R.H.F. Manske
The Alkaloids
Volume VIII

—CHAPTER 21—

THE ERGOT ALKALOIDS

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I. The Biology of Ergot and a Short History of Its Active Principles Up to the Discovery of Ergotamine

The isolation of therapeutically active compounds from metabolic products of fungi is no longer regarded as an extraordinary event. Antibiotics constitute excellent examples of the results produced by modern biochemical research. The fungus ergot has been employed in medicine for centuries, and the quest for its active principles commenced nearly 150 years ago.

The term ergot or *Secale cornutum* designates the dark brown, horn-shaped pegs, projecting from the ripening ears of rye in place of the rye grains. These tuberous bodies are collected before and during the harvesting or are separated from the threshed rye and represent one of the most remarkable drugs of the therapeutic armamentarium. Histologically speaking, they consist of compactly interwoven hyphae of a filamentous fungus [*Claviceps purpurea* (Fries) Tulasne]; biologically speaking, these compact grains are sclerotia, the form in which the fungus passes the winter. Warm weather in the spring causes the ergot, which has become swollen owing to moisture, to germinate and put out bundles of hyphae and, later, long-stalked stromata. The surfaces of these stromata carry numerous perithecia (radially arranged, pear-shaped cavities) in which filamentous ascospores are formed. Upon exposure of the terminal knob or capitulum of the stroma to the light, the ascospores are expelled into the air, are carried upward by rising convection currents, and settle on open rye flowers. Here, by using the stigmata of the flower as nutrient, they form a mycelium. Very soon, conidia are formed from the fungus filaments by abstriction, and these are surrounded by a vast quantity of sweet fluid, the so-called honeydew, which is secreted simultaneously. The infectious secretion is transferred to other rye flowers by insects or when neighboring ears are brought into contact by the wind, so that an infection, caused by the conidia suspension, results.

After a few weeks, the mycelium solidifies to the externally dark-colored, internally white pseudoparenchyma, which forms the so-called sclerotium known as ergot. The fungus *Claviceps purpurea* and related species also attack other plants of the Gramineae (1) family and form sclerotia, the shape and size of which vary with the species of the host plant. The official form of ergot, however, is the product that forms on the ears of rye.

It is not within the scope of this article to describe how devastatingly the population of vast areas was poisoned as a result of the presence of ergot in the grain used for making bread. It should, however, be noted

that the cause of the poisonings was still unknown, even after ergot was already being used in small doses by midwives as a proved means of inducing pains, as described by Adam Lonicer in his "Kreuterbuch" as early as 1582. The history of ergot and the ergot poisonings has been exhaustively described by Barger in his comprehensive monograph "Ergot and Ergotism," Gurney and Jackson, London, 1931. Ergot, however, has only been used in official medicine since the American physician John Stearns (2) reported on the drug's contractive action on the uterus in his publication, "Account of the Pulvis Parturiens, a Remedy for Quickening Child-birth" in 1808. The first pharmaceutical-chemical investigation was published in 1816 by the French pharmacist Vauquelin (3). However, this publication and the numerous publications which appeared in the following 100 years gave no convincing data on the chemical nature of the specific active principles of ergot. Opinions regarding the chemical nature of the active principles changed frequently up to the beginning of the present century, even after the French pharmacist Tanret (4, 5) succeeded in isolating a crystalline alkaloid preparation "ergotinine cristallisée" in 1875 and the English research workers Barger and Carr (6, 7) and the Swiss pharmacist Kraft (8, 9) simultaneously isolated compounds from ergot in 1906 which they named ergotoxine and hydroergotinine, respectively, and which were later found to be identical. Our seventh treatise on the ergot alkaloids (10) reported the history of ergotoxine and ergotinine in great detail and showed that the two preparations, described in the literature, were not of a uniform nature but consisted of variable components. It is probable that the resulting fluctuations in activity were partly responsible for the fact that ergotinine and ergotoxine preparations found no lasting clinical application. Nevertheless, it was with ergotoxine preparations that the pharmacologist Dale (11) was first able to demonstrate the uterotonic effect typical of ergot. He also noted that they inhibited those functions controlled by the sympathetic nervous system and that they exhibited a specific antagonistic action to adrenaline. These observations were of the greatest importance to the subsequent practical application of ergot alkaloids. On the basis of disappointing toxicological observations, however, Kraft (12) advised that the alkaloids of ergot extracts should be removed even more carefully than had hitherto been the case. Even the 1923 edition of the British Pharmaceutical Codex still expressed the opinion that ergotoxine was not the specific active component of ergot. Many of the prescriptions given in the pharmacopoeia led to preparations which, though containing small and varying quantities of a water-soluble active principle, did not contain alkaloids of the ergotoxine type.

Thus, the necessity of obtaining an ergot preparation for the treatment

of post partum uterine atony, constant and reliable in its action, remained. This need could only be satisfied by producing the pure natural active principle. The well-known fact that storage caused the activity of ergot to decrease proved that the active principle of ergot could decompose. Furthermore, upon administration of the ergot extracts, the contracting action occurred only after a latent period, so that the molecule constituting the active principle could be assumed to be relatively large (13, 14) and would thus undergo oxidative and fermentative changes upon storage. Mild conditions of the type developed in the preparation of chlorophyll, for example, suitably adapted to the isolation of the active principles of ergot, were thus a prerequisite for the success of the isolation.

We worked on the assumption that the specific active principle of ergot was a base, e.g., an alkaloid. In order to protect this substance against conversion or oxidation, it was left under the protection of the amphoteric cell material. This was made weakly acid, and all the soluble, acid, and neutral components were exhaustively extracted with an inert solvent, e.g., benzene. By making the cell material alkaline, e.g., by treating it with ammonia, it was possible to extract, with the aid of the same solvent, the basic components of the drug, relatively free from impurities. These components could then be obtained by evaporating the extract. Crystallization of the resulting crude alkaloid from aqueous acetone resulted in diamond-like, glistening crystals. These were homogeneous and possessed all the typical biological properties of ergot. The alkaloid was named ergotamine (15).

The susceptibility of ergotamine to light and to air and the fact that, under the influence of acid, it is easily converted to a difficultly soluble isomeric form, ergotaminine, explains why previous research workers, who had not taken the same precautions, were unsuccessful in its isolation. Ergotamine was thus the first homogeneous specific active principle of ergot, and its production formed the basis for dependable clinical research. As little as 0.25 mg of the tartrate form in 0.5 ml of isotonic solution generally causes powerful contractions of the human uterus and arrests dangerous post partum hemorrhage.

Pure ergotamine enabled pharmacological and clinical investigations to expand and intensify in the field of the vegetative nervous system, thus providing the basis for the widespread use of ergot's active principles in internal medicine and neurology.

With the preparation of pure ergotamine, chemical research on ergot also entered a new phase so that, after many decades, it finally became possible to elucidate the structure of the ergot alkaloids and to achieve their total synthesis. This will be shown in the remainder of this chapter.

