The Alkaloids
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Volume VII

CHAPTER 10

The Indole Alkaloids*

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* This material is supplementary to Volume II, Chapter 13.

I. Introduction

During the period that has elapsed since the publication of Volume II of this series, significant contributions have been made to our knowledge of almost all subgroups of Indole alkaloids, but the most important advances have been made in the field of the *Rauwolfia* alkaloids. In 1950 seven bases of unknown constitution had been isolated from *Rauwolfia serpentina* Benth.; at the end of 1956, upwards of 40 alkaloids had been isolated and characterized from various *Rauwolfia* species, and the structures of many of them had been elucidated. The principal stimulus behind this intense activity was the isolation in 1952 from *R. serpentina* of the alkaloid reserpine, which has attained great importance as a hypotensive and sedative drug, and which is one of the chief constituents responsible for the pharmacological activity of *Rauwolfia* extracts, known for centuries in India and prescribed for the treatment of a wide variety of disorders. Several additional groups of alkaloids, e.g., those of *Vinca*, *Voacanga*, *Picralima*, *Mitragyna*, and *Uncaria*, are now known to be derived from tryptamine and are thus included in this rapidly expanding section. The alkaloids of *Cryptolepis* species and of *Pentaceras australis* Hook. have not been discussed in this chapter, since they have previously been summarized in Chapter 48 of Volume V.

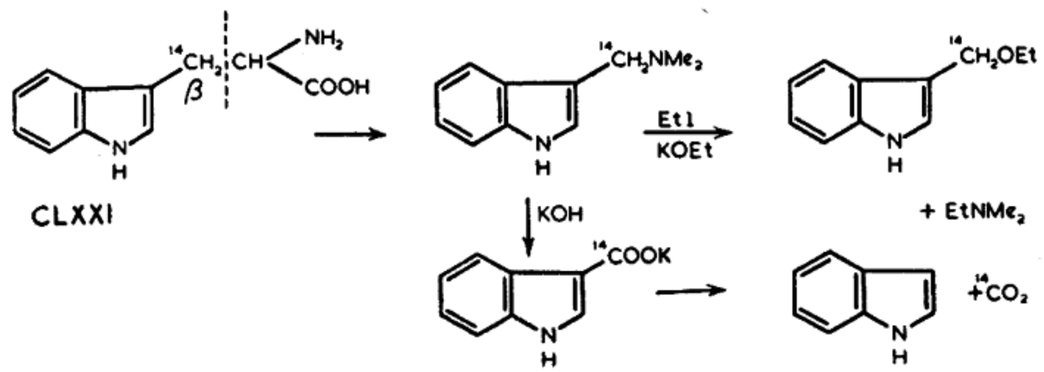
In some respects, the order of discussion in this supplement has been modified compared with Chapter 13 of Volume II. The alkaloids are now grouped together, as far as possible, according to their botanical origin. The principal exception to this classification concerns the alkaloids of Rubiaceae, which are either of yohimbine (yohimbehe bark) or oxindole (*Uncaria* and *Mitragyna* alkaloids) type. The latter are discussed after the oxindole alkaloids of *Gelsemium sempervirens*. For convenience, the formula and reference numbers follow consecutively those of the earlier chapter.

II. The Simple Bases

1. Gramine

Recent studies on this alkaloid have been concerned with its biogenesis in barley (*Hordeum vulgare* L.). Administration of *dl*-tryptophan-β-C^{14} (CLXXI) to sprouting barley led to the formation, in the leaves, of radioactive gramine, in which the activity resided in the same position as in the original tryptophan (710). Fusion of the gramine with potassium hydroxide gave potassium indole-3-carboxylate, which was decarboxylated to indole and C^{14}-carbon dioxide. Reaction of the gramine with ethyl iodide and potassium ethoxide yielded active

3-ethoxymethylindole and inactive ethyldimethylamine:



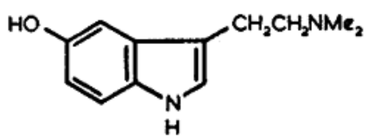
CLXXI

The conversion of C^{14}-tryptophan to C^{14}-gramine in the plant was followed by means of radioautographs, taken at daily intervals (711). In the early stages of growth, a radioactive area appeared at the bottom of the leaves, owing to free tryptophan. Later, this activity diminished, and an area, consisting mainly of active gramine, developed at the tips of the leaves. In a further study (712), a mixture of *dl*-tryptophan-2-C^{14} and *dl*-tryptophan-β-C^{14}, with a known ratio of activity in the 2- and β-positions, was fed to sprouting barley. The radioactive gramine isolated showed that activity was present in the 2-position and the methylene group of the side chain only, and that the ratio of these activities was the same as that in the administered tryptophan. These results indicate that tryptophan is the precursor of gramine, and that the transformation proceeds without fission of the indole-alanine linkage. Instead, fission must occur between the α- and β-carbon atoms of the amino acid, as indicated in CLXXI. Hence, the biosynthesis suggested earlier, from indole, formaldehyde, and dimethylamine equivalents, which is attractive because of its simplicity and feasibility *in vitro*, does not operate. The origin of the tryptophan is still obscure. When phenylalanine-2-C^{14} was administered to sprouting barley, the gramine isolated was inactive. Hence phenylalanine is not the precursor of gramine and consequently cannot be the precursor of tryptophan (713).

2. The Alkaloids of *Piptadenia* Species

Bufotenine, 5-hydroxy-*N*,*N*-dimethyltryptamine (CLXXII), has recently been isolated from the leguminous shrubs, *Piptadenia peregrina* Benth. (714, 715) and *P. macrocarpa* Benth. (715). The seeds of these plants have been used for centuries by certain Indian tribes of South America and the Caribbean islands as the source of a ceremonial narcotic snuff called cohoba, which is inhaled through a bifurcated tube. Small

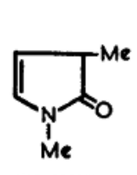
doses of this snuff produce hallucinations and a kind of intoxication;



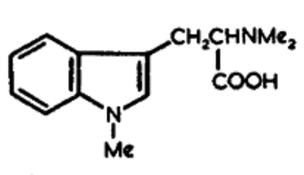
CLXXII

excessive doses cause a violent temporary derangement. Bufotenine appears to be the principal hallucinogenic agent and is present to the extent of 0.94% in the seeds of *P. peregrina* (714). Its identity was confirmed by comparison of the base and its methiodide (m.p. 213–214°), picrate (m.p. 176–177°), oxalate (m.p. 82–84°), and *m*-nitrobenzoate (m.p. 255–257°) with authentic synthetic samples. The isolation of bufotenine from vegetable sources demonstrates its ubiquitous nature. It also occurs in the secretion of the parotid gland of the toad (*Bufo vulgaris*, and several other *Bufo* species) (716–721), in certain fungi (e.g., *Amanita mappa*) (722), and in human urine (723). It is frequently found in association with serotonin (5-hydroxytryptamine) (721, 723), and may be a product of tryptophan metabolism, although its biosynthesis and its function are unknown.

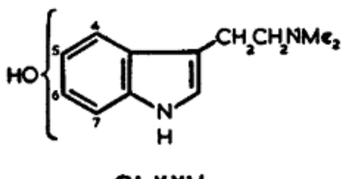
Bufotenine was first isolated from *Bufo vulgaris* in 1893 by Bertrand and Phisalix (716), but it was not fully characterized. Handovsky (724) later isolated the same oil and obtained a crystalline oxalate, among other salts, which appeared to have the formula, $C_{14}H_{18}O_6N_2$, and from which he deduced that the base had the composition C_6H_9ON. Since the base gave a pine-splinter color test, it was assigned a structure (CLXXIII) based on pyrrole (724). Wieland *et al.* reinvestigated these toad secretions, and from the basic fraction isolated two interconvertible, crystalline picrates, m.p. 178°, which were formulated as derivatives of a base, $C_{14}H_{18}O_2N_2$. The free base was not obtained crystalline, but since a relationship with hypaphorine was suspected from its general properties, the constitution CLXXIV was tentatively proposed (725). However, this



CLXXIII



CLXXIV



CLXXV

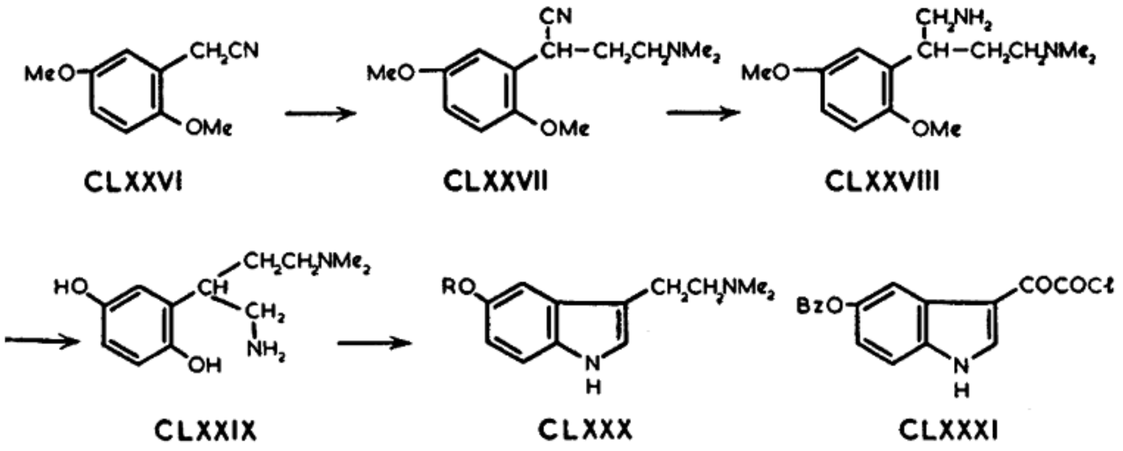
hypothesis was considerably weakened by comparison of bufotenine with *ind*-*N*-methyltryptophan, and was completely invalidated by its eventual crystallization and purification, when the molecular formula

$C_{12}H_{16}ON_2$ was established (717). Bufotenine was known to contain a 3-substituted indole nucleus and a tertiary amino group; the weakly acidic properties were now shown to be due to a phenolic hydroxyl group. A free imino group was also present, since the base contained two active hydrogens, and yielded a diacetate. These data were combined in the formula CLXXV, in which the position of the phenolic group was unspecified; however, positions 4 and 7 were provisionally eliminated, since at that time no derivatives of 4- or 7-hydroxyindole had been found among natural products. The synthesis of the two remaining isomers was therefore undertaken. Methylation of 6-methoxytryptamine, already known in connection with investigations in the harmine series (725a), with methyl iodide and thallium hydroxide, gave a quaternary iodide, which coincided in melting point (182–183°) with *O*-methylbufotenine methiodide (m.p. 183–184°) and corresponded closely in physical and chemical properties, but which gave a depression of almost 40° of melting point on admixture. 5-Methoxy-*N*,*N*-dimethyltryptamine, m.p. 183°, was subsequently synthesized from 5-methoxyindole, by condensation of the Grignard derivative with chloroacetonitrile, followed by reduction with sodium and alcohol, and methylation of the 5-methoxytryptamine with methyl iodide and thallium ethoxide. The product was shown to be identical with *O*-methylbufotenine methiodide in all respects (717).

The synthesis of bufotenine itself followed closely upon the proof of its structure. Hoshino and Shimodaira reduced the ethyl ester of 5-ethoxyindole-3-acetic acid by the Bouveault-Blanc procedure to the corresponding primary alcohol, which was treated with phosphorus tribromide and then dimethylamine, to give the ethyl ether of bufotenine, which was demethylated with aluminum chloride (726). A later synthesis involves the application of a novel route to indoles, developed by Harley-Mason. 2,5-Dimethoxybenzyl cyanide (CLXXVI) was alkylated by Eisleb's method with dimethylaminoethyl chloride in the presence of sodamide to give 1-(2,5-dimethoxyphenyl)-3-dimethylaminopropyl cyanide (CLXXVII), which was then hydrogenated over Raney nickel to yield 2-(2,5-dimethoxyphenyl)-4-dimethylaminobutylamine (CLXXVIII). Demethylation of this with hydrobromic acid, followed by oxidation of the product (CLXXIX) with potassium ferricyanide, yielded bufotenine (CLXXX, R = H), via the related quinone (727).

