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A NEW SYNTHETIC ROUTE TO (±) LYSERGIC ACID[1]

R. RAMAGE†*, V. W. ARMSTRONG and S. COULTON
The Robert Robinson Laboratories, University of Liverpool, Liverpool L69 3BX, England

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Abstract A route to the synthesis of lysergic acid, **1** is described based on a mechanism proposed for the racemisation of lysergic acid and related compounds. The strategy involves cyclisation of the aminodienoic esters **19** and **22** to produce tetrahydropyridine systems. A modified Curtius degradation sequence is described.

Ergot is the product of the filamentous fungus *Claviceps purpurea* (Fries) Tulasne which grows parasitically on the rye plant and as early as the seventeenth century it was established[2-4] that ergot was responsible for epidemics known as St. Anthony's Fire. From historical survey it became clear that outbreaks of such epidemics followed wet and barren seasons when the flour of rye, infested by ergot, was used for bread manufacture. Of the two forms of the disease convulsive ergotism caused twitching and convulsions whilst gangrenous ergotism was characterised by violent burning pains in the limb which often resulted in amputation. Although the adverse results of the pharmacological activity of ergot alkaloids have long been known, as well as the more recent recognition of the hallucinatory properties of lysergic acid diethylamide,[5] it is important to remember that ergot alkaloids exhibit a broad and useful spectrum of pharmacological properties. The positive pharmacological importance of ergot alkaloids was first recognised during the Middle Ages and led to introduction of crude preparations of ergot into medical practice for induction of uterine contractions.

During the twentieth century isolation and structural elucidation of the components of ergot have led to the identification of two main classes of ergot alkaloids,[6,7] one of which is based on the structure of lysergic acid **1**[8-10] and is constituted of amides having the following representative structures: ergine **2**, ergonovine **3**, and a series of peptide alkaloids having the general formula **5**. The naturally occurring alkaloids are known in isomeric pairs which differ only in the stereochemistry at C-8. This epimerisation may be accomplished by either acid or alkali and it is of significance that the constituents of fresh ergot are optically active and belong to the pharmacologically active 8β-series. The acidity of the C-H bond at C-8 also plays an important role in the chemistry and stability of lysergic acid and its derivatives. Careful stereochemical arguments based on hydrogenation studies,[11,12] as well as the transformation of both lysergic and isolysergic acids by hot acetic anhydride into the same lactam **10**,[9] showed that isolysergic acid **6** is epimeric at C-8 but retains the same configuration at C-5 as in lysergic acid **1**. The absolute configurations of the two acids were elucidated by both optical rotary dispersion[13] and degradative methods.[14] In 1974 the conjugated acid, **8**, was isolated[15] from saprophytic cultures of a strain of *Claviceps paspali* (Stevens and Hall) whereupon it was established[16] that this isomer could be transformed easily by alkaline treatment into lysergic acid **1** in which the olefinic bond is preferentially conjugated with the indole system rather than the carbonyl function. From a biosynthetic standpoint[17] it is interesting to note that free lysergic acid **1** is never found in large quantities whereas paspalic acid **8** occurs abundantly in certain *Claviceps* strains.

The retrosynthetic planning which controlled our approach to the synthesis of *racemic* lysergic acid **1** was founded upon the observation[18] that both (+)-lysergic acid **1** and (+)-isolysergic acid **6** could be converted into *racemic* lysergic acid **1** by barium hydroxide in aqueous solution at high temperatures. Further evidence of the stereochemical lability of the lysergic system is to be found in the formation of the *racemic* hydrazide **7** by hydrazine treatment of the natural alkaloids having the general structure **5**.[19] These two observations involve loss of stereochemical integrity at both the C-5 and C-8 positions which is at first sight surprising since only the carboxyl function at C-8 would be expected to undergo the epimerisation which relates **1** and **6**. In order to rationalise the epimerisation at the apparently unactivated C-5 position Woodward proposed[20] that the racemisation process proceeded through the achiral tricyclic intermediate **9** which could be formed by retro-Michael fragmentation of **1**, **6** or **8**. Since the postulated intermediate **9** is achiral, any subsequent cyclisation of the amino function by Michael addition to the dienoic acid system to form ring D must produce racemic products which would be epimeric at C-8. It has to be assumed that the isolation of (±)-lysergic acid **1** and the (±)-hydrazide **7** is due to the equilibria in these reactions being displaced by the greater insolubility of the β- and α- epimers of these compounds respectively under the reaction conditions employed. The failure to isolate (±)-paspalic acid **8** from the cyclisation of intermediate **9** can be explained by the aforementioned facile equilibration of **8** to lysergic acid **1** as a consequence of their relative thermodynamic stabilities. A major consideration in favour of the intermediacy of **9** is that such a structure

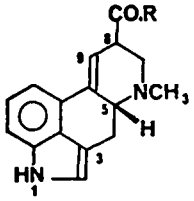
†Dedicated to the late Prof. R. B. Woodward with whom it was both a privilege and a pleasure to be associated in research.

*Present address: Department of Chemistry, UMIST, Manchester M60 1QD

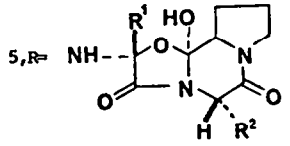
would be chemically stable towards hydrolytic cleavage under the alkaline reaction conditions. Alternative mechanisms involving imonium intermediates would be expected to yield hydrolysis products during the prolonged alkaline treatment leading to racemisation. It is significant to note, in the context of the racemisation mechanism proposed by Woodward, that the alternative mode of cleavage of ring D in lysergic acid **1** is responsible for the formation of the chiral methylene lactam **10** from **1** and **6** on treatment[9] with acetic anhydride by a path which probably proceeds *via* the chiral intermediate **11**.