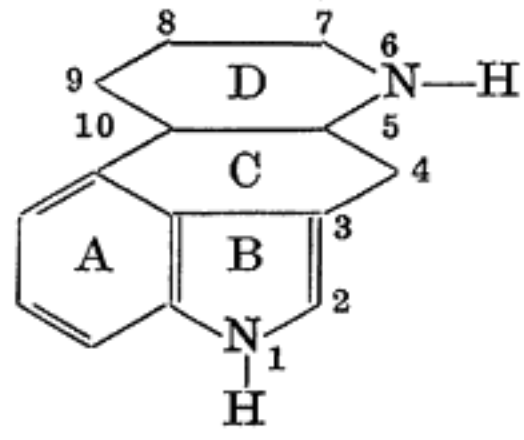
It should be noted at this stage that, in some ergot types, other bases having a similar structure, e.g., those of the ergotoxine group, may occur in addition to or in place of ergotamine. Furthermore, mention should be made of the water-soluble, low molecular weight alkaloid ergometrine (ergobasine), which exhibits a powerful and quick-acting constrictor action on the smooth muscle of the uterus but is practically devoid of actions on the vegetative nervous system.

In addition, a new group of ergot alkaloids, found especially in ergot grown on wild grasses, was later discovered. These alkaloids belong to a new type of structural group, the so-called clavine type of ergot alkaloids.

Detailed analytical investigations of commercial samples of ergot showed that the alkaloid content varied from 0.00 to 0.30%. The source of the ergot strongly influences the type of compounds contained therein, i.e., whether they are alkaloids of the ergotamine or of the ergotoxine type. This was a further reason necessitating the production and use of pure compounds for pharmacological investigations and clinical use. After the report on the chemical results, we shall include a final section as a summary of the pharmacological and clinical results obtained.

II. Structural Types with Tables of the Natural Ergot Alkaloids

If the stereoisomer forms are regarded as a single alkaloid in each case and those bases which, though shown to exist by means of paper chromatography, have not had their structure elucidated are ignored, a total of approximately two dozen ergot alkaloids have been described to date. All these alkaloids are formed from the same tetracyclic ring system that Jacobs and Gould (16) named ergoline (I).

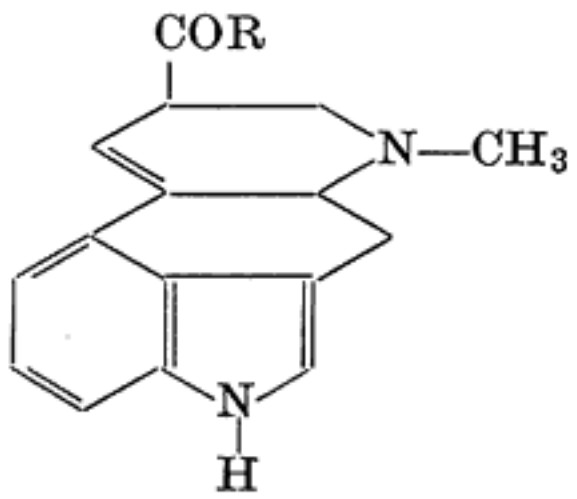


I
Ergoline

On the basis of their structural differences, the ergot alkaloids may be divided into two main groups: one group to include all lysergic acid derivatives of the acid amide type, and the other to include the so-called clavine alkaloids. Further structural groups may be recognized within these main groups, as is shown by Tables I and II.

TABLE I

THE NATURAL ERGOT ALKALOIDS OF THE LYSERGIC ACID SERIES



General formula

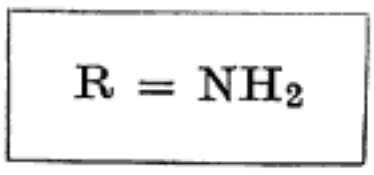
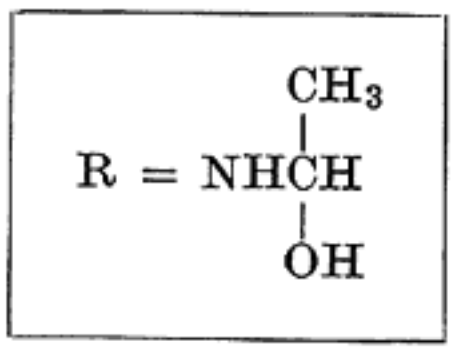
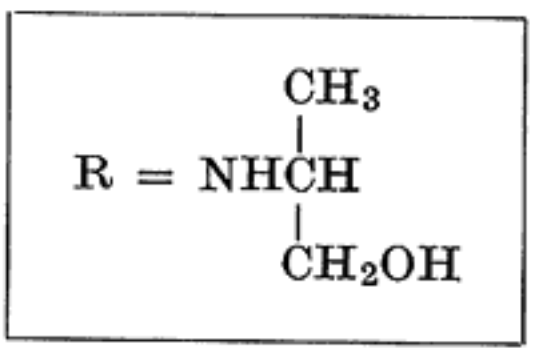
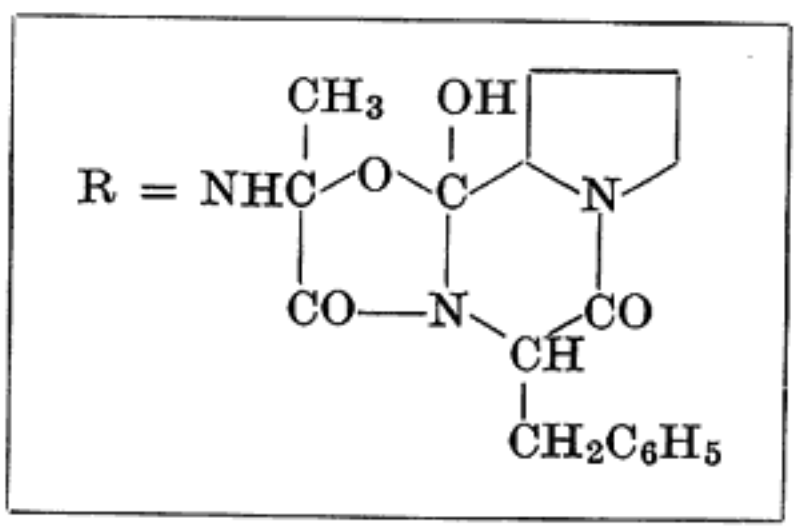
Alkaloid	Formula	Section
A. Simple lysergic acid and isolysergic acid amides		
		
Ergine Erginine	$C_{16}H_{17}ON_3$	IV, A
		
Lysergic acid methylcarbinolamide	$C_{18}H_{21}O_2N_3$	IV, B
		
Ergometrine (Ergobasine) Ergometrinine (Ergobasinine)	$C_{19}H_{23}O_2N_3$	IV, C
B. Derivatives of lysergic acid and isolysergic acid of the peptide type		
Ergotamine group		
		