Two further syntheses have been reported very recently. The first of these employs a new route to tryptamines, which threatens to supersede the older method via gramine derivatives. 5-Benzyloxyindole was treated with oxalyl chloride to give 5-benzyloxy-3-indoleglyoxylyl chloride

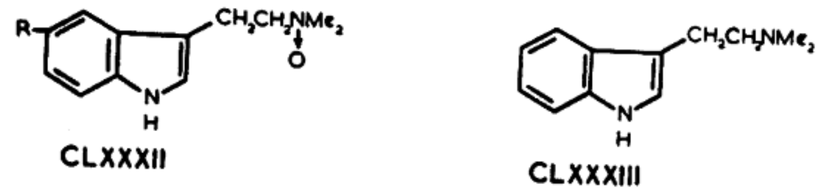
(CLXXXI), which was converted by reaction with dimethylamine into 5-benzyloxy-*N*,*N*-dimethyl-3-indoleglyoxylamide. Reduction of this with excess of lithium aluminum hydride yielded *O*-benzylbufotenine (CLXXX, R = Bz), which was subsequently debenzylated (728).



Finally, Stoll *et al.* have completed a fourth bufotenine synthesis, using the gramine route (729). 5-Benzyloxyindole was converted into 5-benzyloxygramine, and thence into 5-benzyloxyindole-3-acetic acid, by standard procedures. *O*-Benzylbufotenine was prepared from this by conversion into the related acid azide, reaction with dimethylamine, and reduction of the amide with lithium aluminum hydride. Catalytic debenzylation over a palladium catalyst gave bufotenine, identical with that from *Amanita mappa* in all respects except melting point. Whereas bufotenine has been reported in several instances to have m.p. 146–147° (714, 717, 728), Stoll *et al.* found that their sample melted at 138–140° in spite of the most diverse and careful methods of purification. This recalls the behavior of tryptamine, which has been reported to exist in two forms of m.p., 118° (730) and 145° (731).

The seeds of *Piptadenia peregrina* and *P. macrocarpa* also contain bufotenine oxide (CLXXXII, R = OH), *N*,*N*-dimethyltryptamine (CLXXXIII), and *N*,*N*-dimethyltryptamine oxide (CLXXXII, R = H) (715). The pods contain *N*,*N*-dimethyltryptamine, but not bufotenine or the two oxides. *N*,*N*-Dimethyltryptamine is very readily oxidized in solutions exposed to the air, so the oxide of this base may be an artifact, generated during the extraction or chromatographic separation. On the other hand, the formation of bufotenine oxide from bufotenine has never been observed in the absence of a specific oxidizing agent; hence it probably exists as such in the seeds. The occurrence of these oxides is interesting, and it has been suggested that they are intermediates in the metabolism of tryptophan. It also lends support to the

recent suggestion that the formation of amine oxides, and their rearrangement to carbinolamine bases, may be important stages in the biosynthesis of certain alkaloids (732).



III. The Ergot Alkaloids

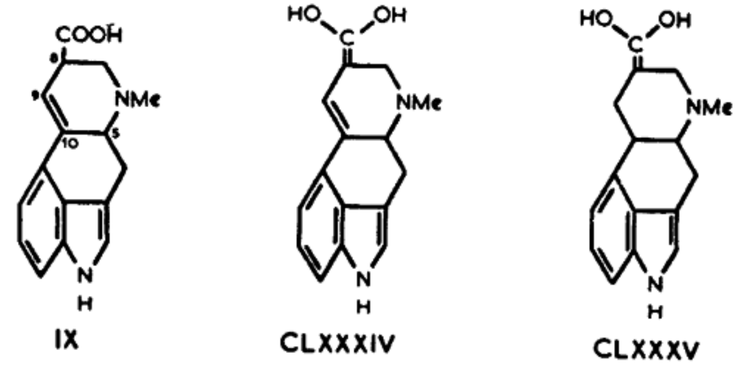
1. Introduction

During the last five years the stereochemistry of lysergic acid, isolysergic acid, and the dihydrolysergic acids has been elucidated, and the structure assigned to lysergic acid has been confirmed by total synthesis. A more satisfactory general formula has been proposed for the alkaloids; the peptide half and the thermal fission products have been synthesized. Several new ergot alkaloids, which are probably simple derivatives of ergoline, have been isolated.

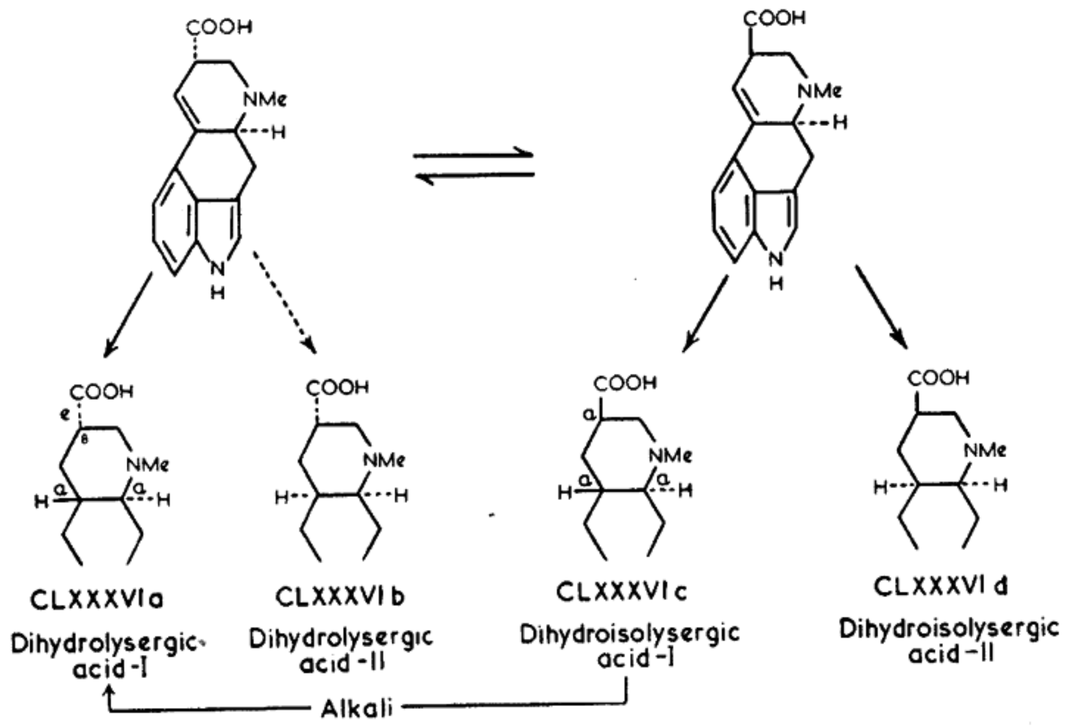
The colorimetric determination of the ergot alkaloids by means of Ehrlich's reagent has received much attention, and several prescriptions for its application to the analysis of ergot preparations have been reported (733–742). Ninhydrin has also been recommended as a reagent for detecting the ergot alkaloids (743). Paper chromatography has proved to be an extremely valuable medium for the analysis of mixtures of ergot alkaloids (740–742, 744–751) and has been used in the detection of new alkaloids.

2. Lysergic Acid, Isolysergic Acid, and the Dihydrolysergic Acids

Lysergic acid (IX) differs from isolysergic acid only in the stereochemistry at C_8. The greater ease of isomerization of the lysergic acids over that of the dihydrolysergic acids can be explained by the readier

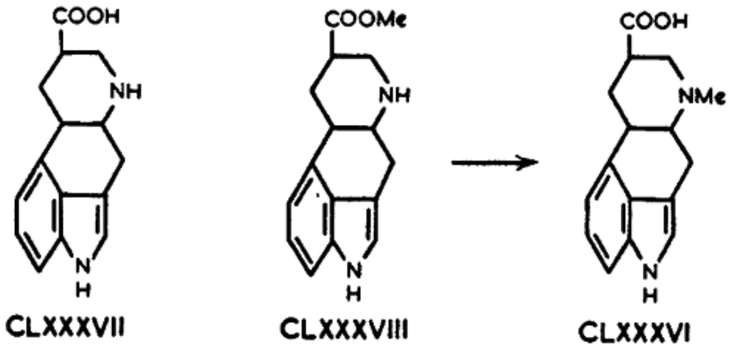


formation of the intermediate fully conjugated enol CLXXXIV, compared with the enol CLXXXV. The relationship between the various acids is shown in the following scheme:



The hydrogenation of lysergic acid proceeds in one sense only, and yields dihydrolysergic acid-I (CLXXXVIa). On the other hand, hydrogenation of isolysergic acid gives a mixture of the two possible products, in yields depending on the conditions employed. Thus, rapid hydrogenation gives a higher yield of dihydroisolysergic acid-II than if the hydrogenation is carried out slowly over a palladium catalyst, when the two isomers are obtained in approximately equal amounts (752). Dihydroisolysergic acid-I differs from dihydroisolysergic acid-II in the configuration at C_{10}, the configuration at C_8 being the same. Further, dihydrolysergic acid-I possesses the same stereochemistry at C_5 and C_{10} as dihydroisolysergic acid-I, and differs only in the configuration at C_8, since these two isomers can be equilibrated in alkaline solution, the equilibrium being predominantly in favor of dihydrolysergic acid-I (753). Although dihydrolysergic acid-II has not been obtained by reduction of lysergic acid, or by total synthesis, it should be obtainable by equilibration of dihydroisolysergic acid-II under strong alkaline conditions. Accordingly, Stoll and Rutschmann (753) heated *d*-dihydroisolysergic acid-II hydrazide under reflux with 12% potassium hydroxide in amyl alcohol for 4 hours, converted the product to the ester, which was an oil, and separated the mixture by chromatography. The resulting ester of the new isomer could still not be crystallized, so it

was converted into the crystalline hydrazide. By this means the hydrazide of *d*-dihydrolysergic acid-II was obtained in 2% yield, from which it was concluded that the acid was present to the extent of not more than 5% at equilibrium. The paucity of the yield obtained in this isomerization precluded the possibility of converting the *d*-dihydrolysergic acid-II hydrazide into the optically pure, crystalline *d*-dihydrolysergic acid-II. It was found, however, that the stability relationships in the dihydronorlysergic acid series (CLXXXVII) were not the same as in the homologous series. The availability of three of the racemates of dihydronorlysergic acid by total synthesis (753a, 754) enabled Stoll and his collaborators to investigate more closely the nature of the isomerism and the possibility of obtaining the fourth isomer. As in the dihydrolysergic acid series, it was hoped to prepare this isomer by equilibration of the noracid-II, which was believed to be dihydronorisolysergic acid-II (753). In accordance with expectations, a mixture of two isomeric acids was obtained when the hydrazide of this isomer was heated with 12%



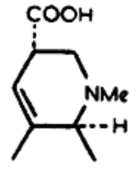
potassium hydroxide in amyl alcohol. Fractional crystallization yielded the two acids, in proportions which indicated that the new isomer was present to the extent of about 20% at equilibrium. By the action of heat on the methyl esters of these two acids (CLXXXVIII), two dihydrolysergic acids (CLXXXVI) were obtained. Unexpectedly, however, the acid which had been designated "dihydronorisolysergic acid-II" (the starting material) yielded dihydrolysergic acid-II, while the new isomer, believed to be dihydronorlysergic acid-II, gave dihydroisolysergic acid-II. Thus, it appeared that in this reaction epimerization at C_8 had accompanied the transmethylation. In a later communication, Stoll and Rutschmann reported that the conversion of the dihydronorlysergic acids into the dihydrolysergic acids could be accomplished smoothly by a reductive methylation procedure, using formaldehyde and hydrogen in the presence of Raney nickel (755). Under these conditions it was highly improbable that epimerization at C_8 would occur. Yet the same results were obtained. Since there was no doubt of the identity of

the dihydrolysergic acids, it was evident that the II-isomer which was obtained by synthesis was not dihydronorisolysergic acid-II, but, in fact, dihydronorlysergic acid-II. It thus appears that in the nor series, dihydronorlysergic acid-II is more stable than dihydronorisolysergic acid-II, and both the transmethylation and reductive methylation procedures occur without epimerization at C_8.

3. Stereochemistry of the Lysergic and Dihydrolysergic Acids

The configuration at C_5 is the same in all four of the dihydrolysergic acids; they must therefore differ in the stereochemistry at C_8 and C_{10}. Two of the dihydrolysergic acids must have a *trans* C/D ring junction, and differ only in the configuration of C_8; the other two must have a *cis* C/D junction, likewise differing in the configuration of C_8. Energetic alkaline hydrolysis of dihydroisolysergic acid-I methyl ester gives dihydrolysergic acid-I, and similarly dihydrolysergic acid-II gives dihydroisolysergic acid-II. It is therefore probable that in dihydrolysergic acid-I and dihydroisolysergic acid-II the carboxyl group is equatorial, whereas in the other two acids it is axially oriented with respect to ring D (752). This conclusion is confirmed by a consideration of other chemical properties. For example, the azide of dihydrolysergic acid-I reacts faster with amines than dihydroisolysergic acid-I azide, while the esters of dihydrolysergic acid-I and dihydroisolysergic acid-II are more rapidly saponified than their C_8 epimers.