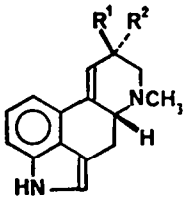
Thus if the elegant explanation put forward by Woodward for the facile racemisation of lysergic acid **1** is correct then it follows that synthesis of the intermediate **9** would, in fact, produce (±)-lysergic acid **1** by spontaneous cyclisation. In order to circumvent the anticipated problems associated with indole-naphthalene tautomerism in **9** it was decided to aim for the modified target **19** which has the masked indolic system employed in the two preceding synthesis[21,22] of (±)-lysergic acid **1** in which the final stage involves oxidation of the indoline system of **30**. The first[21] total synthesis of this important substance was achieved in 1955 by a collaboration of Woodward and the Eli Lilly group. In the course of this classical work a route to the aldehyde **12** was developed, which we have optimised to allow satisfactory production of this key intermediate for the synthesis of **19**. After abortive attempts to synthesise a phosphorane capable of reacting with **12** to give **19** directly it was decided to utilise the readily accessible reagent **13**[22] and introduce the amino function later by selective degradation of a carboxylic acid group using the Curtius degradative procedure.

The stereochemistry of the olefinic double bond formed in the Wittig reaction involving the phosphorane **13** should lead to the *E*-configuration required for the projected synthesis by analogy with the work of House[24] who showed that Wittig reactions involving resonance stabilised ylides afford the predominant stereoisomer having the carbonyl function *trans* to the larger group at the β-position. Reaction of **13** with benzaldehyde afforded **34** as the sole isolated product, the NMR spectrum of which exhibited a 1 H resonance at 7.38 δ consistant with that expected[25] for the β-proton deshielded by the adjacent *cis* ester function. Furthermore reaction of **12** with carbomethoxymethylenetriphenylphosphorane gave the dienoic ester **35** in which the acyclic proton β- to the ester function was found in the NMR spectrum to be deshielded into the aromatic region in accordance with the *E*- configuration shown. The complementary part of the AB system (J = 16 Hz) due to the acyclic

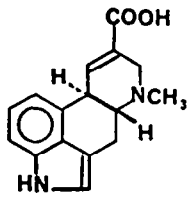


1, R=OH
2, R=NH2
3, R=NH.CH(Me).CH2OH
4, R=NH.CH(Et).CH2OH





1; R¹=COOH, R²=H
6; R¹=H, R²=COOH
7; R¹=H, R²=CO.NHNH2



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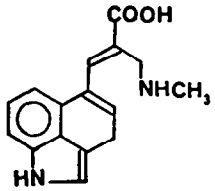

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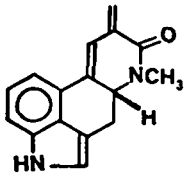

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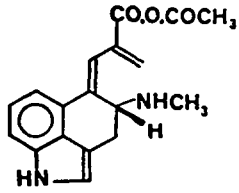

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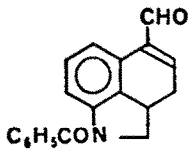

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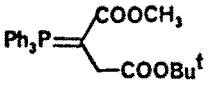

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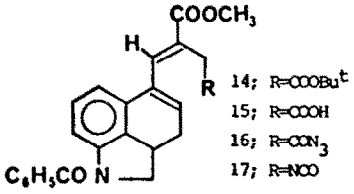
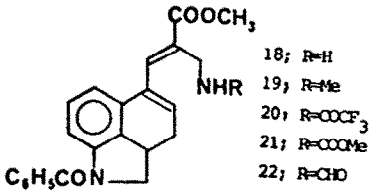
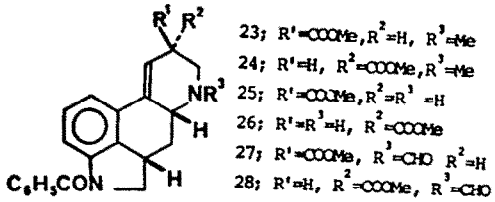


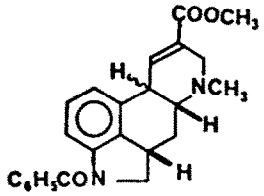
14; R=COOBu^t
15; R=COOH
16; R=CON$_3$
17; R=NCO



18; R=H
19; R=Me
20; R=COCF$_3$
21; R=COOMe
22; R=CHO



23; R'=COOMe, R^2=H, R^3=Me
24; R'=H, R^2=COOMe, R^3=Me
25; R'=COOMe, R^2=R^3=H
26; R'=R^3=H, R^2=COOMe
27; R'=COOMe, R^3=CHO R^2=H
28; R'=H, R^2=COOMe, R^3=CHO



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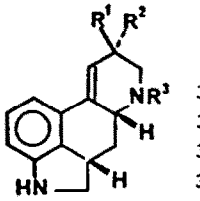


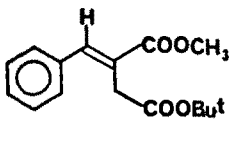
30; R'=COOMe, R^2=H, R^3=Me
31; R'=H, R^2=COOMe, R^3=Me
32; R'=COOMe, R^2=R^3=H
33; R'=R^3=H, R^2=COOMe

proton α to the ester group can be observed approximately 1.2 ppm upfield at 6.35 δ together with the olefinic proton of the tricyclic system. As expected for such a diene, **35** reacted smoothly with 4-phenyl-1,2,4-triazoline-3, 5-dione to give a Diels Alder adduct in almost quantitative yield. Two isomers were formed in the ratio of 9:1 and these were easily separated due to the insolubility of the minor isomer. Consideration of molecular models and the Woodward Hoffmann[26] selection rules strongly indicate that the major isomer has the relative stereochemistry represented in **36** arising from attack of the azo-dienophile from the α-face of the diene system. This allows ring D of the pentacyclic structure to adopt a boat conformation enabling maximum overlap of the π-orbitals in the styrene system which is a consequence of the C H bonds at C-3 and C-5 being *cis* and quasi axial. The same argument has been invoked by the Sandoz researchers[27] in the course of structural assignment of 2,3-dihydrolysergic acid (+)-butanolamide, which is produced by Zn/HCl reduction of the indole ring in the corresponding lysergic acid derivative **4**. As a result of these considerations we would assign the structure **37** to the minor Diels Alder product. It can readily be seen that this synthetic approach could lead to the interesting 7-aza-lysergic system with judicious choice of the azo-dienophile component for reaction with **35**.

