimer (**21**) the major component, upon being heated in methanol.[12]

In addition to the results obtained from the despyrrole analogues (**23**) described in a previous paper,[13] the results given in this paper would indicate that, as a generalisation, isomerisation of the 8-ester group in the ergoline and benzo[*f*]quinoline derivatives is relatively easy in methanol and leads to the respective equilibrium mixtures. Additionally, it was also found that all the 8β-esters, (**17**), (**19**), and (**21**), have larger R_f values than their 8α-ester counterparts, (**18**), (**20**), and (**22**), on h.p.l.c., thus providing a convenient method for their identification.

Then we analysed the n.m.r. spectra of methyl (±)-lysergate (**21**) and methyl (±)-isolysergate (**22**). As a result of the spin-decoupling experiments on the n.m.r. spectrum of methyl (±)-lysergate (**21**), the following assignments of signals as summarised in Table 1 were reached.

Bailey and Grey had reported[14] a detailed study of the conformation of *NN*-dimethyl-lysergamide and *NN*-dimethyl-isolysergamide by n.m.r. spectroscopy. Upon taking these results into consideration, the present assignments for the esters (**17**)—(**20**) allowed us to suggest that methyl (±)-lysergate (**21**) has its C and D rings in the half-chair form as shown in Figure 2.



(**21**) $R^1 = CO_2Me$, $R^2 = H$

(**22**) $R^1 = H$, $R^2 = CO_2Me$

Figure 2.

The reasons for the above conclusion are as follows; we observed an allylic coupling between 2-H and 4-H_{ax}, thus suggesting a *ca.* 90° dihedral angle between these two hydrogens, the signal for 4-H_{eq} appearing at much lower field than that for 4-H_{ax} by virtue of its being almost coplanar with ring B. The observation of an allylic coupling between 5-H and 9-H would suggest a near perpendicular orientation of 5-H with respect to the double bond at the 9,10-position. Further, it has been shown that methine hydrogens in structurally related fragments which are *gauche* to the nitrogen lone pair are deshielded by about 0.6—0.8 p.p.m. relative to those orientated *trans*-axially which are found at δ *ca.* 3.2.[15] Therefore, the chemical shift of 5-H, δ 3.24, suggests its *trans*-axial orientation to the nitrogen lone pair. Such an arrangement can only be realised if ring D exists in that half-chair conformation in which C-5, -10, -9, and -8 are more or less in the same plane. As a result, C-7 is situated above this plane on the same side as 5-H while the nitrogen and its lone pair are directed below. The existence of a long-range W-shaped coupling between 7-H_{eq} and 9-H suggests the half-chair conformation of the ring D where two hydrogens, 7-H_{eq} and 9-H, are in the same plane.

Furthermore, the *pseudo*-equatorial orientation of the 8-methyl ester group is also suggested from the following data; there are couplings with *J* 5 Hz between 7-H_{eq} and 8-H and *J* 11 Hz, between 7-H_{ax} and 8-H, a homoallylic coupling between 5-H and 8-H, and a small coupling with *J ca.* 1 Hz between 8-H and 9-H.

The above conclusion on the conformation of methyl (±)-lysergate (**21**) coincided with that proposed by Stoll *et al.*[16] for lysergic acid.

Next, we carried out a spin-decoupling analysis on the n.m.r. spectrum of methyl (±)-isolysergate (**22**). As shown in Table 2, the chemical shifts of all the protons are assigned. However, the chemical shift of 8-H appeared very close to that of 7-H_{eq} and the signal for 7-H_{ax} overlapped with that of 4-H_{ax}, thus rendering the mutual coupling constants between 8-H, 7-H_{ax}, and 7-H_{eq} indeterminable. In addition, the very close chemical shifts of 5-H and 8-H made the existence of a homoallylic coupling uncertain. On the other hand, the chemical shifts of 2-H, 4-H, and 5-H and their signal patterns are very similar to those observed for compound (**21**) and similar allylic couplings are observed between 2-H and 4-H_{ax}, and 5-H and 9-H as for (**21**). In particular, the almost identical chemical shift of 5-H, δ

Table 3. ^{1}H N.m.r. data (δ; *J* in Hz) for compounds (**17**)—(**22**) in $CDCl_3$ (200 MHz)