The available evidence relating to the stereochemistry of the C/D ring junction is not as unequivocal. Hydrogenation of lysergic acid and its relatives produces derivatives of dihydrolysergic acid-I only, and no derivatives of dihydrolysergic acid-II are formed (755a, 755b). This has been explained by catalyst hindrance. If, in lysergic acid (IX), the C_5 hydrogen and the carboxyl group are *cis* with respect to ring D, then addition of hydrogen on the same side of ring D will be prevented, and hydrogenation will occur to give a *trans* C/D ring junction (752, 756).

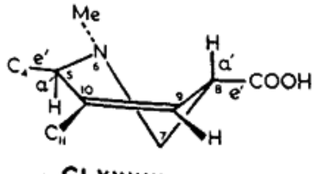


IX

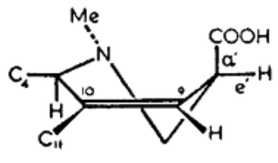
In isolysergic acid, in which the C_5 hydrogen and the carboxyl group are *trans* oriented, no such hindrance will be encountered, and it should be possible to obtain both reduction products, as is in fact found by experiment. Dihydrolysergic acid-I is therefore the *trans* C/D-8-equatorial isomer (CLXXXVIa) and dihydrolysergic acid-II the all-*cis* isomer

(CLXXXVIb). Since dihydroisolysergic acid-I is epimeric with dihydrolysergic acid-I at C_8, it must be the C/D-*trans*-8-axial isomer (CLXXXVIc), and dihydroisolysergic acid-II must be the remaining possibility (CLXXXVId). These inferences are confirmed by the results of the hydrogenation of isolysergic acid derivatives. Rapid reduction of the iso series of alkaloids using a platinum catalyst yields mainly derivatives of dihydroisolysergic acid-II, while slower reduction over a palladium catalyst yields both possible acids in approximately equal amounts (755b). Since rapid reduction frequently leads to the formation of a *cis* C/D ring junction, it can be deduced that dihydroisolysergic acid-II has a *cis* C/D ring junction, and can therefore be formulated as CLXXXVId (752). Stoll and his collaborators adduced further evidence in support of these formulations from a consideration of the pK values, the IR-(infrared) spectra, and the chromatographic behavior of the dihydrolysergic acids.

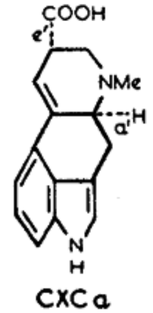
The stereochemical relationship between lysergic and isolysergic acid is not so clearly defined. There is a significant difference in the pK_a values for these two acids, which can be explained only by a direct electrostatic interaction between the $-COO^{\ominus}$ and $=\overset{\oplus}{N}HMe$ of the zwitterion, since the carbon chain separating the two ionizing groups is the same in the two acids, and hence the purely inductive effect will be the same. Increase of distance between the two groups will reduce the extent of zwitterion formation, and will therefore be base-weakening (752, 757). Determination of the pK_a values for lysergic acid (pK_a of base-conjugate acid, 7.68, 7.96) and isolysergic acid (pK_a 8.31, 8.60) shows that the former is the weaker base (757, 757a). The same is true of lysergic acid dimethylamide (pK_a, 6.39) and diethylamide (pK_a,6.37), compared with isolysergic acid dimethylamide (pK_a, 7.42) and diethylamide (pK_a, 7.52) (752). On the assumption that ring D in these acids exists in the pseudo-chair form the two possible conformations may be written as CLXXXIX (a and b), as a first approximation. Since the distance between the amino and carboxyl groups is greater in CLXXXIXa than in CLXXXIXb, it can be inferred that the former



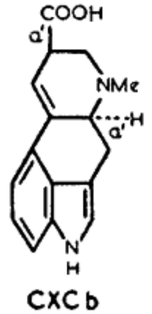
CLXXXIXa



CLXXXIXb



CXCa



CXCb

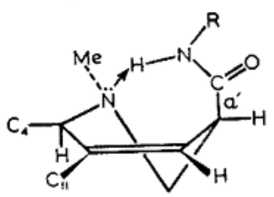
represents lysergic acid, i.e., the carboxyl group has the *quasi*-equatorial conformation (752, 757, 758). This appears to be supported by the rate of esterification of lysergic acid with diazomethane in benzene, which proceeds much faster than the analogous esterification of isolysergic acid (758a). Hence lysergic acid can be represented as CXCa and isolysergic acid as CXCb.

Equilibration of the normal and iso series of alkaloids in alkaline solution provides confirmation of these deductions. The accompanying table shows the proportions of lysergic and isolysergic form present at

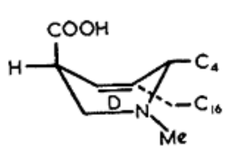
Equilibration of Lysergic Acid Derivatives (752)

	% *of Lysergic Acid Form*	% *of Isolysergic Acid Form*
Lysergic acid dimethylamide	84	16
Lysergic acid diethylamide	88	12
Lysergic acid	54	46
Ergosine	42	58
Ergocryptine	48	52
Ergobasine	52	48

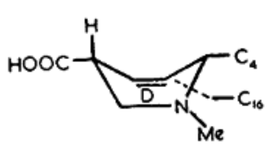
equilibrium. For the dialkylamides, these data indicate a greater thermodynamic stability of the lysergic acid form, compared with the isolysergic acid form; on the other hand, there is evidently little or no difference in the alkaloids themselves, which are monoalkylamides of lysergic acid. This can be interpreted by assuming that hydrogen bond formation occurs between the amide group and the amino nitrogen in the monoalkylamides. Inspection of formulas CLXXXIX (a and b) shows that this is possible only in those isomers which have a *quasi*-axial amide group (CXCI), which, according to earlier conclusions, are the derivatives of isolysergic acid. The data in the table show that this is in fact true, and in the iso series, the monoalkylamides show a greater stability than the dialkylamides vis-à-vis the normal series. This behavior is reflected in the basic strengths of the monoalkylamides. Thus, the pK_a values of lysergic acid diethylamide (6.37) and isolysergic acid diethylamide (7.52) show a difference of 1.15 units, whereas those of lysergic acid monoethylamide (6.09) and isolysergic acid monoethylamide (6.35) show a difference of only 0.26 unit. The considerable weakening of basicity in the iso series is therefore probably due to internal hydrogen bond formation of type CXCI.



CXCI



CXCIa

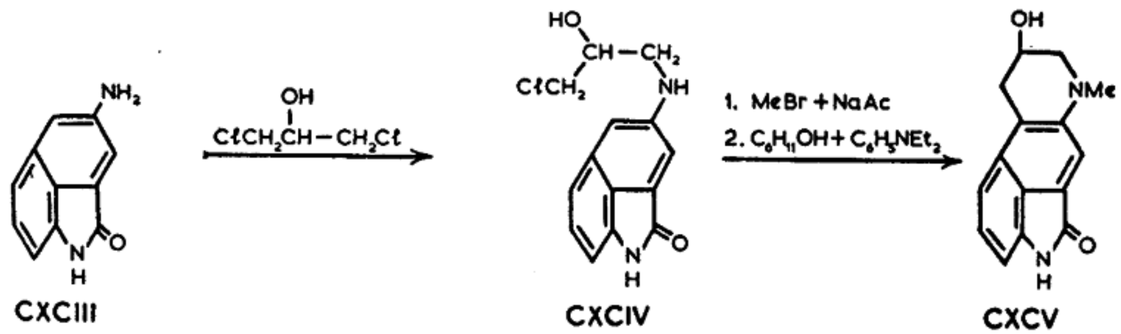


CXCIb

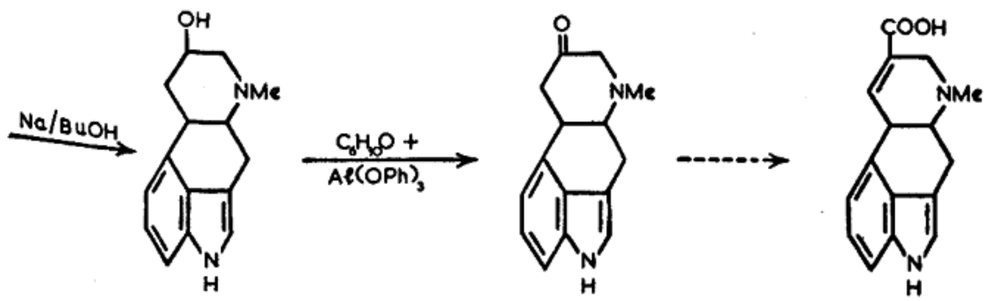
It may be mentioned here that the conformations CXCIa and CXCIb for lysergic and isolysergic acids are favored by Cookson, who assumed that ring D would adopt the half-boat conformation (756). Since thermodynamic data indicate that the half-chair form of cyclohexene is more stable than the half-boat form by approximately 2.7 kcal./mole, it is more than probable that ring D will exist in the half-chair conformation. Another divergence of opinion results from the assumption that spatial proximity of the amino and carboxyl groups will lead to a reduction in basic strength, which is the reverse of the effect postulated by Stenlake and by Stoll and his collaborators. Lysergic acid is thus represented by CXCIa, the carboxyl group occupying the *quasi*-axial orientation. However, this formulation provides no obvious explanation of the weakening of basic strength of the isolysergic acid monoalkylamides compared with the dialkylamides.

4. Syntheses in the Lysergic Acid Series

Several approaches have been used to construct the tetracyclic ring system of lysergic acid. The first successful syntheses used as starting material 4-aminonaphthostyril, in which rings A, B, and C were preformed, although not in the same stage of reduction as in lysergic or dihydrolysergic acid. Ring D was then built up by standard methods, and reduction of rings B and C completed the syntheses (758b, 758c). This approach led to two syntheses of dihydrolysergic acid, but no provision was made for the introduction of the 9,10 double bond. In an