Ergotamine Ergotaminine	$C_{33}H_{35}O_5N_5$	V, C, 1

TABLE I—*continued*

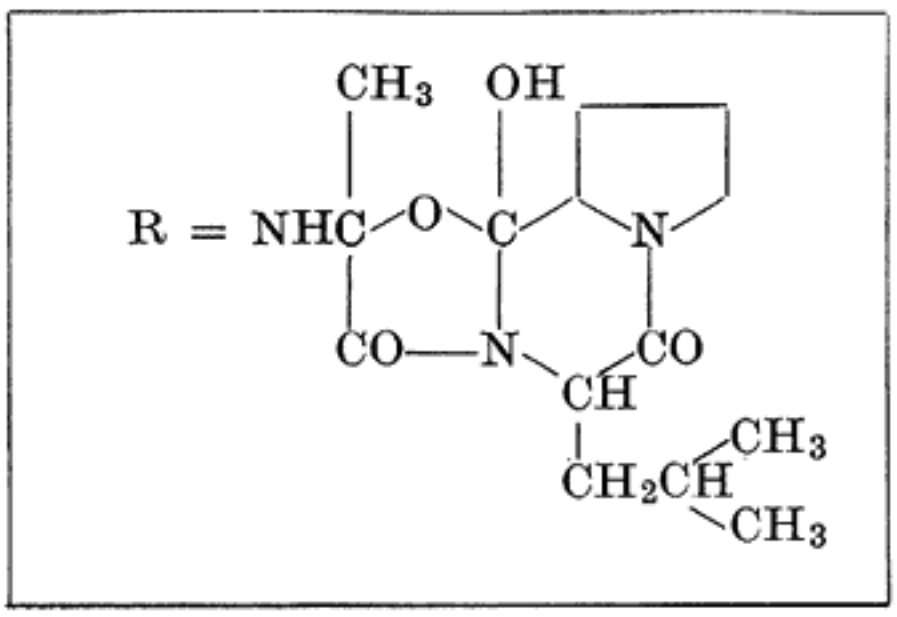
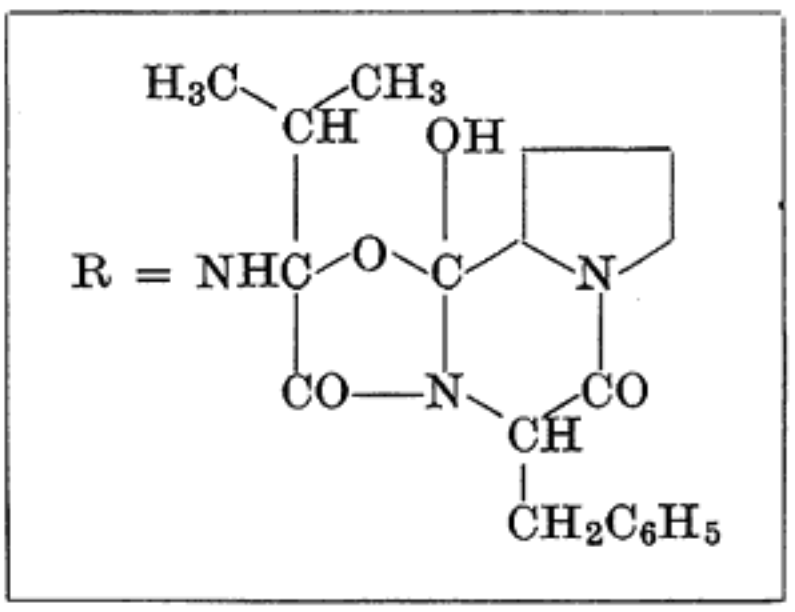
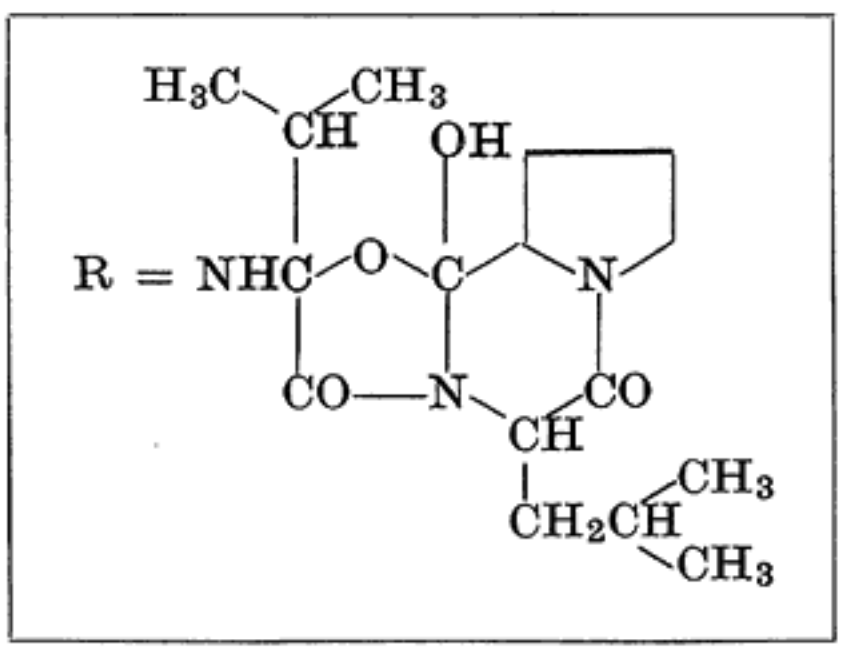
Alkaloid	Formula	Section
		
Ergosine Ergosinine	$C_{30}H_{37}O_5N_5$	V, C, 2
Ergotoxine group		
		
Ergocristine Ergocristinine	$C_{35}H_{39}O_5N_5$	V, C, 3
		
Ergocryptine Ergocryptinine	$C_{32}H_{41}O_5N_5$	V, C, 4

TABLE I—*continued*

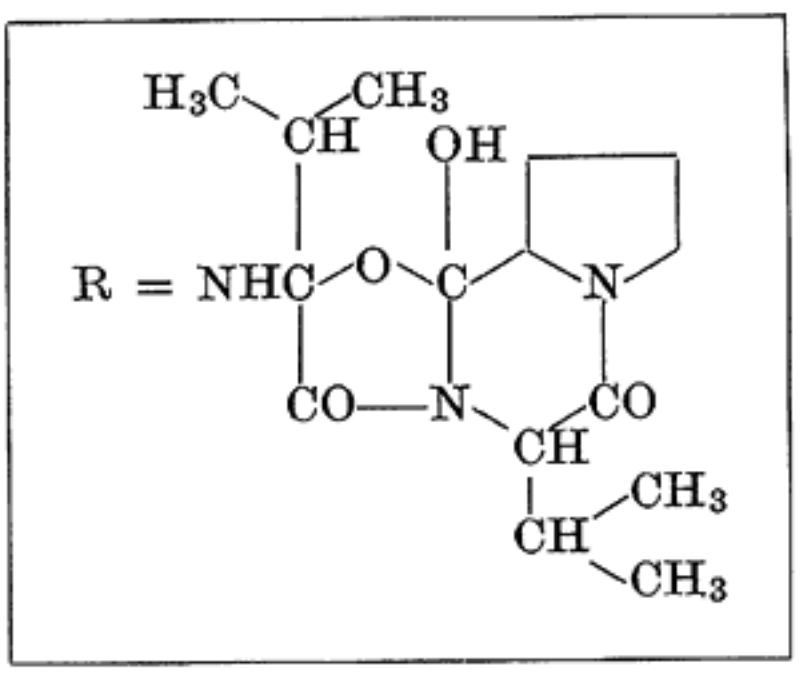
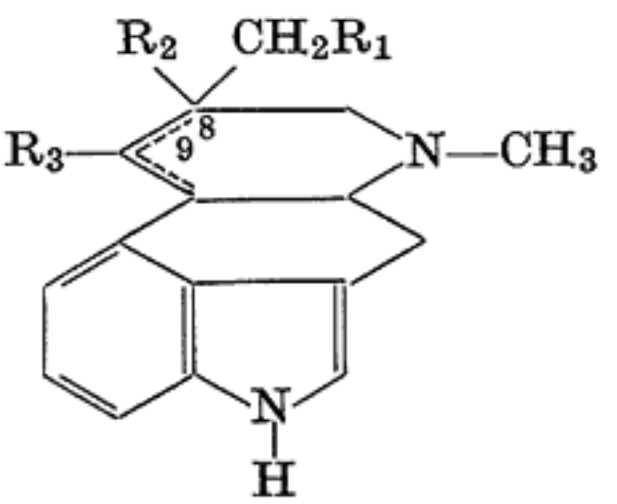
Alkaloid	Formula	Section
		