	(17)	(18)[a]	(19)[c]	(20)[c]	(20)[a]	(21)	(22)
2-H_β	4.34 (br)	4.60—4.10 (m)	3.82—3.60 (m)		3.67 (t, *J* 7)	6.95[d] (t, *J* 2)	6.92[d] (t, *J* 2)
2-H_α	3.70 (t, *J* 10)	3.67 (t, *J* 11)	3.46—3.10 (m)		3.31—3.10 (m)		
3-H	3.42 (m)	3.45—3.30 (m)					
4-H_{eq}	2.57 (m)	2.51 (d, J 6.8)[b]	2.62—2.43 (m)		2.52 (d, *J* 5)[b]	3.55 (dd, *J* 14, 6)	3.44 (dd, *J* 14, 5)
4-H_{ax}	1.40 (q, *J* 12)	1.41 (q, *J* 11.7)	1.43 (q, *J* 12)	1.42 (q, *J* 12)	1.42 (q, *J* 11.5)	2.74 (ddd, *J* 14, 12, 2)	2.75 (ddd, *J* 14, 11, 2)
5-H	3.04 (br d, *J* 12)	2.89 (br dd, *J* 11.7, 2)	3.05 (br d, *J* 12)	2.89 (br d, *J* 12)	2.90 (br dd, *J* 11.5, 2.5)	3.24 (m)	3.22(m)
7-H_{eq}	3.28 (br dd, *J* 11.5, 6)	3.45 (d, *J* 11.7)	3.46—3.10 (m)	3.45 (br d, *J* 12)	3.44 (d, *J* 12)	3.31 (br dd, *J* 11, 5)	3.37 (m)
7-H_{ax}	2.69 (t, *J* 11.5)	2.58 (dd, *J* 11.7, 5)	2.70 (t, *J* 12)	2.62—2.43 (m)	2.57 (dd, *J* 12, 4.7)	2.72 (t, *J* 11)	2.74 (m)
8-H	3.68 (m)	3.18 (br t)	3.82—3.60 (m)	3.46—3.10 (m)	3.31—3.10 (m)	3.77 (m)	3.32(m)
9-H	6.55 (br s)	6.55 (d, *J* 3.2)	6.60—6.48 (m)		6.53–6.49 (m)	6.64 (brs)	6.58 (br d, *J* 4)
CO_2Me	3.76 (s)	3.74 (s)	3.77 (s)	3.74 (s)	3.72 (s)	3.80 (s)	3.74 (s)
NMe	2.51 (s)	2.48 (s)	2.53 (s)	2.50 (s)	2.52 (s)	2.64 (s)	2.59 (s)

[a] We assigned the respective protons from the data reported by Rebek *et al.*[4e] [b] Reported[4e] signal patterns are different from the expected ones. [c] Assigned from the n.m.r. spectrum of a mixture of compounds (**19**) and (**20**) in the ratio 5:2. [d] Signal for 2-H.

3.22, with that in compound (**21**), δ 3.24, and the existence of a long-range W-shaped coupling between 9-H and 7-H_{eq} can only be explained by assuming a conformation for compound (**22**) as shown in Figure 2. Therefore, the 8-methyl ester group would take a *pseudo*-axial orientation as supported by the coupling constant of 4 Hz between 8-H and 9-H. Furthermore, the above conclusion on the conformation of methyl (±)-isolysergate (**22**) coincides with that proposed by Stoll *et al.*[16] for isolysergic acid.

Based upon the assignment of the n.m.r. spectra of compounds (**21**) and (**22**), we then compared the spectra of compound (**17**) and the mixture of esters (**19**) and (**20**). Though Rebek *et al.*[4e] have isolated compounds (**18**) and (**20**) and described the chemical shifts and signal patterns of the peaks, they have not assigned the respective peaks. Therefore, upon comparison of the n.m.r. spectra of compounds (**21**) and (**22**), we have succeeded in the assignment of the respective peaks as summarised in Table 3.

It is clear that the n.m.r. spectra, particularly the chemical shifts and the signal patterns of protons in ring D, which is the common structural moiety in the compounds compared in this study, are very similar depending on the type of compound, as shown by the 8β-esters (**17**), (**19**), and (**21**), and the 8α-esters (**18**), (**20**), and (**22**).

Thus, we conclude that all these compounds have the same conformation under the conditions of the measurements and further we assigned the orientation of the substituents as follows. The orientation of the 8-ester group would not have any effect on the chemical shift of 9-H but would alter its signal pattern. Thus the signal for 9-H, which was coupled with 8-H, appeared as a broad singlet in the spectrum of the 8β-ester, while it appeared as a broad doublet, *J* 3—4 Hz, in the spectrum of the 8α-ester. In addition the n.m.r. signals for the methyl protons in the ester moiety and the N–CH_3 group appear at slightly higher field in the 8α-esters than in the 8β-esters.

In conclusion, the stereostructures of the epimers, including the orientation of the ester group at C-8, can now be deduced from the n.m.r. behaviour of three proton groups, *i.e.*, of the olefinic proton 9-H, and the methyl protons of the methyl ester at C-8 and the N–CH_3 group.