CXCIII CXCIV CXCV

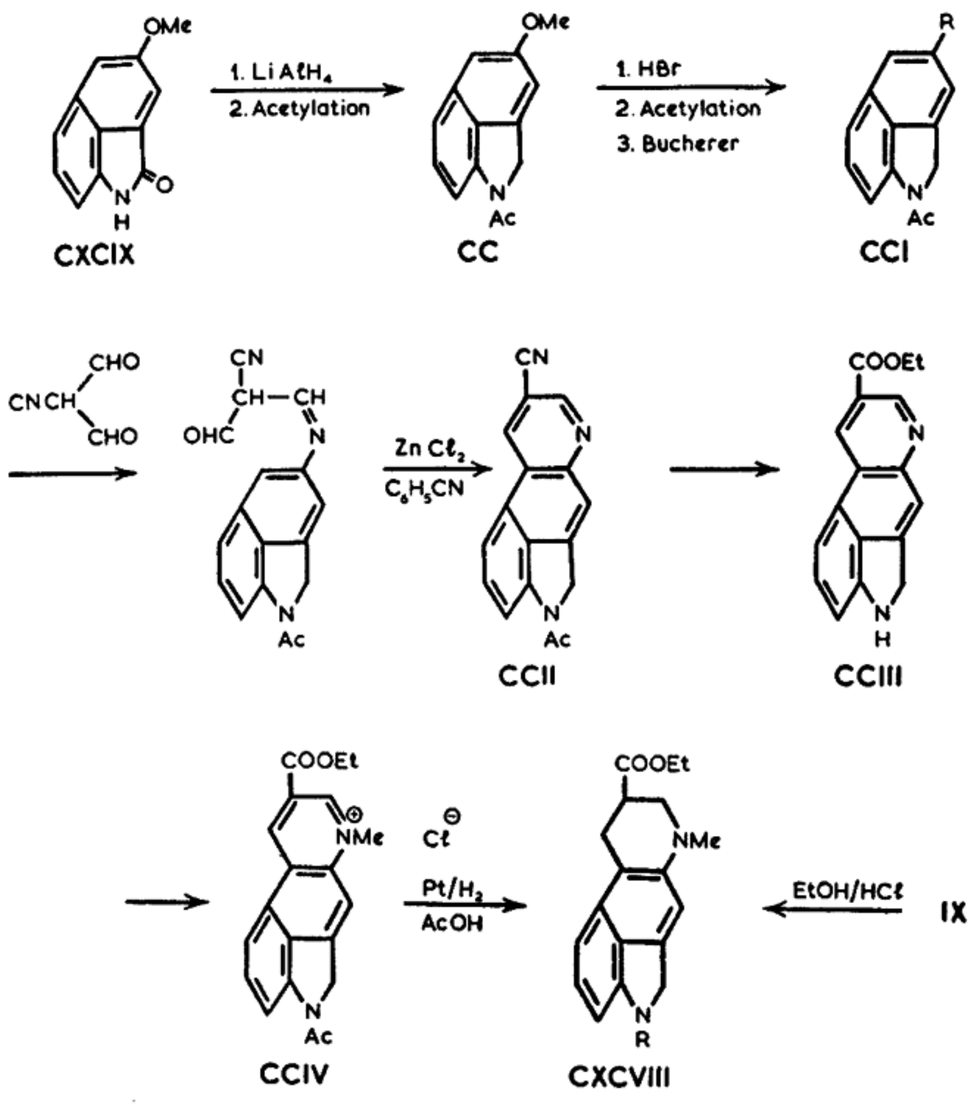


CXCVI CXCII CXCVII

attempt to achieve this, and so to complete the synthesis of lysergic acid, 6-methylergolin-8-one (CXCII) was synthesized (759). 4-Aminonaphthostyril (CXCIII) was condensed with epichlorhydrin to give the secondary amine CXCIV, which was methylated, and cyclized with diethylaniline in cyclohexanol, to give the tetracyclic naphthostyril derivative (CXCV). Reduction of CXCV with sodium and butanol gave a mixture of products, from which *dl*-6-methyl-8-hydroxyisoergoline (CXCVI) was recovered by chromatographic separation. A modified Oppenauer oxidation gave a very small yield of CXCII, together with condensation products of this ketone with cyclohexanone. The original project had been to introduce the C_8 carboxyl group via cyanhydrin formation, and obtain the double bond by dehydration of the α-hydroxy acid formed. This would undoubtedly have given the isomer of lysergic acid with the double bond in the 8,9-position (CXCVII), but it was hoped to rearrange this acid to lysergic acid. However, the yield of 6-methylergolin-8-one (CXCII) obtained in the oxidation stage was so small that it was not possible to complete the synthesis. In any event the nature of the projected last stage would hardly have been sufficiently unambiguous to prove with certainty the position of the double bond in lysergic acid (759).

The principal difficulties inherent in the synthesis of lysergic acid are the production of the indole and 9,10-double bonds. The difficulty associated with the former can be circumvented by the use of naphthostyril derivatives. However, no such device can be used to protect the 9,10-double bond, and there are serious disadvantages against introducing it in the earlier stages of a synthesis, because of the ease with which systems of this type rearrange irreversibly in acid solution into naphthalene derivatives. For example, lysergic acid isomerizes, in the presence of proton donors such as hydrogen chloride in ethanol, into the naphthalene compound CXCVIII (R = H), isolated as its *N*-acetyl derivative (CXCVIII, R = Ac). The reverse reaction, if feasible, would have been extremely valuable in relation to the synthesis of lysergic acid, but in an examination of this reaction, no trace of indole derivative could be found at equilibrium, and the reaction mixture did not even give the very sensitive color reaction with Ehrlich's reagent (760). Calculation of the resonance energies of the ergoline ring system and the naphthalene system present in CXCVIII shows a difference of 20 kcals./mole; it is therefore to be expected that the equilibrium will be completely in favor of the latter.

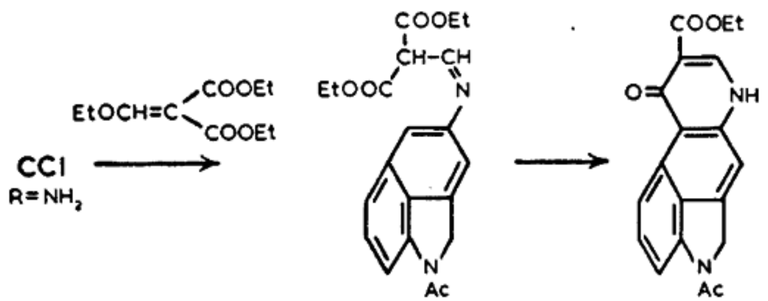
The structure of the rearrangement product was proved by total synthesis. 4-Methoxynaphthostyril (CXCIX) was reduced with excess of lithium aluminum hydride, and the product acetylated, to give CC.

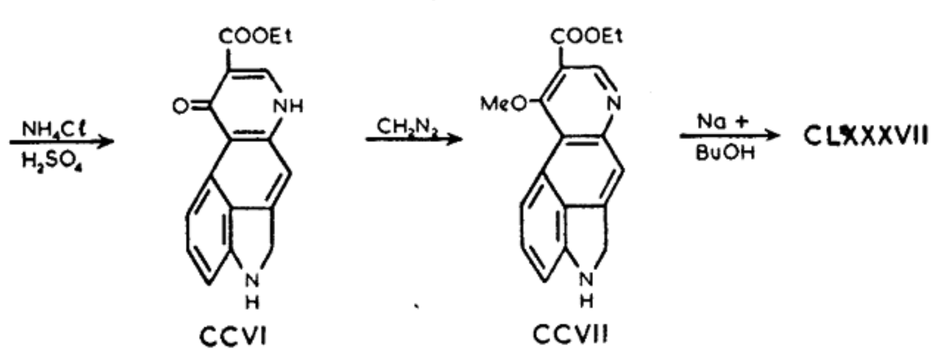


Demethylation with hydrobromic acid and reacetylation gave the acetoxynaphthalene derivative (CCI, R = OAc), which was used directly in the Bucherer reaction to give the amine (CCI, R = NH_2). Condensation of this product with cyanomalonic dialdehyde and ring closure with zinc chloride in benzonitrile gave the tetracyclic nitrile (CCII), which was converted by standard procedures into the quaternary salt (CCIV). Hydrogenation over a platinum catalyst gave a tetrahydro derivative (CXCVIII, R = Ac), which was identical with the product obtained by rearrangement of lysergic acid, followed by acetylation (760). The intermediate ester (CCIII) afforded a third synthesis of the dihydrolysergic acids. Reduction with sodium and alcohol in the presence of a small amount of water to prevent simultaneous reduction of the ester group gave three of the racemates of dihydrolysergic acid, which were esterified and separated by chromatography (754).

By using a variant of these syntheses it was hoped to achieve the total synthesis of lysergic acid, but an unexpected elimination led to the

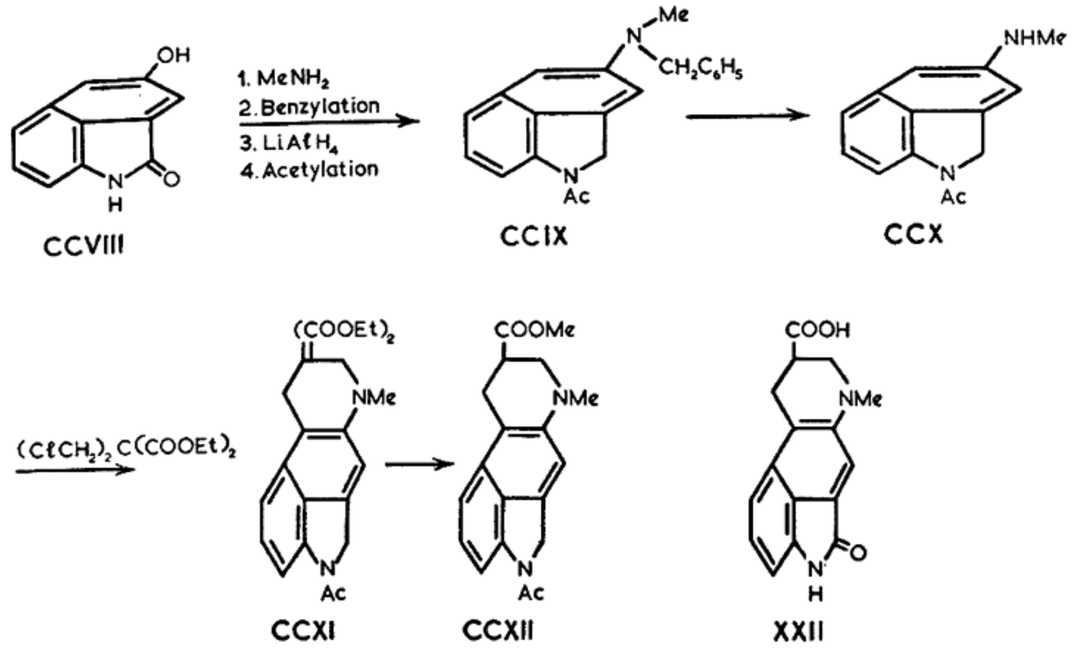
formation of dihydronorlysergic acid. The aminonaphthalene (CCI, R = NH_2) was condensed with ethoxymethylene malonic ester, and the product cyclized in boiling diphenyl to the indoloquinoline derivative (CCV). Removal of the *N*-acetyl group with ammonium chloride and sulfuric acid gave CCVI, which it was hoped to convert by reduction into 9-hydroxydihydronorlysergic acid, and thence by dehydration to lysergic acid. However, attempts to reduce the high-melting, insoluble quinolone (CCVI) met with no success, and reduction of the methyl ether (CCVII) resulted in elimination of methanol, and saturation of ring D, to give dihydronorlysergic acid (CLXXXVII) (754).





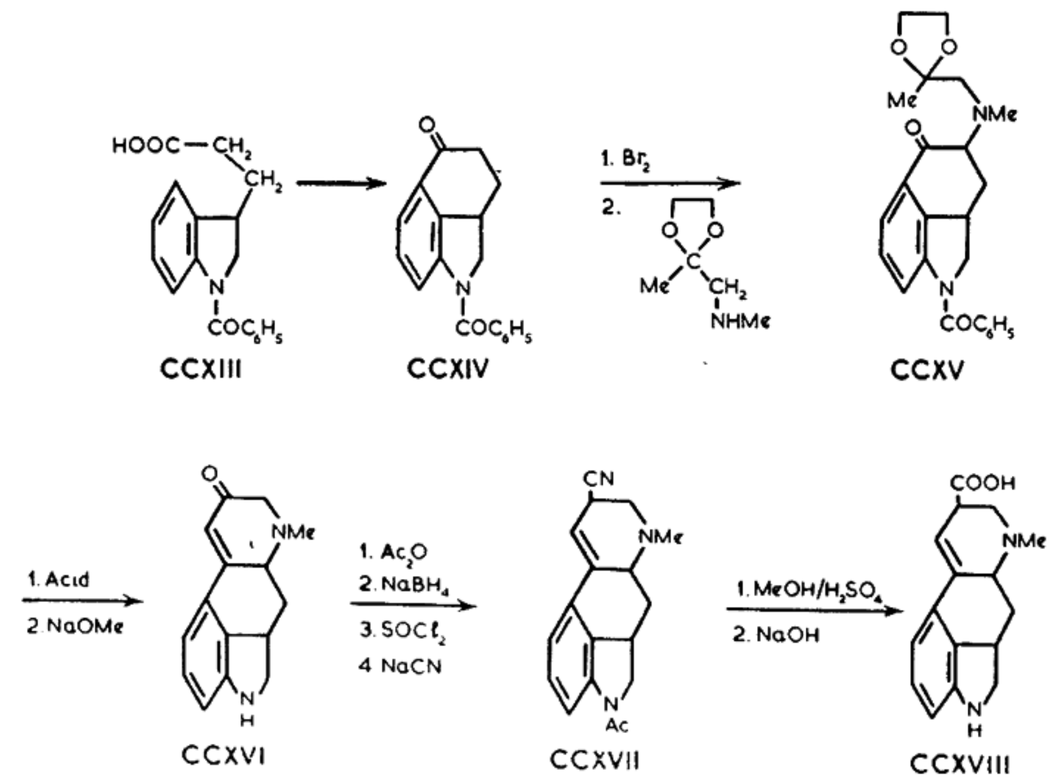
A synthesis of the naphthalene isomer of lysergic acid methyl ester (CCXII) has also been achieved, starting from 4-hydroxynaphthostyril (CCVIII). This was converted by methanolic methylamine into 4-methylaminonaphthostyril, which was benzylated, reduced with lithium aluminum hydride, and acetylated, to the aminobenzindoline CCIX. Catalytic debenzylation gave the secondary amine CCX, which was condensed with ethyl *bis*-(chloromethyl)-malonate by means of potassium carbonate in boiling butanol. Hydrolysis and decarboxylation of the product (presumably CCXI) gave an acid which, after esterification, yielded the methyl ester CCXII, identical with the product of rearrangement and acetylation of lysergic acid methyl ester (761).

A further synthesis of the tetracyclic naphthostyril derivative (XXII) constitutes a new route to *dl*-dihydrolysergic acid (761), since the latter has already been obtained by reduction of XXII (758b).