Ergocornine Ergocorninine	$C_{31}H_{39}O_5N_5$	V, C, 5

TABLE II

The Natural Ergot Alkaloids of the Clavine Series



General formula

Alkaloid	Formula	Section
Ergolene-(8) derivatives		
$R_1 = R_2 = R_3 = H$		
Agroclavine	$C_{16}H_{18}N_2$	VI, B, 1
$R_1 = OH;\ R_2 = —;\ R_3 = H$		
Elymoclavine	$C_{16}H_{18}ON_2$	VI, B, 2

TABLE II—*continued*

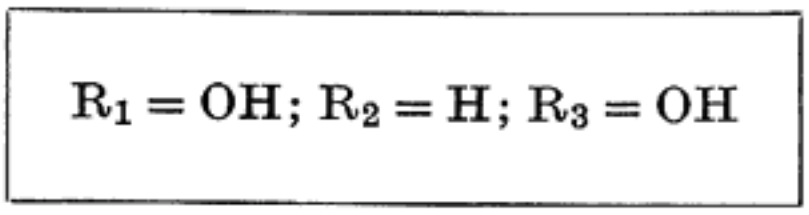
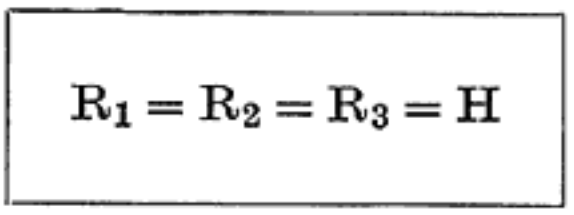
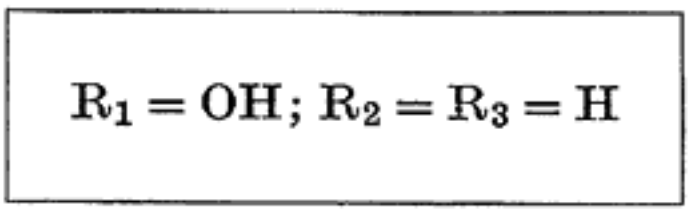
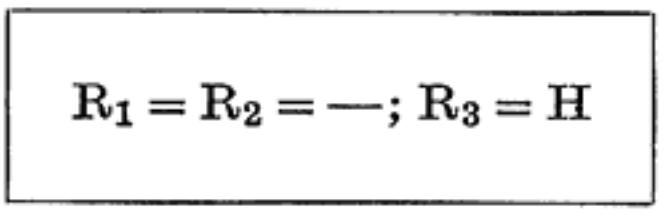
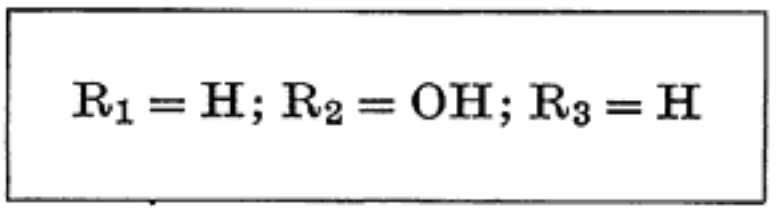
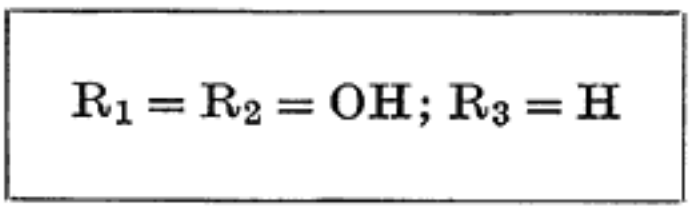
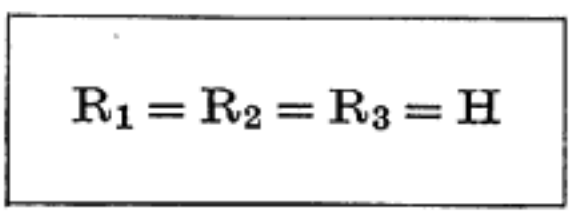
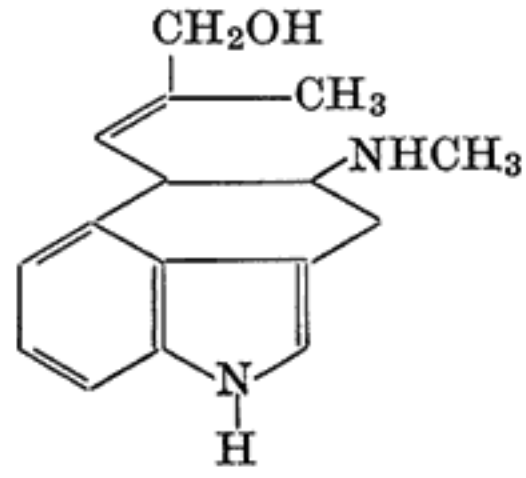
Alkaloid	Formula	Section
		
Molliclavine	$C_{16}H_{18}O_2N_2$	VI, B, 3
Ergolene-(9) derivatives		
		
Lysergine	$C_{16}H_{18}N_2$	VI, B, 4
		
Lysergol	$C_{16}H_{18}ON_2$	VI, B, 5
		
Lysergene	$C_{16}H_{16}N_2$	VI, B, 6
		
Setoclavine	$C_{16}H_{18}ON_2$	VI, B, 7
Isosetoclavine		VI, B, 8
		
Penniclavine	$C_{16}H_{18}O_2N_2$	VI, B, 9
Isopenniclavine		VI, B, 10
Ergoline derivatives		
		
Festuclavine		VI, B, 11
Pyroclavine	$C_{16}H_{20}N_2$	VI, B, 12
Costaclavine		VI, B, 13