The reaction between **12** and **13** was found to be slow but could be induced to give the required diester **14** in 79% yield using benzene/t-butanol (1:1) as solvent at reflux for 4 days. Only one isomer, as indicated by NMR, hplc and tlc analysis was isolated in which the acyclic olefinic double bond may be assigned the *E*-configuration, since the acyclic olefinic proton resonance was observed together with the aromatic protons in the region 6.7–7.8 δ in accord with the chemical shifts quoted for the reference compounds **34** and **35**. With the diester **14** in hand the next task was to effect the transformation to the intermediate **19** required for the crucial cyclisation to the tetracyclic products **23**, **24** and **29**. After acidolytic cleavage of the t-butyl ester function produced the corresponding acid **15**, the introduction of the amino function was accomplished by the Curtius degradation procedure in overall yield of 80%. This optimisation was the result of many preliminary experiments in which the acid azide formation was investigated using carboxyl activation as the acid chloride or carbonic mixed anhydride with either sodium azide or tetramethylguanidinium azide,[28] or directly using diphenylphosphonic azide,[29] The selected conditions employed tetramethylguanidinium azide and the diphenylphosphinic mixed anhydride[30] in CH_2Cl_2. Thermal rearrangement of the acid azide **16** to the isocyanate **17**

proceeded smoothly in refluxing benzene, however it was anticipated that hydration of the isocyanate and decarboxylation of the resulting carbamic acid under the usual aqueous acid conditions would cause untoward hydrolytic side reactions. In order to avoid this occurring, it was decided to effect the acid catalysted hydration using *p*- toluenesulphonic acid monohydrate in anhydrous medium on the premise that the reatent contains sufficient water for hydration and that the subsequent decarboxylation step would be driven by formation of the amine salt. This result was realised by performing the reaction in benzene/ether as solvent, whereupon the *p*-toluenesulphonate of **18** crystallised from the reaction mixture.

The free amine **18** was found to be exceedingly reluctant to cyclise to the tetracyclic compounds, however this result did not cause undue anxiety that the corresponding secondary amine **19** might also be recalcitrant when called upon to cyclise since the work of Harley-Mason[31] on the oxidative cyclisation of a series of substituted dopamines **38** to the bicyclic quinones **39** showed the secondary amines to be vastly superior in this respect. Indeed it was possible to prepare derivatives of the amine **18** such as the trifluoroacetamide **20** and the urethane **21** which were also found to exist as the tricyclic structures in which the N-H IR absorption was particularly diagnostic. If the Woodward hypothesis is a correct representation of the mechanism of lysergic acid racemisation then it follows that any methylation method which produces the secondary amine **19**, however transiently, should afford the 2,3-dihydrolysergic system as a result of spontaneous cyclisation. The method selected for the purpose was the Eschweiler-Clarke reaction using HCOOH/HCHO involving hydride reduction of the intermediate imonium species. Although this would normally be expected to give the dimethylated amine it was found that the intermediate secondary amine preferred to cyclise rather than undergo the second methylation step. This reaction gave 62% yield of three tetracyclic isomers in the ratio 9:3:2 which were assigned the structures **23**, **24** and **29** respectively. Hydrogenation of these compounds in methanol using 10% Pd/C indicated that only one olefinic double bond was present and, therefore, that the products were tetracyclic. A combination of crystallisation and chromatography allowed a separation of the components of the mixture, although the minor isomer **29** could not be isolated in pure form due to contamination with **24** as a result of rearrangement induced by silica chromatography. The major products **23** and **24** exhibited IR CO absorption bands corresponding to saturated ester functions and the UV spectra were in agreement with that expected for the 2,3-dihydrolysergic system.[27] Although both major isomers clearly incorporated an olefinic proton, as indicated by the NMR spectra, it was noteworthy that the signals in **23** (6.52 δ) and **24** (6.19 δ) were consistent with known lysergic and isolysergic analogues. The relative stereochemical assignments at C-8 were clarified by equilibration studies using conditions which are known to favour methyl lysergate over methyl isolysergate.[16] It was found that **24** could be epimerised to **23** in refluxing MeOH whereas, under the same conditions, **23** was unchanged. The relative configuration at C-3 and C-5 are determined during the cyclisation of **13**, and, under thermodynamic control, it is to be expected that the developing π-overlap between the 9, 10 double bond and the



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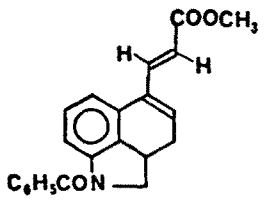

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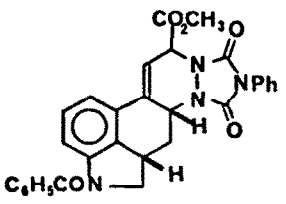

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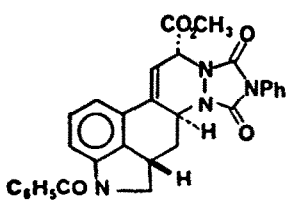

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38 39

aromatic ring should be the dominant factor in product development. This would result in the C-3 and C-5 C–H bonds being *cis* as represented in **23** and **24**. Stadler *et al.*[27] have used the same argument for the relative stereochemistry at C-3 and C-5 in the 2,3-dihydrolysergic system; in their case the C-3 sp^3 stereochemistry was introduced relative to C-5.

The minor product **29** arising from the cyclisation of **19** exhibited the expected IR absorption at 1708 cm^{-1} attributed to the conjugated ester function compared with **23** (1728 cm^{-1}) and methyl lysergate (1728 cm^{-1}). The assignment of the $\Delta^{8,9}$ double bond was also supported by comparison of the UV spectra, the NMR signal due to the 9-H deshielded by the COOMe group to 7.37 δ, and the finding that **29** underwent facile rearrangement to the $\Delta^{9,10}$ isomer **24**. This latter observation is consistent with the known propensity[16] of paspalic acid **8** to rearrange to lysergic acid **1**. The relative stereochemistry at C-3 and C-5 in **29** is the same as in **23** and **24**, however, the assignment at C-10 is not certain.