Several other groups of workers have been engaged in synthetic experiments in the lysergic acid series, but since none of these has so far resulted in a synthesis of lysergic acid or a closely related transformation product, they will not be described in detail (762–766).

The synthesis of lysergic acid was finally achieved by Woodward *et al.*, using a route based on a straightforward classical approach. The difficulties associated with the potential naphthalenoid system of compounds related to lysergic acid were circumvented by working with dihydroindole derivatives. By this means a new dihydrolysergic acid was synthesized, and the final stage involved dehydrogenation (767, 768). *N*-Benzoyl-3-(β-carboxyethyl)-dihydroindole (CCXIII) was converted into the acid chloride, and cyclized with aluminum chloride, to the tricyclic ketone CCXIV. Bromination to the monobromoketone was followed by reaction with methylaminoacetone ethylene ketal in benzene, to give CCXV, which was hydrolyzed with acid to the methyl ketone, and cyclized with sodium methoxide to the tetracyclic unsaturated ketone, 9 - keto - 7 - methyl - 4,5,5a,6,6a,7,8,9 - octahydroindolo - [4,3-*fg*]-quinoline (CCXVI). The secondary amino group in CCXVI was protected by acetylation, and the ketone was then converted into the nitrile (CCXVII) by successive treatment with sodium borohydride, thionyl chloride in sulfur dioxide, and sodium cyanide in anhydrous hydrogen cyanide. Methanolysis of this nitrile gave the corresponding ester, which was hydrolyzed to the new dihydrolysergic acid (CCXVIII). Dehydrogenation was effected using deactivated Raney nickel in aqueous solution in the presence of sodium arsenate, giving, as sole product, *dl*-lysergic acid (IX), which was converted, by known procedures, into



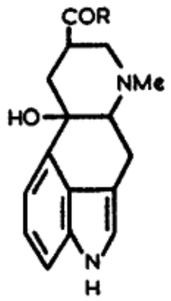
dl-isolysergic acid hydrazide. Both the acid and the hydrazide were exhaustively compared with samples prepared from natural materials (767, 768). Since *dl*-isolysergic acid hydrazide had already been resolved (768a) and converted into ergometrine (ergonovine, ergobasine, XXXI) (768b), this constitutes the first complete synthesis of an ergot alkaloid as well as that of lysergic acid.

The synthetic experiments in the lysergic acid series have not been confined exclusively to the total synthesis of the alkaloids and their transformation products, and numerous close relatives of lysergic and dihydrolysergic acid have been prepared. Stoll and Rutschmann (755), making use of the availability of dihydronorlysergic acid by total synthesis, obtained many homologs of dihydrolysergic acid by the reductive *N*-alkylation procedure. Following the discovery of the

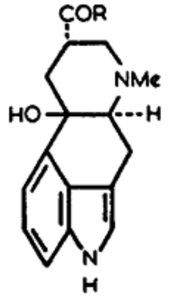
remarkable physiological effects of lysergic acid diethylamide and butanolamide (CCXIX), numerous amides of lysergic acid were synthesized and examined for physiological activity (769–773). Lysergic acid butanolamide exceeds ergometrine in its effect on the uterus, and is therefore very valuable as an oxytocic (769). The physiological activity exhibited by lysergic acid diethylamide is of a very different type. Ingestion of minute doses (20–50 μg.) induces psychic states in which the subject becomes aware of repressed memories and other unconscious material in a setting of clear consciousness. These effects are of particular importance in psychiatric analysis, since afterwards the patient is frequently able to relate his experiences under the drug with remarkable clarity. In many respects, for example, the schizophrenic effect, and the ability to produce hallucinations and a kind of depersonalization of the subject, lysergic acid diethylamide resembles mezcaline, although the doses required are very much smaller (774, 775).

5. Light-Transformation Products of the Ergot Alkaloids

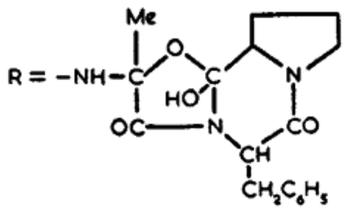
When the ergot alkaloids are allowed to stand in aqueous acid solution in the presence of light, and especially on irradiation with UV- (ultraviolet) light, the characteristic fluorescence displayed by the alkaloids disappears, and from the resulting solution two products can be obtained. For example, ergotamine yields mainly lumi-ergotamine-I (m.p. 247°), together with a very small yield of lumi-ergotamine-II (m.p. 192°). These isomeric products, which have the molecular formula $C_{33}H_{37}O_6N_5$, are evidently obtained from ergotamine, $C_{33}H_{35}O_5N_5$, by addition of the elements of water. The characteristic maximum at 318 mμ in the UV-spectra of the ergot alkaloids is replaced by a typical indole spectrum, with maxima at 224 mμ and 285 mμ. The spectra are thus identical with those of the dihydrolysergic acids. Addition of water to the 9,10-double bond can proceed to give either the 9-hydroxy- or 10-hydroxy-dihydro derivative, but the facile removal of the hydroxyl group on reduction with sodium and butanol suggests that these products are tertiary alcohols, and so they are formulated as stereoisomers of CCXX. The reaction appears to be quite general, and "lumi" products have also been obtained from ergometrine, lysergic acid, and lysergic acid diethylamide (776). The addition of water to the 9,10-double bond produces a new asymmetric center, and hence two products are possible. By analogy with the behavior of lysergic acid, which gives on reduction only dihydrolysergic acid-I, the isomer predominating in the irradiation of ergotamine is designated lumi-ergotamine-I, and is presumed to have the structure CCXXI, while lumi-ergotamine-II is its C_{10} epimer (776, 795).



CCXX

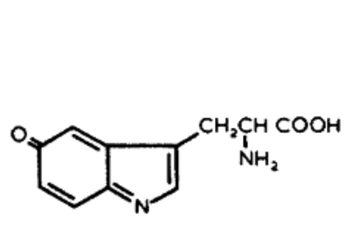


CCXXI

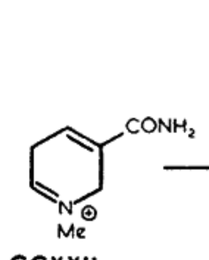


6. Biogenesis of Lysergic Acid

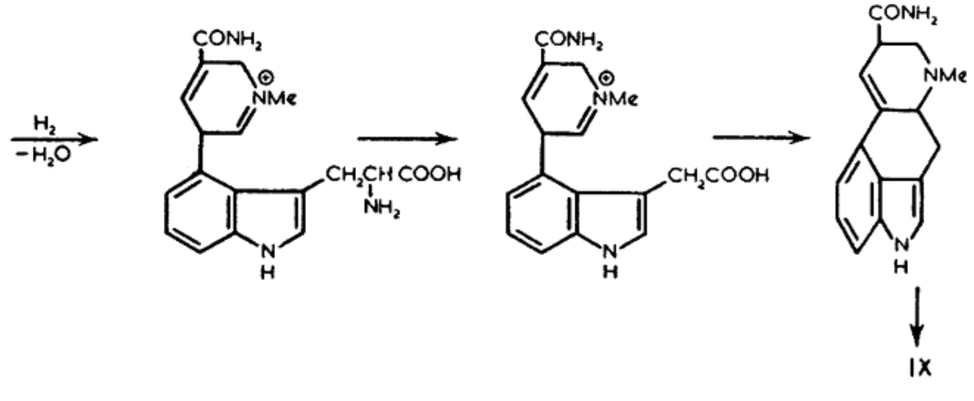
In recent years much speculation has centered on the biogenesis of lysergic acid, and several routes have been proposed, starting from tryptophan or 5-hydroxytryptophan. The first of these postulates an initial condensation of dihydronicotinic acid, or equivalent (e.g., CCXXII), with a didehydro-5-hydroxytryptophan (CCXXIII), the activated 5-position of the former coupling with the 4-position of the latter. The subsequent stages are not without analogy, and lead to the amide of lysergic acid by conventional means (777). Since nicotinic acid (and hence, presumably, dihydronicotinamide) can be produced in biological systems by degradation of tryptophan, and since both tryptophan and 5-hydroxytryptophan are possibly formed from tyrosine, the whole biosynthesis can be achieved by starting from tyrosine; it is therefore noteworthy that this amino acid has been found to be associated with the ergot alkaloids (778). In this connection, it is also of



CCXXIII

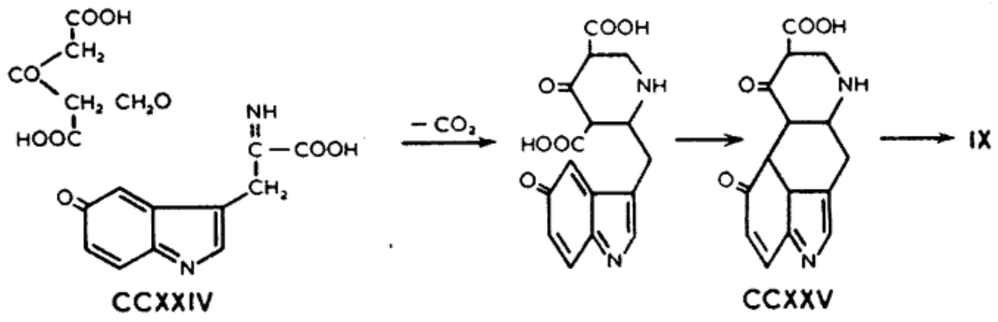


CCXXII



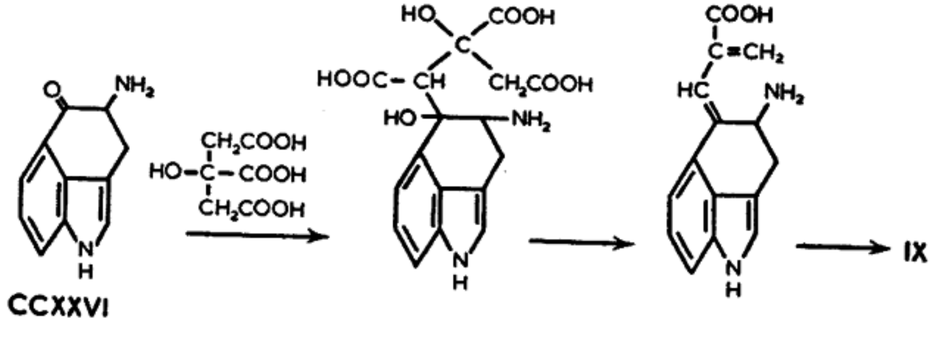
interest that in the culture of *Claviceps purpurea* nicotinic acid has been shown to be a metabolite of tryptophan, but lysergic acid is not formed (779). On the other hand, tryptophan significantly inhibits the growth of the organism (780). Commenting on this biosynthesis, Sir Robert Robinson has pointed out that although all the stages are feasible, no 5-hydroxyindole analogs of lysergic acid have been found in nature, as might be expected if this scheme were correct (781).

The fundamental requirement of the other biosyntheses which have been proposed is that the two nitrogen atoms of lysergic acid are those contained in the tryptophan precursor. Harley-Mason (782) favors a Mannich-type condensation between a tetradehydro-5-hydroxytryptophan (CCXXIV), formaldehyde, and acetonedicarboxylic acid, followed by decarboxylation and cyclization stages to the intermediate (CCXXV), which is reduced, dehydrated, and methylated, to give lysergic acid (IX).