TABLE II—*continued*

Alkaloid	Formula	Section
$R_1 = R_2 = H$; $R_3 = OCOCH_3$		
Fumigaclavine A	$C_{18}H_{22}O_2N_2$	VI, B, 14
$R_1 = R_2 = H$; $R_3 = OH$		
Fumigaclavine B	$C_{16}H_{20}ON_2$	VI, B, 15
With open ring D:  Chanoclavine		
Chanoclavine	$C_{16}H_{20}ON_2$	VI, B, 16

III. Lysergic Acid and Isolysergic Acid

The structural element common to all the alkaloid pairs shown in Table I is lysergic acid or its stereoisomer, isolysergic acid. Fresh ergot almost exclusively contains the pharmacologically highly active lysergic acid alkaloids. These are all levorotatory or only slightly dextrorotatory. By using old ergot or unsuitable methods of isolation, however, considerable quantities of the isomeric alkaloid forms are obtained. Isolysergic acid is the characteristic component of these alkaloids which have only a weak activity and are strongly dextrorotatory. The names of all the members of this group end in *-inine*. Lysergic acid and isolysergic acid, as well as the alkaloids derived therefrom, are readily reversibly interconvertible (17, 18), and an equilibrium of the isomeric forms is reached especially quickly in an alkaline medium (19).

Lysergic acid, $C_{16}H_{16}O_2N_2$, was first obtained by vigorous alkaline hydrolysis of ergot alkaloids (20, 21, 22). Recently, it was also found in

its free form in saprophytic cultures of the ergot fungus (23). It crystallizes from water in thin, long, hexagonal leaflets, containing 1 mole of water of crystallization, and it has a melting point of 238° that is not well defined; $[\alpha]_D^{20}$ +32° in pyridine.

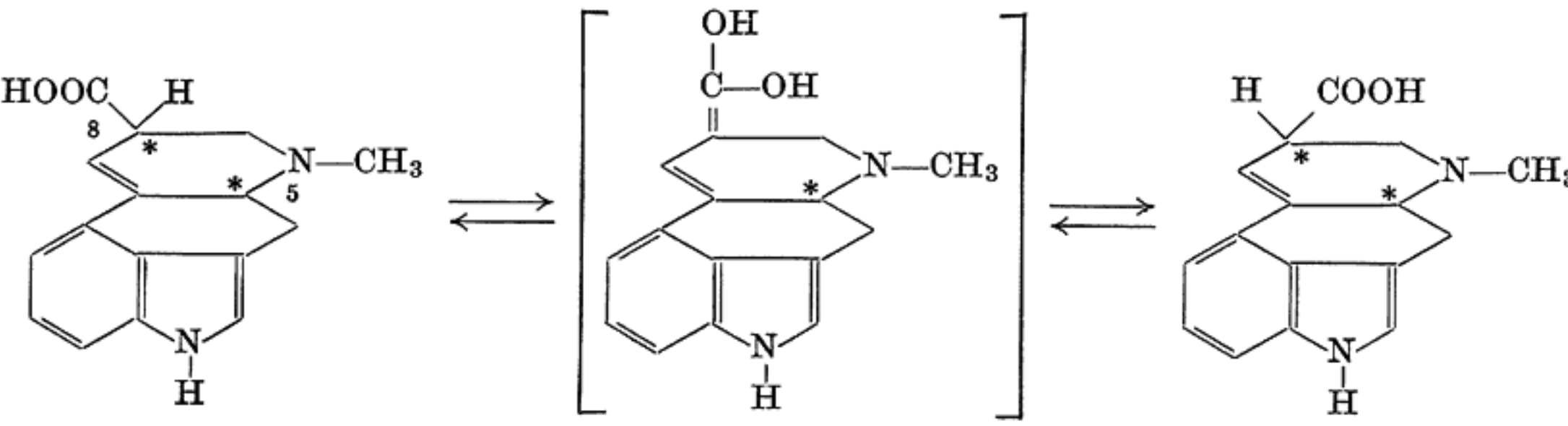
Isolysergic acid, $C_{16}H_{16}O_2N_2$, is somewhat more easily soluble in water than is lysergic acid, and it crystallizes therefrom with $2H_2O$; mp 218° (dec.), $[\alpha]_{5461}^{20}$ +368° in pyridine (18).

The natural dextrorotatory lysergic acid was named *d*-lysergic acid and its iso form, *d*-isolysergic acid (24). Their optical antipodes do not occur in nature but may be produced by racemization of *d*-lysergic acid (24) or via the racemic hydrazides resulting from the splitting of lysergic or isolysergic acid amides with hydrazine (25). Naturally, total synthesis of lysergic acid (26) also yields racemates.

Lysergic acid, isolysergic acid, and their derivatives give typical color reactions. The color reactions most commonly used are those of Keller (27), i.e., with concentrated sulfuric acid and glacial acetic acid containing iron chloride, and of van Urk-Smith (28, 29), i.e., with *p*-dimethylaminobenzaldehyde in a sulfuric acid solution. A blue color results from both reactions and is used for the qualitative and quantitative determination of ergot alkaloids in galenical preparations and in drug analysis (30, 31, 32).

A. Elucidation of Structure

By oxidizing ergot alkaloids and lysergic acid, Jacobs and Craig obtained quinoline-betaine-tricarboxylic acid (33, 21, 34), and by fusion of dihydrolysergic acid with alkali, they obtained methylamine, propionic acid, 1-methyl-5-aminonaphthalene, and 3,4-dimethylindole (35, 36). These cleavage products led to the deduction that lysergic acid contained, as its main structural entity, a new tetracyclic ring system which was named ergoline (I). By comparing the UV-spectra of lysergic acid and isolysergic acid on the one hand and dihydrolysergic acid (Fig. 1) on the other, it was deduced that lysergic acid and isolysergic acid possessed a double bond situated outside the indole system, but conjugated therewith (37). The position of the carboxyl group was ascertained from pK measurements (38) and the results of a β-aminocarboxylic acid cleavage of dihydrolysergic acid (39). Removal of the asymmetry center at the C-8 position, in which the carboxyl group is situated, yielded identical products in the case of lysergic acid and isolysergic acid. This proved lysergic acid and isolysergic acid to be diastereomers at C-8, as shown by structures II and III (40).