Experimental

^{1}H N.m.r. spectra were measured with JEOL PMX-60 and Varian XL-200 instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference), i.r. spectra for solutions in chloroform with a Hitachi 215 spectrophotometer, and mass spectra with a Hitachi M-80 machine. H.p.l.c. was carried out on a Waters Associates instrument with a u.v. detector at 254 nm using a Microporasil column (30 cm × 7.8 mm i.d.). M.p.s were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixtures were washed with water and dried over anhydrous sodium sulphate. The photochemical reactions were carried out by irradiation at 4—10 °C with a high-pressure mercury lamp (300 W) (Eikosha PIH-300). Ether refers to diethyl ether.

N-(1-*Benzoyl*-1,2,2a,3-*tetrahydrobenz*[cd]*indol*-4-*yl*)-N-*methylfuran*-3-*carboxamide* (**2**).—Anhydrous methylamine gas was bubbled into a boiling solution of 1-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-4-(5*H*)-one (**1**)[6] (2 g) in benzene (200 ml) under a nitrogen stream for 5 h; water was removed as it formed. The mixture was refluxed further to remove the excess of methylamine by the bubbling nitrogen. To the resulting ice-cooled, stirred solution were added dropwise triethylamine (1 g) and then a solution of freshly prepared furan-3-carbonyl chloride (1.13 g) in anhydrous benzene (30 ml). After being refluxed for 2 h the mixture was ice-cooled and diluted with benzene, washed, and dried. The solvent was removed under reduced pressure and the residue was recrystallised from methanol–ether to afford the *enamide* (**2**) (2.66 g, 96%), m.p. 130—131 °C; $\nu_{max.}$ 1 640—1 620 cm^{-1} (2NCO); δ (*inter alia*) 6.45 (1 H, br s, 5-H) and 3.27 (3 H, s, NMe) (Found: C, 74.8; H, 5.15; N, 7.45. $C_{24}H_{20}N_2O_3$ requires C, 75.0; H, 5.25; N, 7.3%).

Reductive Photocyclisation of the Enamide (**2**).—A solution of a mixture of the enamide (**2**) (1.5 g) and sodium borohydride (1.5 g) in benzene–methanol (5:1; 900 ml) was irradiated for 3 h. The reaction mixture was washed, dried, and evaporated to give a viscous oil which was triturated with ethanol to afford crystals (1.22 g, 81%). These were found to be a mixture of three lactams (**3**), (**4**), and (**5**) in the proportions 10:4:1 by h.p.l.c. [1 500 p.s.i.; 5% MeOH–MeCN (0.4 ml min^{-1}); (**3**) R_t 45.6 min; (**4**) R_t 49.6 min; (**5**) R_t 48.8 min]. Repeated recrystallisation of the crystals from methylene dichloride–ethyl acetate afforded pure (3aβ,5aβ,6aβ,11bα,11cβ)-8-benzoyl-5,5a,6,6a,7,8,11b,11c-*octahydro*-5-*methylfuro*[3,2-c]*indolo*[4,3-fg]*quinolin*-4(3aH)-