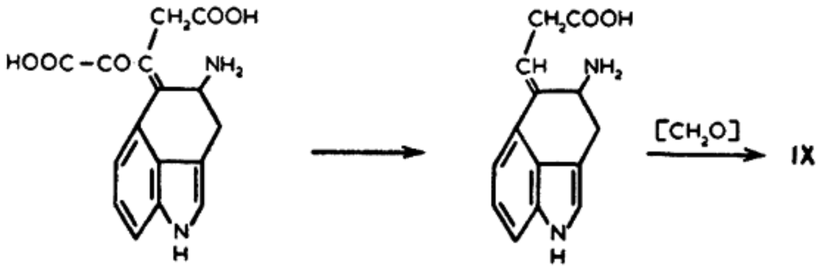
CCXXIV CCXXV

Wendler's proposal involves an initial cyclization of tryptophan to a tricyclic ketone (CCXXVI), followed by combination with citric acid, dehydration, and ring closure (783). The precise stage at which *N*-methylation occurs is not specified, and may take place at any convenient point in the synthesis. Alternatively, condensation of CCXXVI



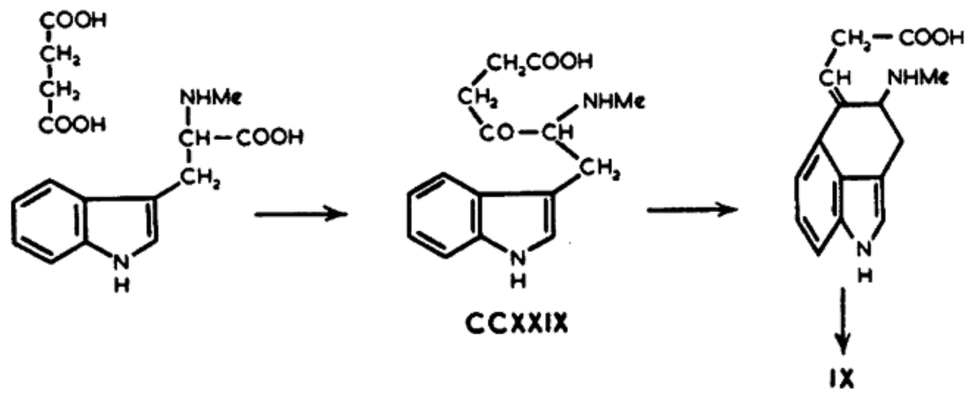
CCXXVI

with α-ketoglutaric acid may occur, to give CCXXVII, from which lysergic acid can be derived by well-known reactions (784). The intermediate formation of an unsaturated acid of the type CCXXVIII



CCXXVII CCXXVIII IX

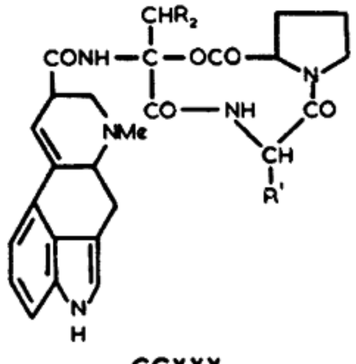
is also a feature of an earlier scheme proposed by Robinson (781). Condensation of methyltryptophan and succinic acid leads to the keto acid CCXXIX, which then cyclises to the *N*-methyl derivative of CCXXVIII. A Mannich condensation with a formaldehyde equivalent completes the synthesis. The ketonization of methyltryptophan to give the hypothetical intermediate CCXXIX is analogous to the known formation of aminolevulic acid from glycine and succinic acid (785).



CCXXIX IX

7. The Structure of the Peptide Half of the Ergot Alkaloids

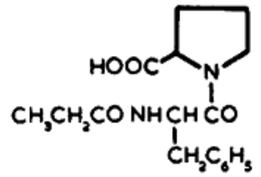
The formulation CCXXX for the ergot alkaloids, originally proposed by Barger in 1938 (786), is supported by the results of cleavage of the alkaloids and their dihydro derivatives with anhydrous hydrazine



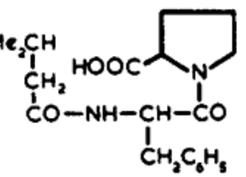
CCXXX

Ergotamine: R=H; R′=$CH_2C_6H_5$
Ergosine: R=H; R′=CH_2CHMe_2
Ergocristine: R=Me; R′=$CH_2C_6H_5$
Ergocryptine: R=Me; R′=CH_2CHMe_2
Ergocornine: R=Me; R′=$CHMe_2$

(786a). For example, fission of dihydroergotamine gives propionyl-L-phenylalanyl-L-proline (CCXXXI), and dihydroergocristine yields

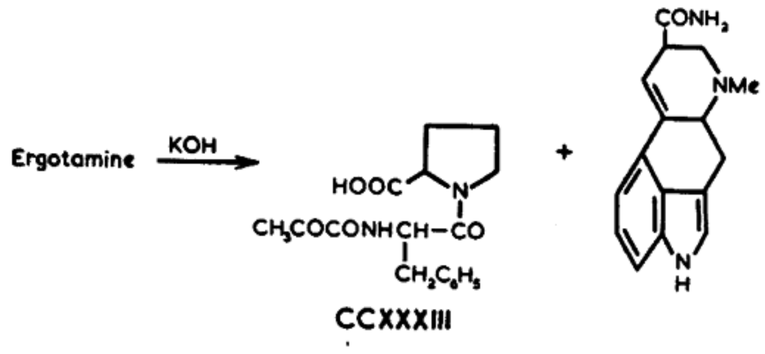


CCXXXI



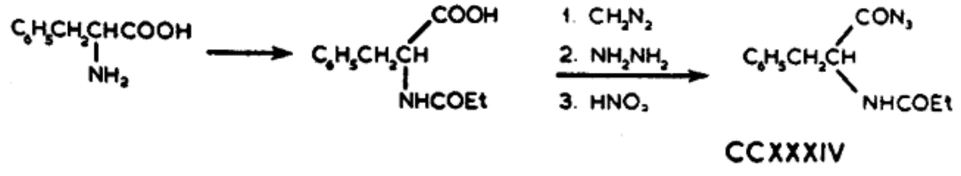
CCXXXII

isovaleryl-L-phenylalanyl-L-proline (CCXXXII). The potential keto acid portion of the molecule appears in the degradation product in the reduced form, owing to a Wolff-Kishner reduction during the reaction. When the alkaloids are degraded by hydrolytic fission using 1 equiv. of aqueous alcoholic potassium hydroxide, the keto acid appears as such, and the products from ergotamine are CCXXXIII and lysergic acid amide (786b).

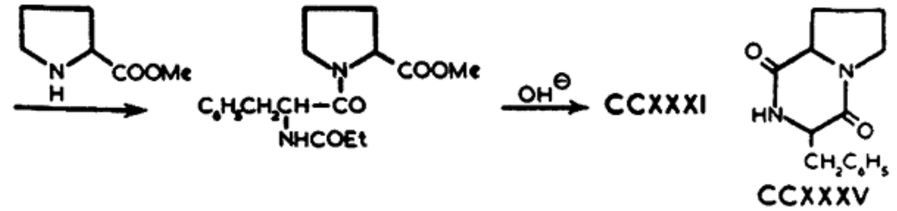


CCXXXIII

The constitutions of the degradation products obtained with hydrazine have been fully confirmed by synthesis. Thus, propionyl-L-phenylalanyl-L-proline (CCXXXI) was prepared by propionylation of L-phenylalanine with propionic anhydride, followed by conversion to the azide (CCXXXIV), which, on coupling with L-proline methyl ester and saponification, gave the desired product (CCXXXI), identical with the hydrazine degradation product (786a).

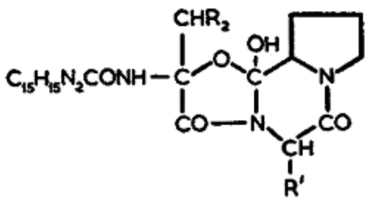


CCXXXIV

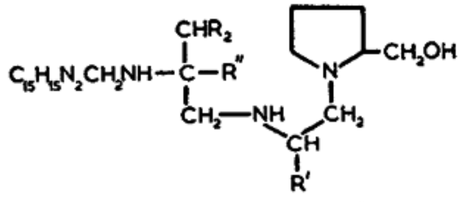


CCXXXI CCXXXV

Although these results are perfectly consistent with the structure CCXXX for the alkaloids, it is apparent that it is not a completely satisfactory formulation, since a by-product in the hydrazine degradation of dihydroergotamine is phenylalanylproline lactam (CCXXXV) (786a). This diketopiperazine derivative is also obtained when dihydroergotamine is hydrolyzed with rather less than 1 equiv. of alkali (786b).



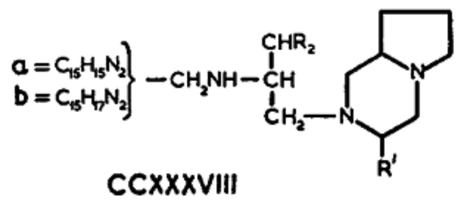
CCXXXVI



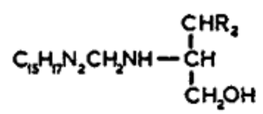
CCXXXVII a, R″ = OH, b, R″ = H

The presence of this product is significant, since it is obtained under conditions which preclude its formation from amino acid components. It can therefore be concluded that the diketopiperazine ring of CCXXXV is actually present in the peptide portion of the alkaloid molecule. This can be accommodated within the framework of the earlier formula by subdivision of the nine-membered lactone ring into two rings of six and five atoms, as shown in CCXXXVI (787).

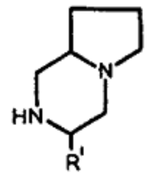
This new formulation provides a completely satisfactory explanation of the behavior of the alkaloids on reduction and thermal cleavage. Lithium aluminum hydride reduction of compounds of type CCXXX should lead to long-chain polyamino alcohols, e.g., CCXXXVIIa, or, more likely CCXXXVIIb, since the former is a carbinolamine. On the other hand, if the ergot alkaloids contain a preformed diketopiperazine ring, as in CCXXXVI, reduction would be expected to yield a bicyclic polyamine, of formula CCXXXVIIIa. In a comprehensive series of lithium aluminum hydride reductions of the dihydro alkaloids, Stoll and co-workers (787) obtained not only polyamines of type CCXXXVIIIb, but also the two reduced fragments of the polypeptide half, CCXXXIX and CCXL, formed by severance of the five-membered ring. For example, dihydroergosine gave dihydrolysergyl-alanyl-1,2-trimethylene-5-isobutylpiperazine (CCXLI), while dihydroergocristine gave the polyamine CCXXXVIIIb (R = Me, R′ = $CH_2C_6H_5$), the amino alcohol CCXXXIX (R = Me) and 1,2-trimethylene-5-benzylpiperazine (CCXL, R′ = $CH_2C_6H_5$). The appearance of CCXXXIX (R = Me) is not so important, since it can presumably be obtained also from cyclic peptides of formula CCXXX, but the production of both CCXXXVIII and CCXL strongly suggests that the piperazine ring is already present in the alkaloids themselves. Since, during the reduction,



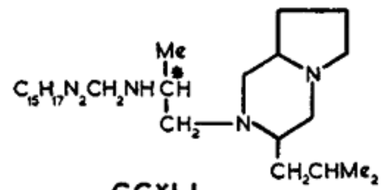
CCXXXVIII



CCXXXIX

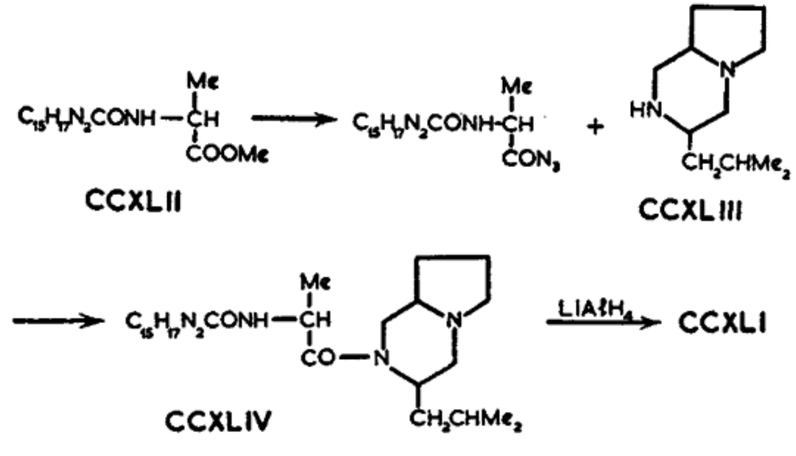


CCXL



CCXLI

a change of substituent occurs on one of the asymmetric carbon atoms (marked with an asterisk in CCXLI), partial racemization will occur at this position. Since the configuration of the asymmetric carbon atom of the proline residue is also in doubt (hydrolysis yields D-proline derivatives, but hydrazine fission yields L-proline derivatives), four stereoisomers must be synthesized in order to allow full comparison to be made with the lithium aluminum hydride reduction products. In fact, only two polyamines were obtained, showing that racemization occurred at only one carbon atom during the reaction. The synthesis of the polyamines -I and -II derived from dihydroergosine was achieved by condensation of dihydrolysergic acid azide with alanine methyl ester to give the amide-ester CCXLII, which was then converted via the hydrazide into the corresponding azide. Condensation of this with the piperazine CCXLIII gave the dihydrolysergylamide derivative CCXLIV, which was reduced with lithium aluminum hydride to the polyamine CCXLI. The four stereoisomers synthesized were derived from L-leucine, D- and L-proline, and D- and L-alanine. The two polyamines



CCXLII

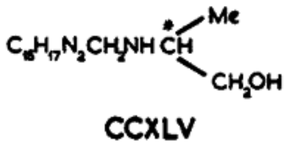
CCXLIII

CCXLIV

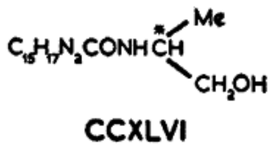
CCXLI

obtained from the alkaloids were shown by comparison to be derived from L-leucine, L-proline, and D- and L-alanine. It thus appears that hydrazine fission of the alkaloids proceeds by retention of configuration of the proline component, but that in alkaline hydrolytic processes, this asymmetric carbon atom suffers inversion (787).