The mixture of **23** and **24** was treated with HCl in MeOH to afford a mixture of methyl 2,3-dihydrolysergate **30** and the 8α-epimer, **31** in the ratio 5:2. Methanolysis of the N-benzoyl group of **23** or **24** separately gave the same mixture of **30** and **31** which was found to be identical in all respects with material used in the first synthesis of lysergic acid **1**.[21] Although this had been thought to be solely the 8β-epimer **30**, the mixture of epimers could be detected only by NMR, and hplc; two techniques not available to the researchers in 1955. Accurate mass fragmentation data on **23** and **30**/**31** exhibited an important ion corresponding to P-C_2H_5N which would result from retro-Diels Alder fragmentation of ring D. Since the intermediate methyl 2,3-dihydrolysergate **30** together with the 8α-epimer **31** have previously been transformed into lysergic acid **1** by Kornfeld *et al.*[21] the route described above not only constitutes a synthesis of lysergic acid but also lends support to Woodward's proposal about the racemisation mechanism and, additionally, helps to rationalise the greater thermal and photochemical stability of the 9,10-dihydro series of lysergic acid derivatives.

In order to extend this synthetic route based on cyclisation of **19** other derivatives of the parent amine **18** were prepared. As stated previously the trifluoroacetamide **20** and the urethane **21** did not cyclise to tetracyclic structures analoguous to **23**, however formylation of the primary amine **18** using formic acetic mixed anhydride gave the mixture of isomers **27** and **28** which could be separated by fractional crystallisation. The tetracyclic nature of the products was substantiated by hydrogenation with 10% Pd/C to afford dihydro compounds which could be compared readily with the product derived by hydrogenation and formylation of **18**. Support for the structures **27** and **28** was afforded by the IR data which lacked the NH absorption expected for **22**, which would be a tricyclic product of similar type to **20** and **21**, but did exhibit an absorption at 1725 cm^{-1} due to the saturated ester functions of cyclised products. The NMR spectrum of the epimeric mixture of **27** and **28** displayed singlets due to the formyl protons at 8.16 and 8.21 δ in addition to the important olefinic resonances at 6.28 and 6.50 δ due to the vinyl proton at C-9 in the two epimers. The absence of signals due to the N–H proton and the associated characteristic 2 H doublet at 4.2 δ of the methylene protons adjacent to the non-indoline nitrogen in tricyclic structures such as **20** and **21** further supports the tetracyclic structure as opposed to **22**. Further evidence for the structures **27** and **28** was given by the UV maxima at 251 and 304 nm which are consistant with that expected for the 2,3-dihydrolysergic system.[16] Having obtained the tetracyclic N-formyl derivatives it was hoped to methanolyse selectively the formamide function to give both epimeric secondary amines **25**/**26** which would then allow structural modification specifically at N-6.[32] Unfortunately this could only be accomplished in low yield; the major product being the *bis*-secondary amine as a mixture of 8α and 8β epimers **32** and **33** which were isolated as the mixture of bis-hydrochlorides. This route to the lysergic system through N-formylation and cyclisation of intermediates derived from **18** has great potential for producing a range of N-alkylated derivatives of lysergic acid which would be of considerable pharmacological interest.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined using a Unicam SP200 and UV spectra obtained using a Unicam SP800 spectrometer. Mass spectra were obtained from AEI MS12 and MS902 instruments (the latter with an on-line computer). NMR spectra were measured using Varian HA100, XL100 spectrometers. Hplc was carried out using a Waters ALC204 machine with a Model 440 UV detector and M660 solvent gradient system.

1-*Benzoyl*-5-*formyl*-1,2,2*a*,3-*tetrahydrobenz*[cd]*indole*[21], **12**. To MeCN (320 ml) at 58° were added the Na salt of 1-benzoyl-5-carboxymethyl-α, 5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole[21] (16.0 g, 44.8 mmole) and pyridinium hydrobromide perbromide (14.4 g, 45 mmole). The stirred mixture was illuminated for 15 min with a 750 watt lamp, and then cooled to 40° without illumination. A soln of semicarbazide HCl (14.98 g, 134.3 mmole) and $NaOAc.3H_2O$ (7.39 g, 54.33 mmole) in H_2O (30 ml) was added then the mixture stirred at 40° for 3 hr. The solvent was removed *in vacuo* followed by addition of H_2O (350 ml) and filtration. The crude solid product was washed with H_2O then digested with hot MeOH, Et_2O and dried to give the semicarbazone of **12** (12.2 g, 79%), m.p. 227–9° (lit.[21] m.p 231–2°).

The semicarbazone of **12** (26.5 g, 76.6 mmole) was suspended in $CHCl_3$ (332 ml) and on addition of freshly distilled MeCO.COOH (102.5 g, 1.16 mmole) and *p*-toluenesulphonic acid H_2O (0.265 g, 1.39 mmole) soln was attained. After addition of H_2O (26.5 ml) the soln was stirred at 25° for 18 hr. The precipitated solid was filtered and washed with $CHCl_3$, then the $CHCl_3$ filtrate was washed with H_2O (3x), sat. $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the crude aldehyde **12** which was digested with hot MeOH, filtered then washed with MeOH, Et_2O and dried to give **12** (20.7 g, 94%) m.p. 177–179° (lit.[21], 179.5–180.5°) which was identical with authentic material.