one (**3**) (813 mg, 54%), m.p. 204—206 °C; $\nu_{max.}$ 1 660—1 620 cm^{-1} (2NCO); δ (*inter alia*) 6.46 (1 H, t, *J* 2 Hz, 2-H), 5.37 (1 H, t, *J* 2 Hz, 3-H), 4.88 (1 H, dd, *J* 11 and 10 Hz, 11c-H), 4.44 (1 H, br, 7-H_β), 3.87 (1 H, dt, *J* 11 and 2 Hz, 3a-H), 3.76 (1 H, t, *J* 12 Hz, 7-H_α), 3.63 (1 H, br dd, *J* 12 and 10 Hz, 5a-H), 3.40 (1 H, m, 6a-H), 3.08 (3 H, s, NMe), 3.03 (1 H, t, *J* 10 Hz, 11b-H), 2.68 (1 H, br d, *J* 12 Hz, 6-H_{eq}), and 1.68 (1 H, q, *J* 12 Hz, 6-H_{ax}); *m/z* 386 (M^+) (Found: C, 72.95; H, 5.8; N, 7.05. $C_{24}H_{22}N_2O_3 \cdot \frac{1}{3}AcOEt$ requires C, 73.2; H, 6.0; N, 6.75%). The residue obtained from the mother liquor was chromatographed on silica gel. The first fraction eluted with chloroform gave (3aβ,5aβ,6aα,11bα,11cβ)-8-*benzoyl*-5,5a,6,6a,7,8,11b,11c-*octahydro*-5-*methylfuro*[3,2-c]-*indolo*[4,3-fg]*quinolin*-4(3aH)-*one* (**5**) (81 mg, 5%), m.p. 250—252 °C (decomp.) (from methylene dichloride–ethyl acetate); $\nu_{max.}$ 1 660—1 620 cm^{-1} (2NCO); δ (*inter alia*) 6.38 (1 H, t, *J* 2 Hz, 2-H), 5.33 (1 H, t, *J* 2 Hz, 3-H), 5.10 (1 H, t, *J* 10 Hz, 11c-H), 4.52 (1 H, br, 7-H_α), 4.17 (1 H, dt, *J* 10 and 2 Hz, 3a-H), 3.73 (1 H, t, *J* 10 Hz, 7-H_β), 3.60 (1 H, m, 6a-H), 3.28 (1 H, q, *J* 10 Hz, 5a-H), 3.00 (3 H, s, NMe), 2.97 (1 H, t, *J* 10 Hz, 11b-H), and 2.38—2.02 (2 H, m, 6-H_2); *m/z* 386 (M^+) (Found: C, 74.3; H, 5.75; N, 7.25. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.75; N, 7.25%). The second fraction eluted with chloroform gave (3aβ,5aα,6aα,11bα,11cβ)-8-*benzoyl*-5,5a,6,6a,7,8,11b,11c-*octahydro*-5-*methylfuro*[3,2-c]-*indolo*[4,3-fg]*quinolin*-4(3aH)-one (**4**) (325 mg, 22%), m.p. 219—221 °C (from methylene dichloride–ethyl acetate); $\nu_{max.}$ 1 660—1 620 cm^{-1} (2NCO); δ (*inter alia*) 6.41 (1 H, t, *J* 3 Hz, 2-H), 5.34 (1 H, t, *J* 3 Hz, 3-H), 4.59 (1 H, t, *J* 10 Hz, 11c-H), 4.38 (1 H, br, 7-H_α), 3.85 (1 H, dt, *J* 10 and 3 Hz, 3a-H), 3.74 (1 H, t, *J* 11 Hz, 7-H_β), 3.66 (1 H, m, 5a-H), 3.43 (1 H, m, 6a-H), 3.30 (1 H, dd, *J* 10 and 6 Hz, 11b-H), 3.10 (3 H, s, NMe), 2.38 (1 H, m, 6-H_{eq}), and 1.55 (1 H, q, *J* 12 Hz, 6-H_{ax}); *m/z* 386 (M^+) (Found: M^+, 386.1637. $C_{24}H_{22}N_2O_3$ requires *M*, 386.1629).

(3aβ,5aβ,6aβ,11bα,11cβ)-8-*Benzoyl*-3a,4,5,5a,6,6a,7,8,11b,11c-*decahydro*-5-*methylfuro*[3,2-c]*indolo*[4,3-fg]*quinoline* (**7**).—To an ice-cooled solution of the C/D-*trans*-lactam (**3**) (970 mg) in anhydrous ether–tetrahydrofuran (THF) (1:2; 150 ml) was added lithium aluminium hydride (970 mg) in small portions. The mixture was refluxed under a nitrogen stream for 2 h. Usual work-up afforded the *N*-debenzoylated amine (**6**) [$\nu_{max.}$ 3 400 cm^{-1} (NH); δ (*inter alia*) 4.85 (1 H, t, *J* 2.5 Hz, 3-H) and 2.40 (3 H, s, NMe)], which was without further purification rebenzoylated by refluxing in benzene (95 ml) with benzoyl chloride (640 mg) in the presence of triethylamine (500 mg) to afford the N-*benzoate* (**7**) [688 mg, 74% from (**3**)], m.p. 187—189 °C (decomp.) (from benzene–ether); $\nu_{max.}$ 1 640 cm^{-1} (NCO); δ (*inter alia*) 6.47 (1 H, br s, 2-H), 4.98 (1 H, br s, 3-H), 4.68 (1 H, t, *J* 10 Hz, 11c-H), 4.34 (1 H, br, 7-H_β), 3.68 (1 H, t, *J* 11 Hz, 7-H_α), 3.44—3.22 (2 H, m, 3a- and 6a-H), 3.14 (1 H, dd, *J* 13 and 7 Hz, 4-H_{eq}), 3.14 (1 H, t, *J* 10 Hz, 11b-H), 2.60 (1 H, dd, *J* 13 and 4 Hz, 4-H_{ax}), 2.46 (3 H s, NMe), 2.42 (1 H, m, 6-H_{eq}), 2.22 (1 H, td, *J* 10 and 2 Hz, 5a-H), and 1.43 (1 H, q, *J* 10 Hz, 6-H_{ax}) (Found: C, 77.5; H, 6.45; N, 7.65. $C_{24}H_{24}N_2O_2$ requires C, 77.4; H, 6.5; N, 7.5%). Similar reduction of a mixture of the C/D-*trans*- and *cis*-lactams (**3**) and (**4**) (5:1; 970 mg) with lithium aluminium hydride gave a mixture of the corresponding *N*-debenzoylated amines (**6**) and (**8**), which were also rebenzoylated as described above and separated by column chromatography on silica gel to afford the *N*-benzoate (**7**) (569 mg, 61%) and (3aβ,5aα,6aα,11bα,11cβ)-8-*benzoyl*-3a,4,5,5a,6,6a,7,8,11b,11c-*decahydro*-5-*methylfuro*[3,2-c]-*indolo*[4,3-fg]*quinoline* (**9**) (83 mg, 9%), m.p. 172—174 °C (decomp.) (from benzene); $\nu_{max.}$ 1 640 cm^{-1} (NCO); δ (*inter alia*) 6.43 (1 H, br s, 2-H), 4.94 (1 H, br s, 3-H), 4.46 (1 H, t, *J* 10 Hz, 11c-H), 4.36 (1 H, br, 7-Hα), 3.70 (1 H, t, *J* 10 Hz, 7-Hβ), 3.48 (1 H, m, 3a-H), 3.42—3.22 (2 H, m, 6a- and 11b-H), 2.92 (1 H, ddd, *J* 11, 7, and 3 Hz, 6-H_{eq}), 2.79 (2 H, d, *J* 8 Hz, 4-H_2), 2.50 (3 H, s, NMe), 2.22 (1 H, br d, *J* 11 Hz, 5a-H), and 1.44 (1 H, q, *J* 11 Hz, 6-H_{ax}) (Found: M^+, 372.1843. $C_{24}H_{24}N_2O_2$ requires *M*, 372.1837).