The amino alcohol CCXLV isolated in addition to the polyamines from the lithium aluminum hydride reduction of dihydroergosine should be obtainable by the reduction of the corresponding amide (CCXLVI), which is dihydroergometrine. Comparison of the products from dihydroergosine and dihydroergometrine, however, showed that they did not possess the same melting points and optical rotations. Since racemization of the alanine component accompanies the formation of CCXLI, it is evident that racemization at the same carbon atom must also occur in the production of CCXLV. As expected, mixtures of equal amounts of the diastereoisomers of CCXLV derived from L- and D-aminopropanol were identical in all respects with the reduction product of dihydroergosine (CCXLV) (787).



CCXLV



CCXLVI

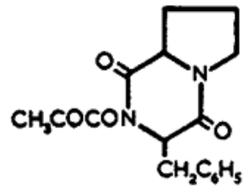
The structure of the third reduction product proved relatively easy to determine. Dihydroergocryptine, for example, yielded a piperazine which was identified by synthesis from L-leucine and L-proline as L,L-1,2-trimethylene-5-isobutylpiperazine (CCXLIII) (787).

Thermal cleavage of the dihydro alkaloids provides further evidence in support of the formula CCXXXVI. At 200°, decomposition occurs, to give dihydrolysergic acid amide and a second cleavage product which contains all the carbon atoms of the peptide half. Thus, for dihydroergotamine, the following result is obtained:

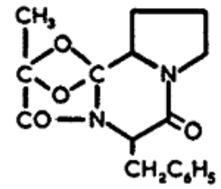
$$C_{15}H_{17}N_2.CONHC_{17}H_{19}O_4N_2 \rightarrow C_{15}H_{17}N_2CONH_2 + C_{17}H_{18}O_4N_2$$

This peptide fragment is neutral in reaction, possesses no active hydrogen, and does not absorb hydrogen in the presence of palladium or platinum catalysts. Although fairly stable to acids, it is readily hydrolyzed by alkali to pyruvic acid and a diketopiperazine (CCXXXV). Analogous results are obtained with the other alkaloids (787). Hence, the thermal cleavage product from dihydroergotamine must be the pyruvoyl-diketopiperazine CCXLVII, or be closely related to it. Grob and Meier (791) believe that it is simply CCXLVII, but Stoll *et al.* (787) interpret its resistance to hydrogenation as indicating the absence

of carbonyl groups, other than amide groups; the molecule must therefore be tetracyclic, or, at least, tricyclic. Since a bond between the carbonyl group of the pyruvic acid fragment and one of the amide groups of the diketopiperazine unit is already presumed to be present in the parent alkaloid, the thermal cleavage product is formulated as

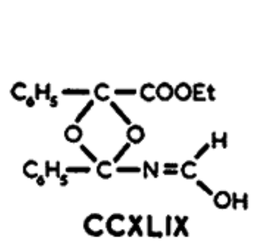


CCXLVII

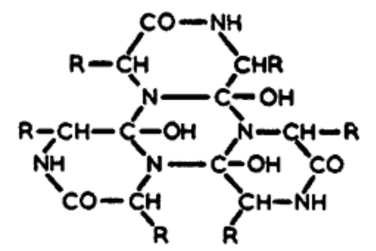


CCXLVIII

CCXLVIII. An unusual feature of this type of structure is the combination of an oxazolidone ring with a dioxacyclobutane ring. No fully authenticated examples of this type of compound are known, although Diels and Pillow have reported the preparation of a substance, claimed to be CCXLIX, which, like the thermal cleavage product, is resistant to acids but readily hydrolyzed by alkalis (788).



CCXLIX

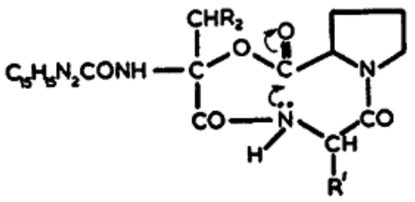


CCL

These data are sufficient to establish the formulas of the ergot alkaloids as either CCXXX or CCXXXVI beyond all reasonable doubt. Owing to the ease and frequency with which diketopiperazine derivatives are obtained on degradation, the latter is preferred. However, a highly unorthodox characteristic of this "cyclol" formula is the carbinolamine linkage in the peptide half, which is formed, not from simple carbonyl and amine precursors, but from a lactone carbonyl group and an amide nitrogen atom. Moreover, the hydroxyl group so produced is encountered in the free state in the alkaloids. No other authentic representatives of this type of structure are known, although Wrinch has postulated a similar constitution (e.g., CCL) in a cyclol theory for the structure of peptides (789).

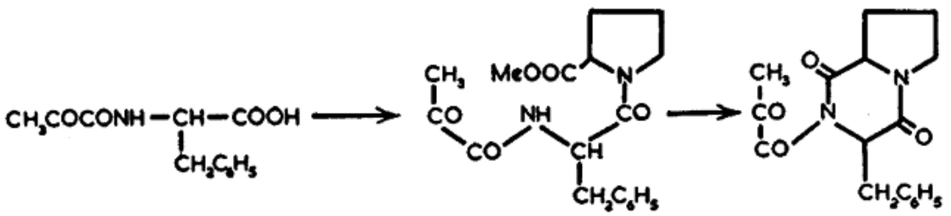
It has been questioned whether the cyclol formula possesses any stabilizing factors over the earlier lactone formula, particularly in view of the fact that large-ring lactones are widespread in nature (768). It may be that in the alkaloids the spatial proximity of the amide nitrogen

and the lactone carbonyl group leads to a transannular amide-type neutralization (cf. cryptopine) (790). The peptide half of the molecule can then be written as CCXXXVIa, and the ease of formation of diketopiperazine or piperazine derivatives on degradation becomes apparent.



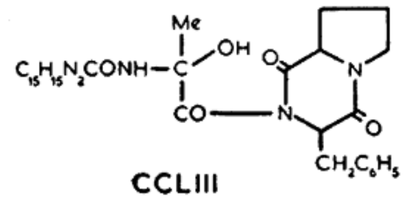
CCXXXVIa

Attention has recently been directed to the synthesis of the thermal cleavage product from ergotamine, CCXLVII or CCXLVIII, and two syntheses have been reported. Grob and Meier prepared *N*-pyruvoyl-DL-phenylalanine (CCLI), converted it into the acid chloride, which was not isolated, and reacted this with DL-proline methyl ester to give *N*-pyruvoyl-DL-phenylalanyl-DL-proline methyl ester (CCLII). This was saponified, and the acid cyclized with acetic anhydride and sodium acetate, to yield racemic *N*-pyruvoyl-phenylalanylproline lactam (CCXLVII). This is the inactive form of the thermal degradation product, and behaves similarly in all respects except in regard to optical rotation and melting point. Thus, mild hydrolysis with water, dilute alkali, methanol, or ammonia gives the appropriate pyruvic acid derivative, and DL-phenylalanylproline lactam (CCXXXV) (791). In addition, the synthetic product is extremely difficult to reduce catalytically, and using a platinum catalyst in acetic acid, hydrogen is absorbed only very slowly. This parallels the behavior of the thermal degradation product. The IR-spectra of the latter and the synthetic compound CCXLVII are almost completely superimposable. In the carbonyl region there are three prominent peaks, at 5.79, 5.86, and 5.97μ; it is probable that the first of these corresponds to the absorption of the ketone carbonyl group, while the other two are associated with the three amide functions. However, this is by no means unequivocal, and Grob and Meier conclude, from an inspection of the IR-absorption



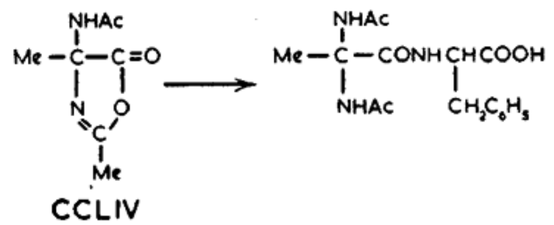
CCLI CCLII CCXLVII

of pyruvic acid diethylamide, that it is not possible to estimate with certainty the contribution of the ketone carbonyl group in the presence of three amide groups. On the basis of these results, the thermal cleavage product of ergotamine is believed to be an optically active form of CCXLVII, and its formation occurs by two simple stages, via the intermediate CCLIII (791).

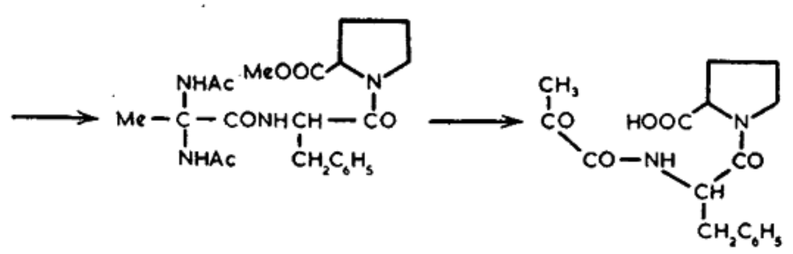


CCLIII

In the second synthesis of this degradation product, the azlactone CCLIV was condensed with L-phenylalanine, and a further peptide linkage introduced by reaction of the product with L-proline methyl ester, to give CCLV, from which the free keto acid (CCXXXIII) was



CCLIV



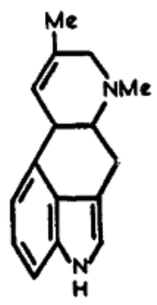
CCLV CCXXXIII

obtained by successive alkaline and acid hydrolysis. The dimethylpyruvoyl derivative corresponding to CCXXXIII was also synthesized, and shown to be identical with the product of alkaline hydrolysis of ergocristine. Treatment of CCXXXIII with acetic anhydride and pyridine or sodium acetate at 80–100° gave a neutral, crystalline product, identical in all respects, including optical rotation, with the thermal cleavage product of ergotamine. The analogous degradation products of ergocristine, ergocryptine, and ergocornine were also synthesized in optically active form. The dioxacyclobutane formula for these products (e.g., CCXLVIII) is still favored by these investigators. The proline residue has the D-configuration, whereas in the acids from which they

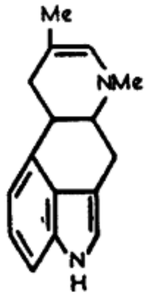
are prepared, it has the L-configuration. It is not known whether it must have the D-configuration in order to cyclize, or whether in the resulting product the D-form of the diketopiperazine ring is the more stable isomer. However, Stoll *et al.* believe that the fact that the fission product appears to be stable only when the proline unit has the D-configuration indicates that the pyruvoyl or dimethylpyruvoyl residue is not linear in these products, but is cyclized on to the diketopiperazine ring (792).

8. Agroclavine

Agroclavine, $C_{16}H_{18}N_2$, m.p. 206° (dec.), $[\alpha]_D^{20}$ −151° (chloroform), is elaborated by ergot fungi parasitic on *Elymus mollis* Tri., *Agropyrum semicostatum* Nees, *Imperata cylindrica* var. *koenigii*, and the tropical spike-millet, *Pennisetum typhoideum* Rich. (747, 793, 794, 796, 797). It can also be obtained from the saprophytic culture of ergot fungi originating on *Elymus mollis* or *Pennisetum typhoideum* (794, 796, 807). Agroclavine is readily soluble in organic and mineral acids, gives a blue coloration with Ehrlich's reagent, a blue color with sulfuric acid (794), and a violet-blue color with Keller's reagent (796). Its UV-spectrum is typical of unconjugated indole derivatives, with maxima at 227, 284 and 293 mμ (796). The molecule contains a double bond, which is not reduced by sodium and amyl alcohol, but can be reduced catalytically, to give dihydroagroclavine, m.p. 233–237° (798). Agroclavine is stable to acids, and cannot be isomerized under conditions used for the equilibration of lysergic and isolysergic acids (799). These properties indicate that this alkaloid is a simple derivative of ergoline, with a double bond not conjugated with the indole nucleus, and Abe has proposed the alternative formulas, CCLVIa or CCLVIb (799). Since solutions of agroclavine and dihydroagroclavine hydrochlorides show the

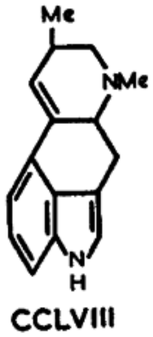


CCLVIa



CCLVIb

CCLVII



CCLVIII

same pH value, it is unlikely that agroclavine is a vinylamine, and hence CCLVIa is preferred (800). Oxidation of agroclavine with nitric acid gives oxalic acid and a dibasic acid, $C_{14}H_{11}O_6N$, m.p. > 360°, which, on distillation over soda-lime, yields 3-methylquinoline, methylamine,

and an unknown acid, m.p. 216–220°. The isolation of 3-methylquinoline confirms the position assigned to the methyl group, at C_8 of the ergoline nucleus (800).