t-Butyl-3-*methoxycarbonyl*-4-*phenyl*-3-*propenate*, **34**. Distilled PhCHO (0.41 g, 3.87 mmole) was added to **13**[23] (2.0 g, 4.46 mmole) in dry t.BuOH under N_2 atmosphere. After 48 h reflux the solvent was removed *in vacuo* leaving crude product which was chromatographed on grade III alumina (60 g). Elution with benzene–40/60 petroleum ether (4:1) gave the diester which crystallised from hexane (0.97 g, 87%) m.p. 55–6°; ν_{max}($CHCl_3$) 1700, 1720, 1640 cm^{-1}; λ_{max}(EtOH) 267 nm (ε 15,800); ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H) 3.47 (s, 2 H), 3.79 (s, 3 H), 7.32 (s, 5 H), 7.83 (s, 1 H) (Found: C, 69.77; H, 7.54. $C_{16}H_{20}O_4$ Requires: C, 69.54; H, 7.33%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonylethylene*)*benz*[*cd*]*indole*, **35**. A soln of **12** (15.0 g, 52 mmole) and methoxycarbonylmethylenetriphenylphosphorane (17.37 g, 52 mmole) in dry benzene (1.3 l) was refluxed under N_2 for 18 hr. The soln was concentrated to 30 ml *in vacuo* then chromatographed on grade III alumina (1 kg). Elution with benzene gave the product **35** which was crystallised from EtOAc 60/80 petroleum ether (7.50 g, 42%); m.p. 131 3°; ν_{max} ($CHCl_3$) 1705, 1635, 1615 cm^{-1}; λ_{max}(EtOH) 250 nm (ε 29,000); ^1H NMR ($CDCl_3$) δ 7.0–7.8 (9 H, m), 6.2–6.5 (2 H, m), 4.41 (1 H, m), 3.75 (3 Hs), 3.3–3.9 (2 H, m) 2.0 2.9 (2 H, m); *m/e* 345.1362 - $C_{22}H_{19}NO_3$ (−1 ppm), 286.1208 $C_{20}H_{16}NO$ (−8 ppm), 240.1017 $C_{15}H_{14}NO_2$ (−3 ppm) (Found: C, 76.49; H, 5.47; N, 4.18. $C_{22}H_{19}NO_3$ Requires: C, 76.50; H, 5.55; N, 4.06%).

4-*Phenyl*-1,2,4-*triazoline*-3,5-*dione adducts*, **36**/**37**. The ester **35** (6.0 g, 17.4 mmole) and 4-phenyl-1, 2,4-triazoline-3,5-dione (3.05 g, 17.4 mmole) were dissolved in dry acetone (11) and the soln refluxed under N_2 for 2 hr. During this time the deep red soln became colourless and the solvent was removed *in vacuo* to give a white solid which was digested in EtOAc and filtered to afford two isomeric adducts (8.28 g, 92%) in the ratio 9:1. Crystallisation from EtOAc effected separation of the soluble isomer **36**, m.p. 263–6°, ν_{max}($CHCl_3$) 1775, 1750, 1720, 1640, 1610, 1595 cm^{-1}; λ_{max}(EtOH) 228 (ε 24550), 245 (ε 23, 443), 305 (ε 4898) nm; ^1H NMR ($CDCl_3$) δ 7.0 7.8 (13 H, m), 6.35 (1 H, dd, J = 5), 5.26 (1 H, dd, J = 5), 4.45 (2 H, m), 3.77 (3 H, s), 1.2–3.9 (4 H, m). (Found: C, 68.89; H, 4.52; N, 10.46. $C_{30}H_{24}N_4O_5$ Requires: C, 69.22; H, 4.65; N, 10.76%). The least soluble isomer was extremely insoluble hence a comparable spectral analysis could not be obtained for **37**, m.p. 295°; ν_{max}(Nujol) 1762, 1735, 1700, 1642, 1590 cm $^{-1}$; *m/e* 520 $-C_{30}H_{24}N_4O_5$.

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-2′-*t*-*butyloxycarbonylmethylethylene*)*benz*[*cd*]-*indole*, **14**. A soln of **13** (56.0 g, 12.5 mmole) in dry benzene/t-BuOH (1:1; 480 ml) was added to a suspension of **12** (24.2 g, 8.35 mmole) in dry benzene/t-BuOH (1:1; 300 ml) and the mixture refluxed under N_2 for 4 days. After removal of the solvent *in vacuo* the residue was dissolved in benzene and washed with 2 N HCl, H_2O, sat. $NaHCO_3$, then dried ($MgSO_4$). Concentration of the solution *in vacuo* followed by chromatography on silica (2 kg). Elution with benzene/EtOAc (9:1) gave an oil which crystallised from EtOAc–60/80 petroleum ether to afford **14** (26.11 g, 79%) m.p. 162–4°; ν_{max} ($CHCl_3$) 1710, 1640, 1620, 1600 cm^{-1}; λ_{max}(EtOH) 235 (ε 26, 303), 254 (ε 26, 915) nm; ^1H NMR ($CDCl_3$) δ 6.7–7.7 (9 H, m), 6.05 (1 H, br. d), 4.4 (1 H, m), 3.4 3.9 (2 H, m), 3.80 (3 H, s), 3.34 (2 H, s), 2.0–2.9 (2 H, m), 1.44 (9 H, s); *m/e* 459.2067 $C_{28}H_{29}NO_5$ (+5 ppm), 403.1433—$C_{24}H_{21}NO_5$ (+3 ppm), 105.0342—C_7H_5O (+2 ppm) (Found: C, 73.00, H, 6.28; N, 3.08. $C_{28}H_{29}NO_5$ Requires: C, 73.18; H, 6.36; N, 3.05%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-2′-*carboxymethylethylene*)*benz*[*cd*]*indole*, **15**. The diester **14** (10.0 g, 24.8 mmole) in 90% TFA (100 ml) was allowed to stand for 2 hr at 25° then diluted with benzene (100 ml). After removal of the solvent *in vacuo* the crude product was azeotroped with benzene (3x) then dissolved in benzene and extracted with sat.$NaHCO_3$ (2x). The aqueous extracts were combined, washed with benzene and acidified with 2 N HCl. After extraction of the product with $CHCl_3$ (2x), the organic solution was dried ($MgSO_4$) and evaporated *in vacuo* to give a crude product which on crystallisation from MeOAc/Et_2O (1:1) afforded **15** (7.73 g, 88%) m.p. 175–7°; ν_{max}($CHCl_3$) 2500–3500, 1710, 1610, 1590 cm^{-1}; λ_{max} (EtOH) 254 (ε 26, 915) nm; ^1H NMR ($CDCl_3$) δ 9.80 (1 H, br.s), 6.7–7.7 (9 Hm), 6.04 (1 H, br. d), 4.40 (1 H, br. m), 3.5–3.9 (2 H, m), 3.74 (3 H, s), 3.45 (2 H, s), 2.0 2.8 (2 H, m); ^{13}C NMR δ 28.4 (t), 33.8, 33.9 (t), 52.2 (q), 58.7 (t), 118.1 (d), 127.2, 127.4, 128.5, 129.5, 130.5, 130.8, 131.3, 132.7 (s), 138.9 (d), 140.7 (s), 167.2 (s), 168.9 (s), 175.0 (s); *m/e* 403.1438—$C_{24}H_{21}NO_5$ (+4 ppm), 385.1298 $C_{24}H_{19}NO_4$ (−4 ppm), 372.1259—$C_{23}H_{18}NO_4$ (+6 ppm), 358.1472 $C_{23}H_{20}NO_3$ (+8 ppm), 344.1254—$C_{22}H_{18}NO_3$ (−10 ppm) (Found: C, 71.57; H, 5.40, N, 3.53. $C_{24}H_{21}NO_5$ Requires: C, 71.45; H, 5.25; N, 3.47%).