Hydroxylation of the N-*Benzoate* (**7**).—(*a*) To a solution of the *N*-benzoate (**7**) (600 mg) and pyridine (1 ml) in anhydrous THF (15 ml) was added a solution of osmium tetraoxide (410 mg) in anhydrous THF (3 ml) at −30 °C. The reaction mixture was kept at −30 °C for 2 h, and then the solvent was evaporated off to give a solid which was washed with ether and dissolved in methylene dichloride–ethanol (1:1; 20 ml). Hydrogen sulphide was bubbled vigorously into the solution at 0 °C for 1 min and the black precipitate was removed by filtration. The filtrate was evaporated and the residue was crystallised from methanol–ether to give a mixture of two *cis*-glycols (**10**) in the ratio 3:2 (347 mg, 53%); $\nu_{max.}$(Nujol) 3 370 (OH) and 1 640 cm^{-1} (NCO); δ[$(CD_3)_2SO$] (*inter alia*) 6.49 (0.6 H, d, *J* 5 Hz, OH), 6.25 (0.4 H, m, OH), 5.41 (0.6 H, d, *J* 5 Hz, OH), 5.16 (1 H, m, 2-H), 4.73 (0.4 H, d, *J* 6 Hz, OH), 2.24 (3 H, s, NMe), 1.97 (1 H, m, 5a-H), and 1.21 (1 H, br q, *J* 11.5 Hz, 6-H_{ax}); *m/z* 406 (M^+).

(*b*) A solution of osmium tetraoxide (1 mg) in t-butyl alcohol (0.5 ml) was added to a mixture of the *N*-benzoate (**7**) (480 mg), trimethylamine *N*-oxide dihydrate (195 mg), pyridine (0.1 ml), water (0.8 ml), and t-butyl alcohol (10 ml). After being refluxed under a nitrogen stream for 1 h, the solution was cooled and treated with 20% aqueous sodium hydrogen sulphite (50 ml). To the concentrated reaction mixture was added water and the precipitate thus formed was collected and washed successively with water and with methylene dichloride to give a mixture of two *cis*-glycols (**10**) in the ratio 3:2 (435 mg, 83%). This mixture was used in the next step without further purification.