II
Lysergic acid

III
Isolysergic acid

The isomerization proceeds via an intermediate compound that is symmetrical at the C-8 position and that exhibits a continuous conjugated system of double bonds stretching from the enol double bond up to the indole system. Thus, isomerization of dihydrolysergic acids, in

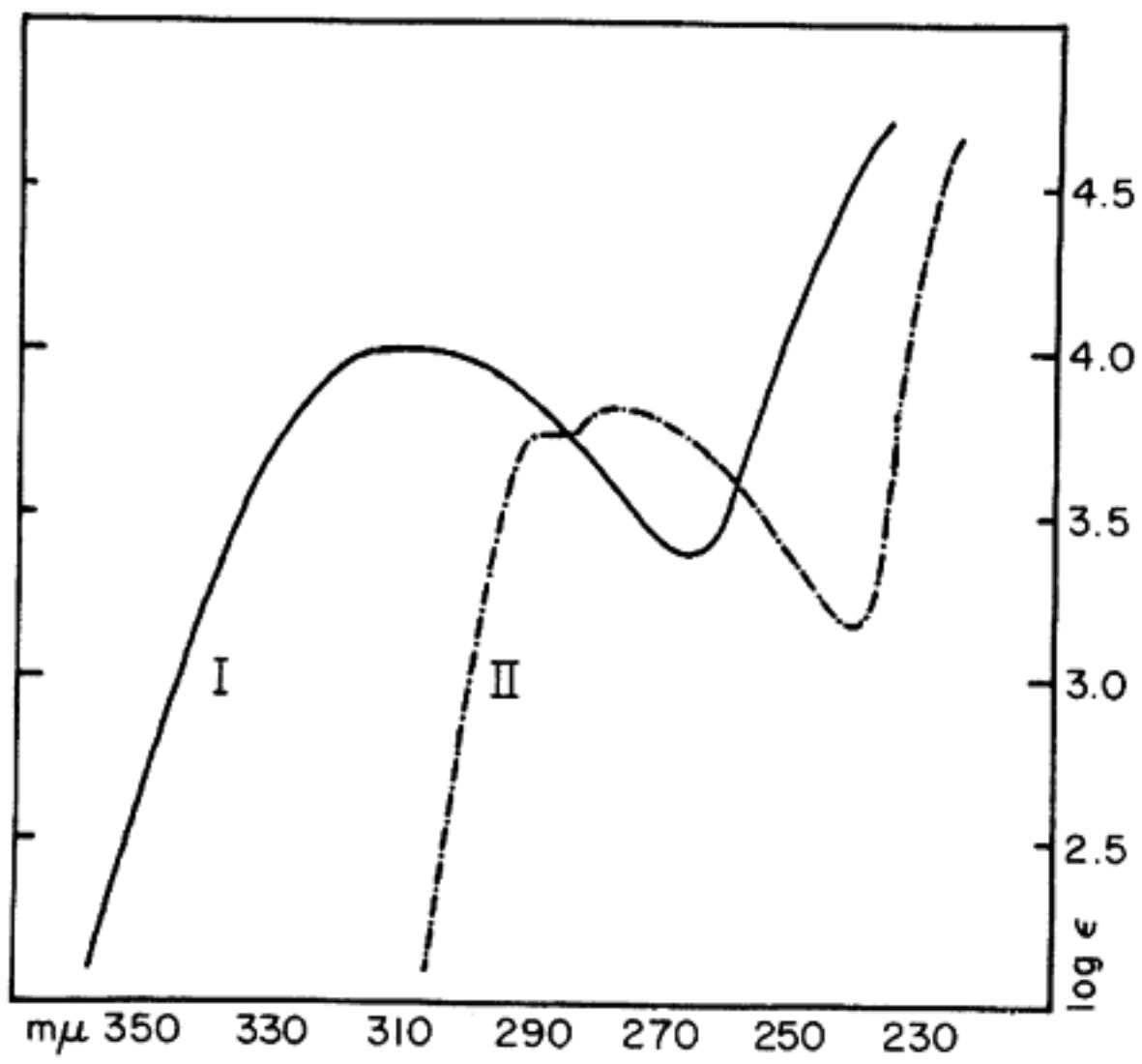


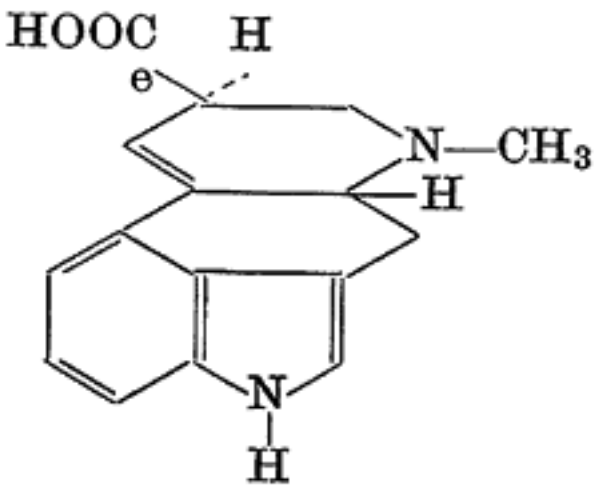
FIG. 1. UV-spectrum in methanol. I: Lysergic acid; II: dihydrolysergic acid.

which this continuous conjugation is interrupted, as well as that of ergolene derivatives, which have no carbonyl function that could be enolated, is more difficult or even impossible. The speed of the isomerization and the position of the equilibrium are both strongly influenced by the nature of the substituent at the carboxyl radical of lysergic acid (19).

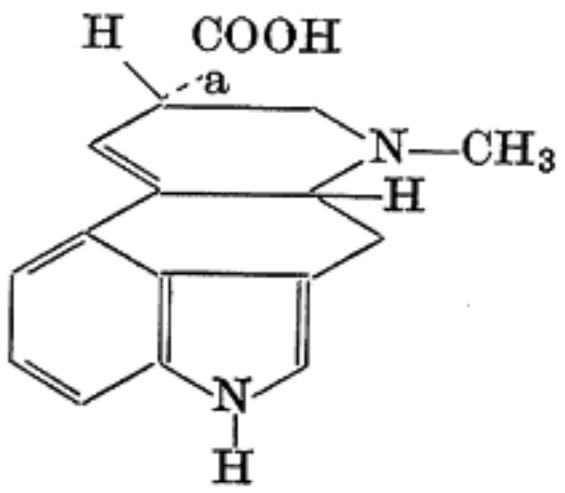
B. Stereochemistry of Lysergic Acid and the Dihydrolysergic Acids

Investigations on the stereoisomer dihydro acids and application of the "conformation theory" (41, 19) allowed the question of the configurative relationships between the two asymmetrical centers in lysergic acid and in isolysergic acid to be solved.

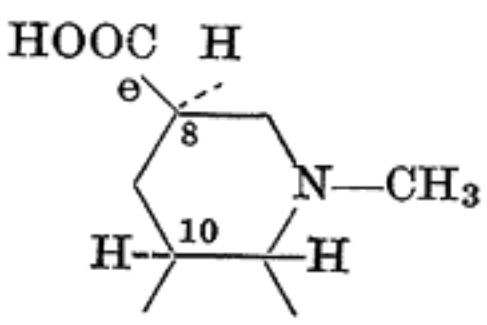
The results of catalytic hydrogenation of the Δ^{9-10}-double bond of lysergic acid, isolysergic acid, and their derivatives (42, 43) are depicted by formulas IV to IX. The absolute configurations, discovered by methods to be discussed later, have already been taken into account in these formulas.