p-*Toluenesulphonate salt of* 1-*benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2-*methoxycarbonyl*-2′-*aminomethylethylene*)*benz*[*cd*]*indole* **18**. The acid **15** (4.0 g, 9.94 mmol) was dissolved in CH_2Cl_2 (250 ml) and cooled to −20°. N-methylmorpholine (1.02 g, 9.94 mmole) and diphenylphosphinyl chloride (2.56 g, 10.82 mmole) were added to the mixture which was then stirred at −20° for 30 min. Tetramethylguanidinium azide (1.86 g, 11.76 mmole) in dry CH_3CN (20 ml) was added to the mixture which was then stirred at 0° for 90 min. The mixture was then poured on to ice-water and the organic layer separated and dried ($MgSO_4$). Removal of the solvent *in vacuo* at 25° gave **16** as a yellow oil, ν_{max} (film) 2150, 1710, 1640 cm^{-1}.

The acid azide was dissolved in dry benzene (50 ml) and refluxed under N_2 for 1 hr. Removal of the solvent *in vacuo* afforded **17** as a yellow oil, ν_{max} (film) 2250, 1705, 1640 cm^{-1}.

The isocyanate was then dissolved in dry benzene (200 ml) and stirred at 25° for 16 hr with a soln of *p*-toluenesulphonic acid, H_2O (1.90 g, 10 mmole) in a minimum volume of dry Et_2O. During this time the product crystallised from the soln to give the *p*-toluenesulphonate of **18** (4.30 g, 80%), m.p. 166–170 ν_{max} (KBr) 2700–3300, 1730, 1640, 1620, 1600 cm^{-1}; λ_{max} (EtOH) 234 (ε 16, 982), 255 (ε 18, 621) nm; ^1H NMR (TFA) δ 6.9 8.2 (15 H, m), 6.26 (1 H, br. s), 6.05 (1 H, br. d), 4.03 (3 H, s), 3.6 4.5 (5 H, m), 2.42 (3 H, s), 2.6 3.2 (2 H, m) (Found: C, 65.54; H, 5.64, N, 4.96. $C_{30}H_{30}N_2O_6S$ Requires: C, 65.92; H, 5.53, N, 5.12%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-2′-*trifluoroacetamidomethylethylene*)*benz*[*cd*]*indole*, **20**. The *p*-toluenesulphonate of **18** (275 mg, 0.50 mmole) was dissolved in pyridine/benzene (1:1, 20 ml) and stirred at 25° for 3 days with trifluoroacetic anhydride (1.49 mg, 0.71 mmole). After removal of the solvent *in vacuo* the residual oil was dissolved in CH_2Cl_2 and washed with 2N.HCl, H_2O then dried ($MgSO_4$). Removal of the solvent *in vacuo*, followed by crystallisation of the residue from EtOAc, gave **20** (127 mg, 54%), m.p. 200–3°; ν_{max} ($CHCl_3$) 3450, 1720, 1640, 1602, 1540. 1500 cm^{-1}; λ_{max} (EtOH) 253 (ε 21, 380) nm; ^1H NMR ($CDCl_3$) δ 6.8–7.8 (8 H, m), 6.73 (1 H, d, J = 8), 6.12 (1 H, br. d, J = 6), 5.03 (1 H, m), 4.32 (2 H, d, J = 6), 4.1–4.6 (1 H, m), 3.84 (3 H, s), 3.3–4.0 (2 H, m), 2.0–3.0 (2 H, m); *m/e* 470.1447—$C_{25}H_{21}N_2O_4F_3$ (−1 ppm), 105.0299—C_7H_5O (−39 ppm), HPLC (Corsasil II-500 p.s.i., 2 ml/min^{-1}, 100% $CHCl_3$) Rt = 18.4 min. (Found: C, 63.35; H, 4.25; N, 6.04, $C_{25}H_{21}N_2O_4F_3$ Requires: C, 63.83; H, 4.50, N, 5.95%).

1-*Benzoyl*-1,2,2*a*,3-*tetrahydro*-5-(2′-*methoxycarbonyl*-N-*methoxycarbonyl*-2′-*aminomethylethylene*)*benz*[*cd*]-*indole*, **21**. The isocyanate **17**, prepared from **15** (1.00 g, 2.49 mmole) as previously described, in dry benzene (125 ml) was treated with *p*-toluenesulphonic acid H_2O (475 mg, 2.5 mmole) in MeOH (10 ml). After 16 hr at 25° the solvent was removed *in vacuo* and the residue chromatographed on silica (30 g). Elution with benzene/EtOAc (4:1) yielded **21** (561 mg, 52%) m.p. 139–140° (crystallised from EtOAc/hexane); ν_{max} ($CHCl_3$) 3440, 1715, 1630, 1600, 1570 cm^{-1}; λ_{max} (EtOH) 255 (ε 29, 512) nm; ^1H NMR ($CDCl_3$) δ 6.9–7.7 (8 H, m), 6.74 (1 H, d, J = 7), 6.18 (1 H, br. s), 5.30 (1 H, br. s), 4.10 (2 H, d, J = 6) 3.78 (3 H, s), 3.56 (3 H, s) 3.3 4.6 (3 H, m) 2.0–3.0 (2 H, m); *m/e* 432.1698—$C_{25}H_{24}N_2O_5$ (+3 ppm), 358.1445—$C_{23}H_{20}NO_3$ (+1 ppm); HPLC (Microporasil 2000 p.s.i., 2.5 ml. min^{-1}, 10% Me CN in CH_2Cl_2) R = 1.9 min. (Found: C, 69.61; H, 5.55; N, 6.70. $C_{25}H_{24}N_2O_5$ Requires: C, 69.43; H, 5.59; N, 6.48%).