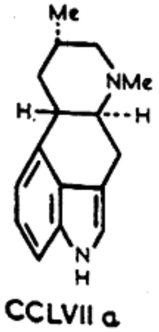
Reduction of agroclavine with sodium and butanol gives a mixture of festuclavine, costaclavine, and pyroclavine (stereoisomers of CCLVII), together with 6,8-dimethyl-Δ^9-ergolene (lysergine) (CCLVIII) (808). The last-named base is undoubtedly the progenitor of the stereoisomers of CCLVII, since it can also be obtained, in excellent yield, by the isomerization of agroclavine with hot sodium butylate, and gives, on reduction with sodium and butanol, a mixture of festuclavine and costaclavine. Catalytic hydrogenation of CCLVIII yields festuclavine exclusively (808).

It is of interest that agroclavine, which does not possess a functional group at C_8, has a high physiological activity, and is active at a dilution of 1/10,000,000 *in vivo* on the uteri of rabbit and guinea pig (793).

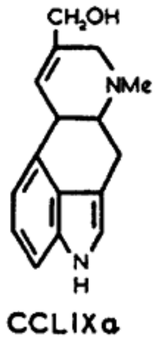
Festuclavine (CCLVIIa), m.p. 242° (dec.), $[\alpha]_D^{20}$ −69° (chloroform) ("Alkaloid Y") has been isolated from the ergots of *Agropyrum* species and also from the saprophytic culture of ergots obtained from *Agropyrum* and *Phalaris* species (797, 807, 809).

9. Elymoclavine

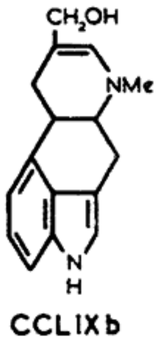
Elymoclavine, $C_{16}H_{18}ON_2$, m.p. 249° (dec.), $[\alpha]_D^{20}$ −109° (EtOH), is produced by the ergot fungus parasitic on *Elymus mollis*, and has also been isolated from the saprophytic culture of a sclerotium obtained from *Pennisetum typhoideum*, using a nutrient medium containing mannitol, ammonium succinate, and inorganic salts (796, 797, 801). It is somewhat soluble in water, and crystallizes as prisms from the common organic solvents. With *p*-dimethylaminobenzaldehyde it gives a deep blue color, and with Keller's reagent a deep purplish-blue color



CCLVII a



CCLIXa



CCLIXb

CCLX

(801). Its UV-absorption spectrum has maxima at 227, 283, and 293 mμ, which is characteristic of unconjugated indole derivatives. Of the two possible constitutions, CCLIXa and CCLIXb, proposed by Abe *et al.*, the former is preferred, by analogy with agroclavine (801); it is

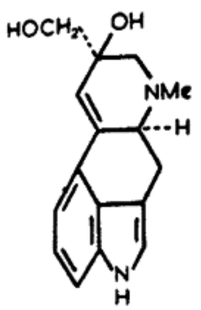
also supported by the results of reduction of elymoclavine. Hydrogenation yields a mixture of dihydrolysergol and dihydroisolysergol (802), while sodium and butanol reduction yields the same two alcohols, together with agroclavine, lysergine, festuclavine, pyroclavine, and costaclavine. The formation of festuclavine and its stereoisomers in this reaction does not proceed via hydrogenolysis of dihydrolysergol and dihydroisolysergol, since these saturated alcohols are unaffected by sodium and butanol (808). Treatment of elymoclavine with hot sodium butylate gives a mixture of lysergol, m.p. 249–250° (dec.), $[\alpha]_D^{27}$ +50° (pyridine), and lysergene, $C_{16}H_{16}N_2$, m.p. 244–245° (dec.), $[\alpha]_D^{20}$ +407° (chloroform) (CCLX) (810). The formulation of the latter as CCLX is confirmed by its UV-spectrum (maxima at 243, 263, and 335 mμ), and by its reduction with sodium and butanol to agroclavine, lysergine, festuclavine, pyroclavine, and costaclavine (810). Evidently, lysergene is the progenitor of these five last-named bases in the reduction of elymoclavine; it may also be assumed that lysergol and isolysergol are the intermediates in the production of their respective dihydro derivatives.

10. Penniclavine and Isopenniclavine

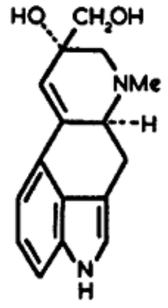
Penniclavine and isopenniclavine form a stereoisomeric pair of alkaloids, which can be obtained from the saprophytic culture of the fungus isolated from *Pennisetum typhoideum* Rich. or from *Elymus mollis* (796, 803, 807). Penniclavine, $C_{16}H_{18}O_2N_2$, crystallizes as rectangular plates from methanol or acetone, m.p. 222° (dec.), $[\alpha]_D^{20}$ +153° (pyridine). Isopenniclavine crystallizes from water as hexagonal plates, m.p. 163–165° (dec.), $[\alpha]_D^{20}$ +146° (pyridine). It is noteworthy that these alkaloids have not yet been isolated directly from natural ergots.

The color reactions of these two alkaloids differ somewhat from those of the ergot alkaloids bearing a substituted amide function at C_8. The Keller and van Urk (*p*-dimethylaminobenzaldehyde) reagents give a yellowish-green, instead of the usual blue, color, while sulfuric acid gives an intense pure blue coloration (807). The UV-spectra of penniclavine and isopenniclavine exhibit maxima at 240 and 315 mμ, in close analogy with the spectrum of lysergic acid. It is thus apparent that a double bond is conjugated with the indole ring system. The oxygen atoms are contained in a glycol grouping, since oxidation with periodic acid gives formaldehyde, identified as its dimedone derivative. Penniclavine and isopenniclavine are thus CCLXIa and CCLXIb, not necessarily respectively. By comparison of their basic strengths and behavior on alumina with the corresponding properties of lysergol (pK_b 6.60) and isolysergol (pK_b 7.10), it may be deduced that penniclavine (pK_b 7.40) is CCLXIa and isopenniclavine (pK_b 8.10) is CCLXIb (807). These two

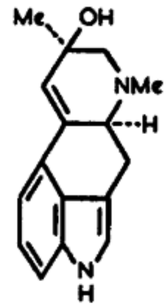
alkaloids can be prepared *in vitro*, in small yield, by the dichromate oxidation of elymoclavine (802, 807).



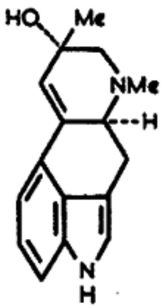
CCLXIa



CCLXIb



CCLXIIa



CCLXIIb

11. Setoclavine, Isosetoclavine, and Triseclavine

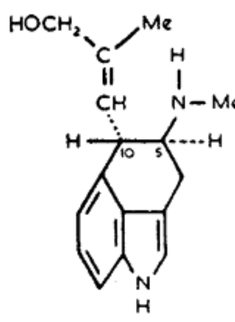
The stereoisomeric pair, setoclavine and isosetoclavine, $C_{16}H_{18}ON_2$, can also be obtained by the saprophytic culture of *Pennisetum typhoideum* (807). Setoclavine crystallizes from methanol or acetone as prisms, m.p. 229–234° (dec.), $[\alpha]_D^{20}$ +174° (pyridine). Isosetoclavine ("Alkaloid V") forms polygons from methanol, m.p. 234–237° (dec.), $[\alpha]_D^{20}$ +107° (pyridine), and has also been isolated from the saprophytic culture of the fungus parasitic on Japanese *Agropyrum semicostatum* Nees, *Trisetum bifidum* Ohwi, and *Festuca rubra* L. (809). The physical constants and chemical properties of triseclavine, m.p. 223°, $[\alpha]_D^{18}$ +137° (pyridine), an alkaloid elaborated by the fungus of *Elymus mollis*, indicate that it is probably a mixture of setoclavine and isosetoclavine (803).

Setoclavine and isosetoclavine contain one *C*-methyl group and two active hydrogen atoms; their UV-spectra are identical with the spectrum of lysergic acid, and their formulation as stereoisomers is supported by the close similarity of their IR-spectra. The oxygen atom is present as a hydroxyl group (active hydrogen and IR-spectrum), which is probably tertiary, since neither of the alkaloids can be acetylated. Moreover, they are both sensitive to acids and can readily be dehydrated to unstable products. The constitutions CCLXIIa and CCLXIIb are confirmed by the dichromate oxidation of agroclavine, which affords a high yield of setoclavine and isosetoclavine. By comparison of the basic strengths of these two alkaloids with the corresponding data for lysergol, penniclavine, and their C_8 epimers, it may be deduced that setoclavine (pK_b 7.45) is CCLXIIa, and isosetoclavine (pK_b 7.95) is CCLXIIb (807).

12. Chanoclavine

Chanoclavine, $C_{16}H_{20}ON_2$, is the only tricyclic ergot alkaloid known to date. It has been isolated from the saprophytic culture of *Pennisetum*

typhoideum Rich., and crystallizes from methanol or acetone as dense prisms, m.p. 220–222° (dec.), $[\alpha]_D^{20}$ −240° (pyridine). Its UV-spectrum is characteristic of unconjugated indole derivatives; the Keller and van Urk reagents give a violet-blue coloration. Owing to the fact that the amino nitrogen is secondary, chanoclavine, pK_b 5.80, is a stronger base than the majority of ergot alkaloids. The molecule possesses one *C*-methyl and one alcoholic hydroxyl group. Acetylation with acetic anhydride and pyridine proceeds readily, to give the nonbasic *O*,*N*-diacetylchanoclavine, m.p. 174–175° (*O*-Ac at 1740 cm.$^{-1}$, *N*-Ac at 1630 cm.$^{-1}$ in the IR-spectrum), which can be saponified to *N*-acetylchanoclavine, m.p. 226–228° (*N*-Ac at ~ 1630 cm.$^{-1}$). Vigorous alkaline hydrolysis of the latter leads mainly to decomposition, but a small yield of chanoclavine can be recovered. These properties are in accord with the formulation of chanoclavine as CCLXIII. The substituents at C_5 and C_{10} must be *trans* oriented, since hydrogenation over a palladium black catalyst gives a small yield of festuclavine, for which the conformation CCLVIIa is favored (807).



CCLXIII

13. Miscellaneous Alkaloids

The saprophytic culture of ergot fungi derived from *Agropyrum semicostatum* Nees has also yielded pyroclavine ("Alkaloid Z"), m.p. 204°, $[\alpha]_D^{20}$ −90° (pyridine), and costaclavine ("Alkaloid U"), m.p. 182°, $[\alpha]_D^{20}$ +44° (pyridine), which are stereoisomers of festuclavine (809).

Secaclavine ("Alkaloid X"), m.p. 210° (dec.), $[\alpha]_D^{28}$ −167° (chloroform), occurs together with festuclavine, agroclavine, and elymoclavine, in the ergots of Japanese *Agropyrum*, *Elymus*, *Phragmites*, and *Phalaris* species (797, 809). It can also be isolated from the ergot of Spanish rye and from the culture of these ergot fungi. Its UV-spectrum is typical of indole derivatives, and it is presumed to be an isomer of dihydroelymoclavine (797).

Molliclavine, $C_{16}H_{18}O_2N_2$, m.p. 253°, has been isolated from the culture of *Elymus mollis* (804). The molecule contains a double bond and can be reduced to dihydromolliclavine, the color reactions of which are indistinguishable from those of agroclavine and lysergic acid.

The increasing use of paper chromatographic techniques has provided evidence for the existence of further ergot alkaloids. For example, Pöhm (805) has investigated the alkaloids of *Claviceps lit.* Kaw., identified ergosine and ergocryptine and their C_8 epimers, and obtained evidence for the presence of two pairs of new alkaloids, ergohexine (ergohexinine) and ergoheptine (ergoheptinine). Croatian ergots are also claimed to contain a new alkaloid, present to the extent of 10–15% (806). The ergots from Spain, Portugal, and Hungary have been investigated by the use of a formamide-benzene-petroleum system, and an alkaloid, designated EK 115, has been isolated. Hydrolysis gives a mixture of amino acids, among which are lysergic acid, proline, and leucine (751).

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