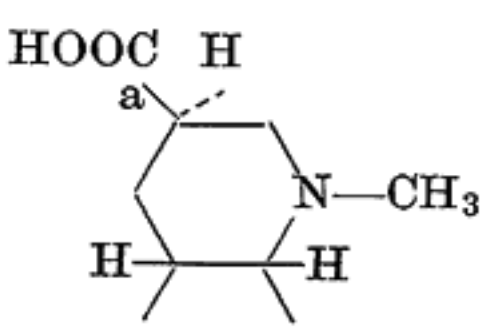
IV
Lysergic acid



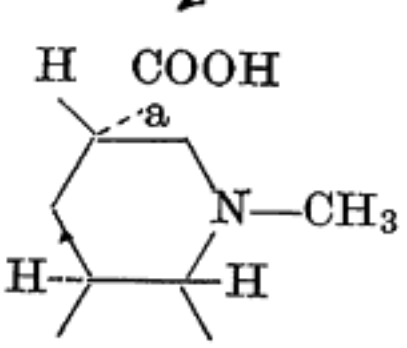
V
Isolysergic acid



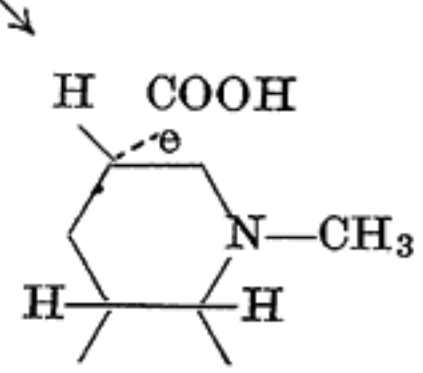
VI
Dihydrolysergic acid-I



VII
Dihydrolysergic acid-II



VIII
Dihydroisolysergic acid-I



IX
Dihydroisolysergic acid-II

Hydrogenation of lysergic acid and its alkaloids yielded only one dihydrolysergic acid. In the iso series, however, both dihydroisolysergic acid-I and dihydroisolysergic acid-II were formed, the latter stereoisomer being predominant upon rapid hydrogenation. In an alkaline medium, dihydroisolysergic acid-I was irreversibly rearranged to form dihydrolysergic acid-I. Dihydrolysergic acid-II could hitherto only be

produced in very small yield by alkaline saponification of dihydroisolysergic acid-II hydrazide. Conversely, saponification of dihydrolysergic acid-II hydrazide yields practically only dihydroisolysergic acid-II. In this case the equilibrium is on the side of the iso compound (44). Dihydrolysergic acid-I and dihydroisolysergic acid-I, as well as dihydrolysergic acid-II and dihydroisolysergic acid-II, differ only in their steric configuration at C-8. Further proof of this is the formation of an identical lactam upon heating of dihydrolysergic acid-I and dihydroisolysergic acid-I with acetic acid anhydride (40), which removes the asymmetrical center at C-8. The spatial configurations at C-10 are identical for all of these acids.

The question of *cis*- or *trans*-linkage of rings C and D may be solved by noting the behavior upon hydrogenation. The fact that only one stereoisomer forms upon hydrogenation of lysergic acid, namely, dihydrolysergic acid-I, can be explained by assuming that the carboxyl group and the hydrogen atom are on the same side of the molecule in lysergic acid, thus screening the double bond on one side (45). The attack of the hydrogen atom must then necessarily occur from the other side, so that the *trans* compound results. On the other hand, the preponderant formation of dihydroisolysergic acid-II under conditions which favor the *cis* compounds (rapid hydrogenation in glacial acetic acid with Pt catalyst), indicates a *cis* configuration in the -II series.

As epimerization conditions favor the formation of dihydrolysergic acid-I and dihydroisolysergic acid-II, it may be assumed that these compounds carry their carboxyl group in equatorial arrangement. In agreement is the fact that, in comparison with their epimers, they are less hindered in the C-8 position during saponification and condensation reactions. Furthermore, their derivatives exhibit a greater tenacity in chromatography.

Dihydrolysergic acid-I thus has the C/D-*trans*-8-equatorial formula VI, whereas the epimeric dihydroisolysergic acid-I has the C/D-*trans*-8-axial arrangement (VIII). In the case of dihydrolysergic acid-II (structure VII) and dihydroisolysergic acid-II (structure IX), both of which have a *cis*-linkage of rings C and D, the carboxyl radical is in the axial and the equatorial position, respectively. Thus, the carboxyl group is in an equatorial position in lysergic acid (IV) and in an axial position in isolysergic acid (V). Consideration of the space model shows that such a constellation is only possible if the ring D has a pseudo-chair form in both epimers.

Measurement of pK values of lysergic acid and dihydrolysergic acid derivatives and the analysis of their IR-spectra confirm that these structural configurations are indeed correct (19).

The foregoing deductions relate only to the relative spatial arrangement at the various asymmetric centers of isomeric lysergic and dihydrolysergic acids. The absolute configuration as depicted by formulas IV–IX was elucidated, on the one hand, by analysis of rotation-dispersion curves (46), and on the other, by chemical degradation of lysergic acid to an amino acid derivative of known absolute configuration (47).

Comparison of the four isomeric lysergic acids (Fig. 2) shows that only the steric relationships at the carbon atom in the 5 position (linkage of