Methyl-1-*benzoyl*-2,3-*dihydrolysergate* **23**, *methyl*-1-*benzoyl*-2,3-*dihydroisolysergate* **25** *and* 1-*benzoyl*-2,3-*dihydro*-6-*methyl*-8-*carbomethoxy*-$\Delta^{8,9}$-*ergoline*, **29**. The *p*-toluenesulphonate salt of **18** (4.0 g, 7.31 mmole) was dissolved in CH_2Cl_2 (250 ml) and stirred with K_2CO_3 soln. The CH_2Cl_2 layer was separated, washed with H_2O and dried ($MgSO_4$) followed by removal of the solvent *in vacuo* to give **18** as an oil, which was dissolved in H.COOH (98%, 200 ml) and H.CHO soln (40%, 40 ml) and heated for 3 hr. After cooling, the

solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and 4 N NaOH. The CH_2Cl_2 layer was washed with H_2O then dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded an oil which was chromatographed over grade III alumina (80 g). Elution with benzene–EtOAc (4:1) gave an oil which was crystallised from EtOAc–hexane to give a mixture (1.76 g, 62%) of **23**, **24** and **29** (9:3:2). Slow crystallisation of this mixture from EtOAc gave **24**, m.p. 149–153°; ν_{max} ($CHCl_3$) 1733, 1633, 1610, 1580 cm^{-1}; λ_{max} 242 (ε 19,953), 305 (ε 4,766) nm; ^{1}H NMR ($CDCl_3$) δ 6.9–7.6 (8 H, m), 6.19 (1 H, br. s $W_{\frac{1}{2}}$ 6 Hz), 4.2–4.6 (2 H, m), 3.73 (3 H, s), 3.0–3.7 (5 H, m), 2.38 (3 H, s), 1.8–2.9 (2 H, m); *m/e* 388; hplc (Corasil II, 1000 p.s.i., 1.0 m. min^{-1}, 10% i-PrOH in CH_2Cl_2) Rt = 10.5 min. A soln of **24** in MeOH was refluxed under N_2 for 2 hr. HPLC and NMR indicated quantitative epimerisation to **23**.

The total mixture of **23** and **29** (1.5 g) was separated by preparative TLC (7% MeOH in $CHCl_3$; silica) to give **23**, m.p. 165–168 (crystallised from EtOAc); ν_{max} ($CHCl_3$) 1728, 1632, 1604, 1590, 1578 cm^{-1}; λ_{max} (EtOH) 253 (ε 38,900), 307 (ε 7,762) nm; ^{1}H NMR ($CDCl_3$) δ 6.8–7.7 (8 H, m), 6.52 (1 H, br. s, $W_{\frac{1}{2}}$ 6 Hz), 4.1–4.5 (1 H, br. m), 3.73 (3 H, s), 2.4–3.7 (7 H, m), 2.48 (3 H, s), 1.2–1.6 (1 H, q, J = 9 Hz), *m/e* 388.1756—$C_{24}H_{24}N_2O_3$ (−8 ppm), 345.1375—$C_{22}H_{19}NO_3$ (+3 ppm), 329.1620—$C_{22}H_{21}N_2O$ (+10 ppm), 105.0363 C_7H_5O (+22 ppm); HPLC (Corasil II, 1000 p.s.i., 1.0 ml min^{-1}, 10% i-PrOH in CH_2Cl_2) Rt = 10.5 min. (Found: C, 74.09; H, 6.11; N, 7.20. $C_{24}H_{24}N_2O_3$ Requires: C, 74.21; H, 6.23; N, 7.21%).

The $\Delta^{8,9}$-ergoline isomer **29**, which was isolated by preparative tlc, could not be obtained completely pure due to transformation on silica to **24**, exhibited the following characteristics m.p. 152–7 (crystallised EtOAc-hexane); ν_{max} ($CHCl_3$) 1708, 1635, 1607, 1598, 1576 cm^{-1}; λ_{max} (EtOH) 220, 292 nm; ^{1}H NMR ($CDCl_3$) δ 6.9–7.7 (8 H, m), 7.37 (1 H, d), 3.73 (3 H, s), 2.44 (3 H, s), 1.50 (1 H, t, J = 8 Hz); *m/e* 388.1791 $-C_{24}H_{24}N_2O_3$ (+1 ppm), 373.1536—$C_{23}H_{21}N_2O_3$ (−4 ppm), 345.1366—$C_{22}H_{19}NO_3$ (0 ppm), 329.1644 $C_{22}H_{21}N_2O$ (−3 ppm); HPLC (Corasil II, 1000 p.s.i., 1.0 ml min^{-1}, 10% i-PrOH in CH_2Cl_2) Rt = 6.0 min.

Hydrogenation of the mixture of isomers **23**, **24**, and **29** (100 mg) in MeOH (50 ml) using 10% Pd/C (50 mg) gave a dihydro- product (100 mg), *m/e* 390.1917 $C_{24}H_{26}N_2O_3$ (−7 ppm).

Methyl 2,3-dihydrolysergate, **30** *and methyl 2,3-dihydroisolysergate*, **31**. The epimeric mixture of **23** and **24** (500 mg, 1.29 mmole) was dissolved in dry MeOH (55 ml) containing conc.HCl (5 ml) and the soln refluxed under N_2 for 6 hr followed by removal of the solvent *in vacuo*. The residue was dried *in vacuo* over P_2O_5 for 16 hr, then dissolved in dry MeOH (20 ml) and a 2 M soln of HCl/MeOH (3.0 ml, 6 mmole). After 24 hr stirring under N_2 the solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and the minimum volume of sat. K_2CO_3 soln required for neutralisation whilst maintaining the soln at 0°. The CH_2Cl_2 layer was washed with H_2O and dried ($MgSO_4$) followed by evaporation *in vacuo* to give the crude product which crystallised from Et_2O to give a mixture of **30**, **31** in the ratio 5:2 (203 mg, 55%) m.p. 157–161°; ν_{max} ($CHCl_3$) 3500, 1730, 1615, 1600 cm^{-1}; λ_{max} 243 (ε 25,704), 318 (ε 2,291) nm; ^{1}H NMR ($CDCl_3$) δ 7.01 (2 H, m), 6.49 (2 H, m), singlets (3 H) at 3.74 (β-COOMe) and 3.71 (α-COOMe), 2.5–3.7 (9 H, m), singlets (3 H) at 2.53 and 2.50, 1.1–1.6 (1 H, m); *m/e* 284.1554—$C_{19}H_{20}N_2O_2$ (+10 ppm), 241.1098—$C_{16}H_{15}NO_2$ (−2 ppm), 225.1378 $C_{16}H_{15}N_2$ (−6 ppm), 182.0964 $C_{13}H_{12}N$ (−3 ppm); HPLC (Microporasil, 2000 p.s.i. 2.5 ml min^{-1}, 15% MeCN in CH_2Cl_2) Rt = 7.6 min. (minor isomer) and R = 9.0 min. (major isomer).