(3β)-2,3-*Dihydroisofumigaclavine B* (**13**).*—A mixture of the glycols (**10**) (100 mg) and sodium metaperiodate (100 mg) in methanol–water (1:1; 80 ml) was stirred at room temperature for 1 h, and then sodium carbonate (100 mg) was added to the reaction mixture which was then stirred for a further 1 h. The reaction mixture was repeatedly extracted with methylene dichloride. The combined extracts were washed, dried, and evaporated to give the 9α-hydroxy-8β-aldehyde (**11**) [$\nu_{max.}$ 3 500 (OH), 1 720 (CHO), and 1 640 cm^{-1} (NCO); δ (*inter alia*) 9.80 (1 H, br s, CHO) and 2.35 (3 H, s, NMe)] which was without further purification dissolved in ethylene glycol (5 ml). To the resulting solution were added sodium hydroxide (40 mg) and hydrazine hydrate (0.5 ml). The mixture was then refluxed under a nitrogen stream for 30 min. The reaction mixture was diluted with water and repeatedly extracted with methylene dichloride. The combined extracts were washed, dried, and evaporated to give a residue which was purified by p.l.c. on silica gel to afford the 8β-*methyl*-9α-*ol* (**13**) (30 mg, 47%), m.p. 182—183 °C (decomp.) (from benzene); $\nu_{max.}$(Nujol) 3 330 cm^{-1} (NH); δ 7.41 (1 H, d, *J* 8 Hz, 12-H), 7.01 (1 H, t, *J* 8 Hz, 13-H), 6.56 (1 H, d, *J* 8 Hz, 14-H), 3.66 (1 H, m, 2-H_β), 3.34 (1 H, t, *J* 10 Hz, 9-H), 3.22—3.10 (2 H, m, 2-H_α and 3-H), 2.99 (1 H, dd, *J* 12 and 4.5 Hz, 7-H_{eq}), 2.82 (1 H, t, *J* 10 Hz, 10-H), 2.46—2.38 (1 H, m, 4-H_{eq}), 2.40 (3 H, s, NMe), 2.28 (1 H, br t, *J* 11 Hz, 5-H), 2.18 (1 H, t, *J* 12 Hz, 7-H_{ax}), 2.00 (1 H, m, 8-H), 1.44 (1 H, q, *J* 11 Hz, 4-H_{ax}), and 1.06 (3 H, d, *J* 7 Hz, CMe) (Found: M^+, 258.1756. $C_{16}H_{22}N_2O$ requires *M*, 258.1731).

Oxidation of the glycols (**10**) (100 mg) with sodium metaperiodate (53 mg) as described above but without treatment with sodium carbonate gave a mixture of two epimeric aldehydes (**11**) and (**12**) in the ratio *ca.* 1:1 [$\nu_{max.}$ 3 500 (OH), 1 720 (CHO), and 1 640 cm^{-1} (NCO); δ (*inter alia*) 9.80 (0.5 H, br s, β-CHO), 9.67 (0.5 H, br s, α-CHO), and 2.35 (3 H, s, NMe)]. Wolff–Kishner reduction of this mixture gave the 8β-methyl-9α-

* Ergoline-type numbering is used for compounds (**11**)—(**20**).

ol (**13**) (25 mg, 40%) as the sole product which was identical with that obtained above.

(±)-*Isofumigaclavine B* (**14**).—(*a*) To a solution of the 8β-methyl-9α-ol (**13**) (18 mg) in chloroform (10 ml) was added manganese dioxide (40 mg). The mixture was stirred at room temperature for 18 h and was then filtered and the residual solid was washed thoroughly with chloroform. The combined chloroform layers were evaporated to give a residue which was purified by p.l.c. on silica gel to afford (±)-*isofumigaclavine B* (**14**) (8 mg, 45%), m.p. 271—273 °C (decomp.) (from methanol) [lit.,[9a] 222—224 °C (sublimed.); lit.,[9b] 278—282 °C (decomp.)]; $\nu_{max.}$(Nujol) 3 495 cm^{-1} (NH); δ ($CDCl_3$–CD_3OD) 7.65 (1 H, d, *J* 8 Hz, 12-H), 7.20 (1 H, d, *J* 8 Hz, 14-H), 7.11 (1 H, t, *J* 8 Hz, 13-H), 6.92 (1 H, d, *J* 1.5 Hz, 2-H), 3.54 (1 H, t, *J* 10 Hz, 9-H), 3.41 (1 H, dd, *J* 14 and 4 Hz, 4-H_{eq}), 3.03 (1 H, t, *J* 10 Hz, 10-H), 2.96 (1 H, dd, *J* 12 and 4 Hz, 7-H_{eq}), 2.79 (1 H, ddd, *J* 14, 11, and 1.5 Hz, 4-H_{ax}), 2.53 (3 H, s, NMe), 2.44 (1 H, ddd, *J* 11, 10, and 4 Hz, 5-H), 2.18 (1 H, t, *J* 12 Hz, 7-H_{ax}), 2.00 (1 H, m, 8-H), and 1.13 (3 H, d, *J* 7 Hz, CMe). The i.r. and n.m.r. spectra and R_F values of (±)-(**14**) were found to be identical with those of natural isofumigaclavine B[9] (Found: M^+, 256.1571. $C_{16}H_{20}N_2O$ requires *M*, 256.1574).

(*b*) A solution of the 8β-methyl-9α-ol (**13**) (10 mg) and benzeneseleninic anhydride (7.2 mg) in THF (1 ml) was stirred at 40 °C under a nitrogen stream for 2 h. After being diluted with methylene dichloride, the solution was washed successively with aqueous sodium carbonate and water, dried, and evaporated to give a residue which was purified by p.l.c. on silica gel to afford (±)-isofumigaclavine B (**14**) (5 mg, 50%).