This product was identical in every respect with an authentic sample kindly supplied by Dr. E. C. Kornfeld and prepared by the first route[21] to lysergic acid.

Epimeric mixture of 1-benzoyl-2,3-dihydro-6-formyl-8-methoxycarbonyl-$\Delta^{9,10}$-ergolines, **27** *and* **28**. The free amine **18**, derived from the *p*-toluenesulphonate (1.2 g, 2.20 mmole), was treated with a soln of H.COOH (60 ml) and Ac_2O (21 ml) which had been precooled to 0°. After 1 hr at 0° followed by 16 hr at 25° the reaction was quenched by the addition of iced water (120 ml) and concentrated *in vacuo* to yield an oil. Crystallisation from EtOAc hexane gave the pure mixture (1:1) of **27** and **28** (768 mg, 87%), m.p. 236–239°; ν_{max}($CHCl_3$) 1725, 1670, 1655, 1610, 1595 cm^{-1}; λ_{max} (EtOH) 251 (ε 22,909), 304 (ε 5,129) nm; ^{1}H NMR ($CDCl_3$) δ singlets at 8.16 and 8.21 (1 H), 6.9–7.7 (8 H, m) doublets at 6.50 and 6.28 (1 H, J = 6), 4.54–5.00 (1 H, m), singlets at 3.72 and 3.74 (3 H), 3.1–4.5 (6 H, m), 1.6–2.6 (2 H, m); *m/e* 402.1558—$C_{24}H_{22}N_2O_4$ (−5 ppm), 105.0345—C_7H_5O (+5 ppm); HPLC (Corasil II, 1000 p.s.i., 1.5 ml min^{-1}, 3% i-PrOH in CH_2Cl_2) Rt = 5.1 min. (Found: C, 71.46; H, 5.46; N, 6.94. $C_{24}H_{22}N_2O_4$ Requires: C, 71.62; H, 5.51; N, 6.9%). The two epimers could be separated by fractional crystallisation from CH_2Cl_2/EtOAc. The most soluble epimer exhibited m.p. 208–233°; ^{1}H NMR ($CDCl_3$) δ 8.16 (1 H, s), 6.9–7.7 (8 H, m), 6.28 (1 H, d, J = 6 Hz), 4.71 (1 H, t, J = 10 Hz); 4.07–4.57 (1 H, m), 3.96 (1 H, d, J = 15 Hz), 3.74 (3 H, s), 3.23–3.85 (4 H, m), 1.7–2.5 (2 H, m).

The epimeric mixture **27**/**28** (500 mg, 1.24 mmole) in dry DMF (125 ml) was hydrogenated using 10% Pd–C (135 mg). After filtration and evaporation of the solvent *in vacuo* the residue was chromatographed over grade III alumina. Elution with CH_2Cl_2 gave a colourless oil which crystallised from EtOAc to give a mixture (3:3:1) of 3 isomers of 1-benzoyl-2,3-dihydro-6-formyl-8-methoxycarbonylergoline (352 mg, 70%) m.p. 214–6°; ν_{max} ($CHCl_3$) 1735, 1655, 1610, 1595 cm^{-1}; λ_{max} (EtOH) 261 (ε 13,490), 290 (ε 8,709) nm; ^{1}H NMR ($CDCl_3$) δ singlets at 8.45, 8.25 (minor) and 8.13 (1 H); *m/e* 404.1762 $C_{24}H_{24}N_2O_4$ (+6 ppm), 260.1069—$C_{18}H_{14}NO$ (−2 ppm), 149.0240—$C_8H_5O_3$ (1 ppm) (Found: C, 71.26; H, 6.13; N, 6.84. $C_{24}H_{24}N_2O_4$ Requires: C, 71.27; H, 5.98; N, 6.93%).

Bishydrochloride salt of 2,3-dihydro-8-methoxycarbonyl-$\Delta^{9,10}$-ergoline, **32**/**33**. The epimeric mixture of **27** and **28** (800 mg, 2.0 mmole) was dissolved in dry MeOH (88 ml) and conc. HCl (8 ml) and the soln refluxed under N_2 for 2 hr. The solvent was then removed *in vacuo* and the residue crystallised from MeOH–Et_2O to give the di-HCl salt of **32**/**33** (400 mg). A further quantity of product was obtained by esterification (MeOH–HCl) of the mother liquors to give a total yield of 560 mg (82%) m.p. > 205°; ν_{max} (KBr) 2300–3000, 1730, 1595, 1580 cm^{-1}; λ_{max} (EtOH) 253 (ε 10,000), 322 (ε 1,778) nm; ^{1}H NMR (TFA) δ 9.25 (2 H, br.) 7.56 (3 H, m), singlets at 6.86 and 6.52 (1 H), 3.93 (3 H, s), 3.5–4.8 (7 H, m), 1.9–3.1 (2 H, m); *m/e* (of free diamine) 270.1358 $C_{16}H_{18}N_2O_2$ (−4 ppm), 241.1104 $C_{15}H_{15}NO_2$ (0ppm), 211.1246—$C_{14}H_{15}N_2$ (+5 ppm) (Found: C, 54.78; H, 6.08; N, 8.19; Cl, 20.17. $C_{16}H_{20}N_2O_2Cl_2.0.5H_2O$ Requires: C, 54.55; H, 6.01; N, 7.95; Cl, 20.13%).

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