Methyl (3β,8β,9α)-1-*Benzoyl*-2,3-*dihydro*-9-*hydroxy*-6-*methylergoline*-8-*carboxylate* (**15**).—To a stirred, ice-cooled solution of the homogeneous 9α-hydroxy-8β-aldehyde (**11**), which was prepared from the glycols (**10**) (200 mg), in methanol–acetone (1:4; 50 ml) was added dropwise a solution (0.5 ml) of 4.0M-chromium trioxide–sulphuric acid in water. The mixture was stirred at 0 °C for 1 h. The precipitate thus formed was filtered and washed with methylene dichloride. The filtrate was washed successively with aqueous sodium carbonate and water. Upon removal of the solvent, the solid obtained was purified by column chromatography on silica gel to give the 9α-*hydroxy*-8β-*methyl ester* (**15**) (75 mg, 38%), m.p. 226—228 °C (from methanol); $\nu_{max.}$ 1 720 (CO_2Me) and 1 630 cm^{-1} (NCO); δ 7.83 (1 H, br d, *J* 8 Hz, 12-H), 7.66—6.90 (7 H, m, ArH), 4.36 (1 H, m, 2-H_β), 4.04 (1 H, t, *J* 10 Hz, 9-H), 3.78 (3 H, s, OMe), 3.65 (1 H, t, *J* 10.5 Hz, 2-H_α), 3.40 (1 H, m, 3-H), 3.27 (1 H, dd, *J* 12 and 5 Hz, 7-H_{eq}), 2.98 (1 H, ddd, *J* 12, 10, and 5 Hz, 8-H), 2.80 (1 H, t, *J* 10 Hz, 10-H), 2.57 (1 H, t, *J* 12 Hz, 7-H_{ax}), 2.42 (3 H, s, NMe), 2.40 (2 H, m, 5-H and 4-H_{eq}), and 1.47 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: C, 71.05; H, 6.45; N, 6.95. $C_{24}H_{26}N_2O_4$ requires C, 70.9; H, 6.45; N, 6.9%).

Oxidation of an Epimeric Mixture of the Aldehydes (**11**) *and* (**12**).—A mixture of the epimeric aldehydes (**11**) and (**12**) (*ca.* 1:1), which was prepared by metaperiodate oxidation of the glycols (**10**) (290 mg) according to the procedure given above but without sodium carbonate treatment, was oxidised with chromium trioxide as described above. Separation of the crude product by p.l.c. on silica gel afforded the 9α-hydroxy-8β-ester (**15**) (33 mg, 11%) and *methyl* (3β,8α,9α)-1-*benzoyl*-2,3-*dihydro*-9-*hydroxy*-6-*methylergoline*-8-*carboxylate* (**16**) (40 mg, 14%), m.p. 195—197 °C (from ethyl acetate); $\nu_{max.}$ 1 710 (CO_2Me) and 1 630 cm^{-1} (NCO); δ 7.90 (1 H, br d, *J* 8 Hz, 12-H), 7.64—6.90 (7 H, m, ArH), 4.24 (1 H, m, 2-H_β), 3.86 (1 H, br dd, *J* 11 and 4 Hz, 9-H), 3.80 (3 H, s, OMe), 3.64 (1 H, t, *J* 12 Hz, 2-H_α), 3.48 (1 H, dd, *J* 12 and 3 Hz, 7-H_{eq}), 3.35 (1 H, m, 3-H), 3.17 (1 H, t, *J* 10 Hz, 10-H), 3.01 (1 H, m, 8-H), 2.47 (1 H, dd, *J* 12 and 3 Hz, 7-H_{ax}), 2.40 (1 H, m, 4-H_{eq}), 2.35 (3 H, s, NMe), 2.12 (1 H, br t, *J* 10 Hz, 5-H), and 1.41 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: M^+, 406.1911. $C_{24}H_{26}N_2O_4$ requires *M*, 406.1891).

Dehydration of the 9α-*Hydroxy*-8β-*ester* (**15**).—To a solution of the 9α-hydroxy-8β-ester (**15**) (42 mg) in anhydrous pyridine (1 ml) was successively added 85% phosphoric acid (0.01 ml) and phosphoryl trichloride (0.2 ml).[11] The solution was warmed at 60 °C under a nitrogen stream for 45 min. The reaction mixture was poured into ice–water, made alkaline by the addition of aqueous sodium carbonate solution, and extracted with methylene dichloride. The organic layer was washed, dried, and evaporated. Purification of the residue by p.l.c. on silica gel gave a solid (22 mg, 55%) which was found to be a mixture of two epimers (**17**) and (**18**) in the ratio 3:1 by h.p.l.c. [1 500 p.s.i.; 5% MeOH–CH_2Cl_2 (0.5 ml min^{-1}): (**17**) R_t 50 min; (**18**) R_t 42.8 min]. Recrystallisation of the solid from ethyl acetate afforded homogeneous methyl (3β)-1-benzoyl-1,2-dihydrolysergate (**17**), m.p. 165—168 °C (lit.,[4c] 165—168 °C); $\nu_{max.}$ 1 725 (CO_2Me) and 1 640 cm^{-1} (NCO). The i.r. and n.m.r. spectra are superimposable with those of the authentic sample reported by Ramage *et al.*[4c] and Rebek *et al.*[4e]

From the n.m.r. spectrum of the equilibrium mixture (**17**) and (**18**) (3:1), the following peaks were assignable for methyl (3β)-1-benzoyl-2,3-dihydroisolysergate (**18**): δ 3.74 (s, OMe), 2.89 (br d, *J* 12 Hz, 5-H), 2.48 (s, NMe), and 1.41 (q, *J* 12 Hz, 4-H_{ax})]. These peaks were found to coincide with those which were present in the n.m.r. spectrum of compound (**18**) reported by Rebek *et al.*[4e]

Each isomer gave the same equilibrium mixture in methanol [(**17**):(**18**) 3:1].

Dehydration of the 9α-*Hydroxy*-8α-*ester* (**16**).—A mixture of the 9α-hydroxy-8α-ester (**16**) (40 mg), anhydrous pyridine (1 ml), 85% phosphoric acid (0.01 ml), and phosphoryl trichloride (0.2 ml) was worked up in the same manner as given for the dehydration of compound (**15**) to give a mixture of compounds (**17**) and (**18**) (17 mg, 44%) in the same ratio (3:1) as described for the dehydration of the 9α-hydroxy-8β-ester (**15**).

Methyl (3β)-2,3-*Dihydrolysergate* (**19**) *and Methyl* (3β)-2,3-*Dihydroisolysergate* (**20**).—To a solution of an epimeric mixture of the esters (**17**) and (**18**) (3:1; 20 mg) in methylene dichloride (4 ml) were added successively sodium carbonate (10 mg) and excess of triethyloxonium tetrafluoroborate at room temperature under a nitrogen stream. After being stirred for 18 h, the reaction mixture was treated with 5% hydrochloric acid (20 ml) for 15 min, neutralised with saturated aqueous sodium hydrogen carbonate, and extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by p.l.c. on silica gel to afford a solid mixture of debenzoylated esters (**19**) and (**20**) (8 mg, 55%) in the ratio 5:2, $\nu_{max.}$ 3 400 (NH) and 1 730 cm^{-1} (CO_2Me). The i.r. and n.m.r. spectra and the ratio of the two isomers (**19**) and (**20**) are identical with those of the authentic sample reported by Ramage *et al.*[4c] This mixture was used in the next step without further purification.

Methyl (±)-*Lysergate* (**21**) *and Methyl* (±)-*Isolysergate* (**22**).—A solution of an epimeric mixture of the esters (**19**) and (**20**) (5:2; 5 mg) and benzeneseleninic anhydride (3 mg) in THF (1 ml) was stirred at 40 °C under a nitrogen stream for 2 h. Usual work-up as in the manner given for compound (**14**) afforded a mixture of methyl (±)-lysergate (**21**) and methyl (±)-isolysergate (**22**) (3 mg, 60%) in the ratio 3:2 (Found: M^+, 282.1389. $C_{17}H_{18}N_2O_2$ requires *M*, 282.1368). This mixture was separated by h.p.l.c. [800 p.s.i.; 3% MeOH–$CHCl_3$ (0.8 ml min^{-1})]: methyl (±)-lysergate: R_t 35.2 min, methyl (±)-isolysergate: R_t 32.8 min. The n.m.r. spectra of (**21**) and (**22**) are

superimposable with those of natural methyl lysergate and methyl isolysergate respectively. Each isomer gave the same equilibrium mixture in methanol [(**21**):(**22**) 3:2].

Equilibrium Experiments.—Two solutions, one of methyl (±)-lysergate (**21**) (1 mg) and the other of methyl (±)-isolysergate (**22**) (1 mg) in methanol (1 ml each), were refluxed under a nitrogen stream. After 3 h, the reaction mixtures were found to isomerise to an equilibrium mixture of these two esters with identical ratio (3:2) with methyl (±)-lysergate (**21**) the major product. The ratio was not changed even after prolonged refluxing.

The isolated 8β-ester (**17**) was also isomerised in a similar manner as above to give an equilibrium mixture of the 8β-ester (**17**) and 8α-ester (**18**) in the ratio 3:1.

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