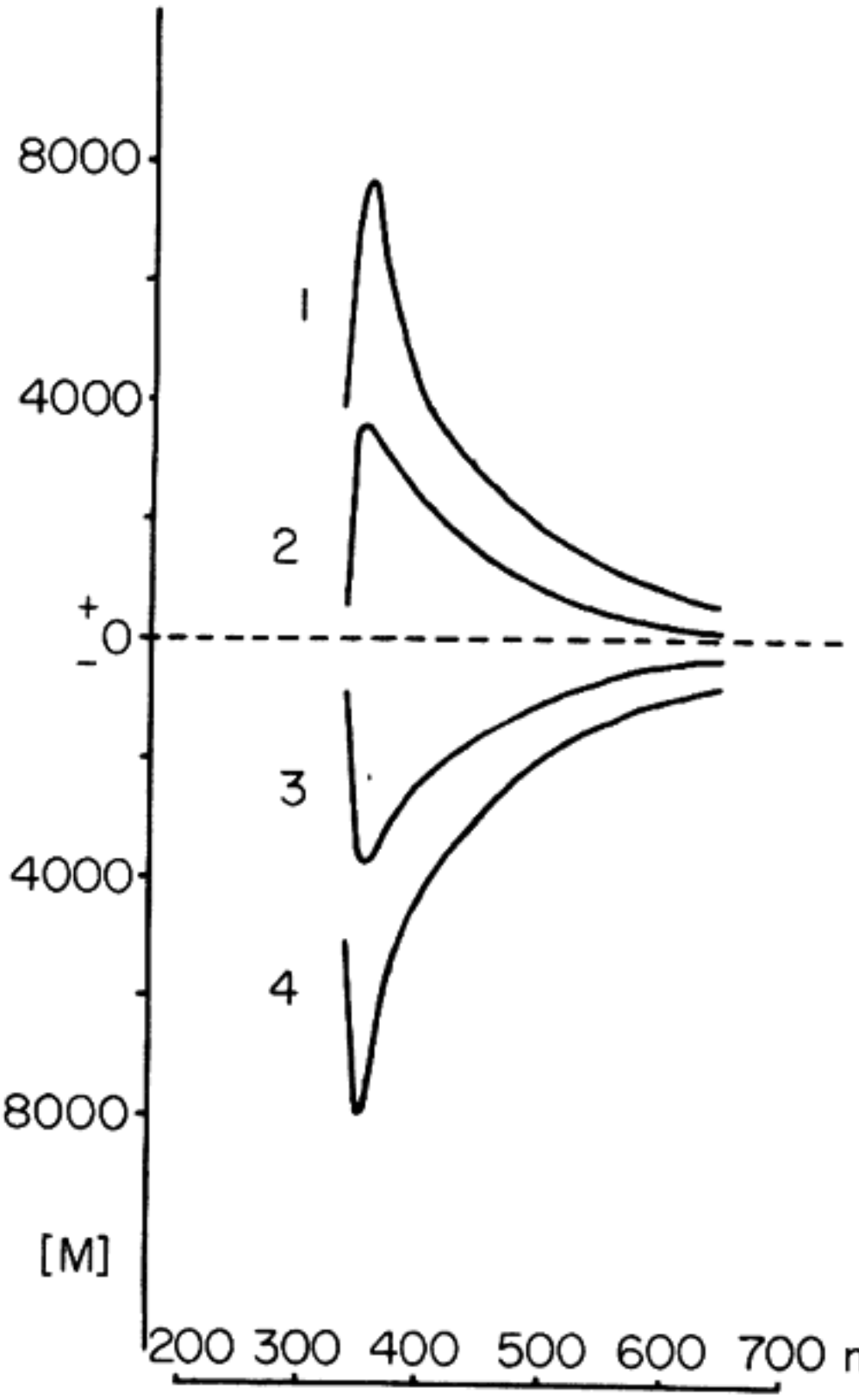


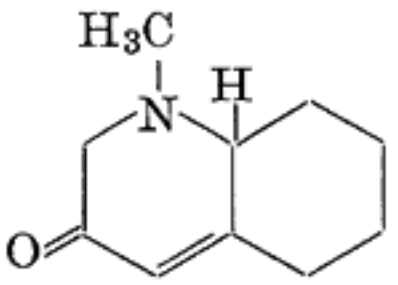
FIG. 2. Rotation-dispersion curves. 1 : *d*-Isolysergic acid; 2 : *d*-lysergic acid; 3 : *l*-lysergic acid; 4 : *l*-isolysergic acid.

rings C and D) are decisive for a positive or negative Cotton effect and that the configuration at C-8 has only an additive or substractive effect.

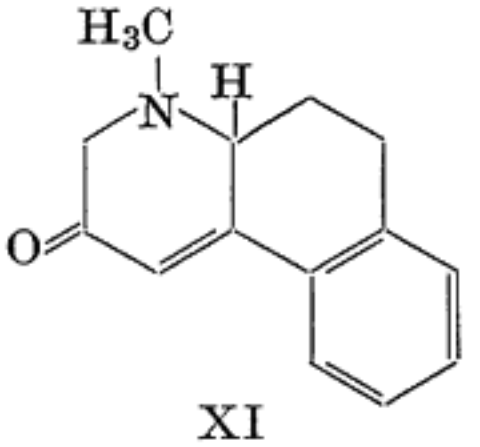
Model compounds, containing rings C and D, or A, C, and D of lysergic acid, were compared with polycyclic compounds of the steroid series, whose absolute configuration, with respect to the spatial arrangement corresponding to C-5 of lysergic acid, was known.

(+)-$\Delta^{4,4a}$-*N*-Methyloctahydroquinolin-2-one (X), (+)-$\Delta^{1,10b}$-*N*-methylhexahydrobenzo[*f*]quinolin-2-one (XI), and the corresponding

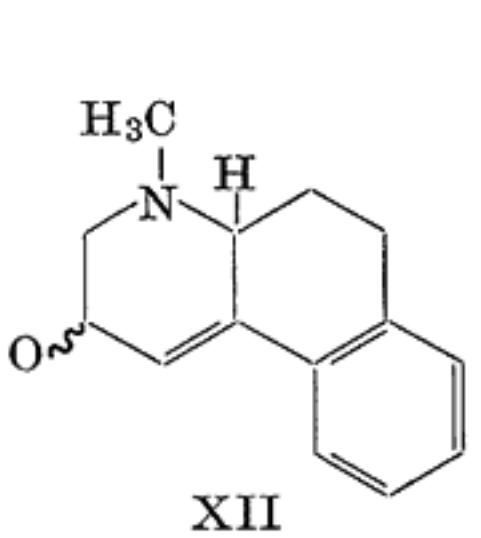
quinolin-2-ol (XII) show a positive Cotton effect (see Figs. 3–5), as does testosterone (XIII). It is thus justifiable to assign the same configuration as occurs in testosterone, namely, the hydrogen atom in β-position, to



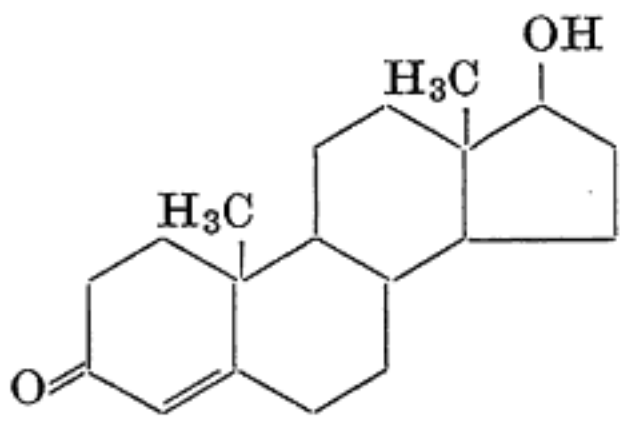
X



XI



XII



XIII

these compounds at the center of asymmetry, which corresponds to C-5 in lysergic acid. Since the tricyclic alcohol base XII corresponds in structure to lysergic acid, save for the absence of the pyrrole ring and the functional group at C-8 which, however, do not affect the direction of rotation of the rotation-dispersion, it was assumed, as a result of analogous rotation-dispersion curves of XII on the one hand, and of *d*-lysergic acid and *d*-isolysergic acid on the other, that the configurations were also analogous. Thus, it may be concluded that natural dextrorotatory lysergic acid has its hydrogen atom at C-5 in the β-position.

This fact was confirmed by oxidative degradation of the *d*-lysergic acid lactam (XIV) to a D-aspartic acid derivative (47). *d*-Lysergic acid as such could not be used for the degradation, as it would yield an aspartic acid (XVIII), dialkylated at the nitrogen atom, which was known to racemize quickly. To obtain a sterically stable degradation product having a secondary nitrogen atom, *N*-norlysergic acid would have had to be used as starting material. As, however, demethylation of lysergic acid was unsuccessful, the lactam XIV, produced by heating lysergic acid in acetic acid anhydride for a short time, was employed (40). The lactam XIV was ozonized in a methylene chloride-methanol-water solution and then oxidized with hydrogen peroxide with the addition of anhydrous formic acid. As attempts to isolate the anticipated tricarboxylic acid XV proved unsuccessful, the reaction mixture was treated with 1 *N* HCl to split off the oxalyl radical. After subsequent

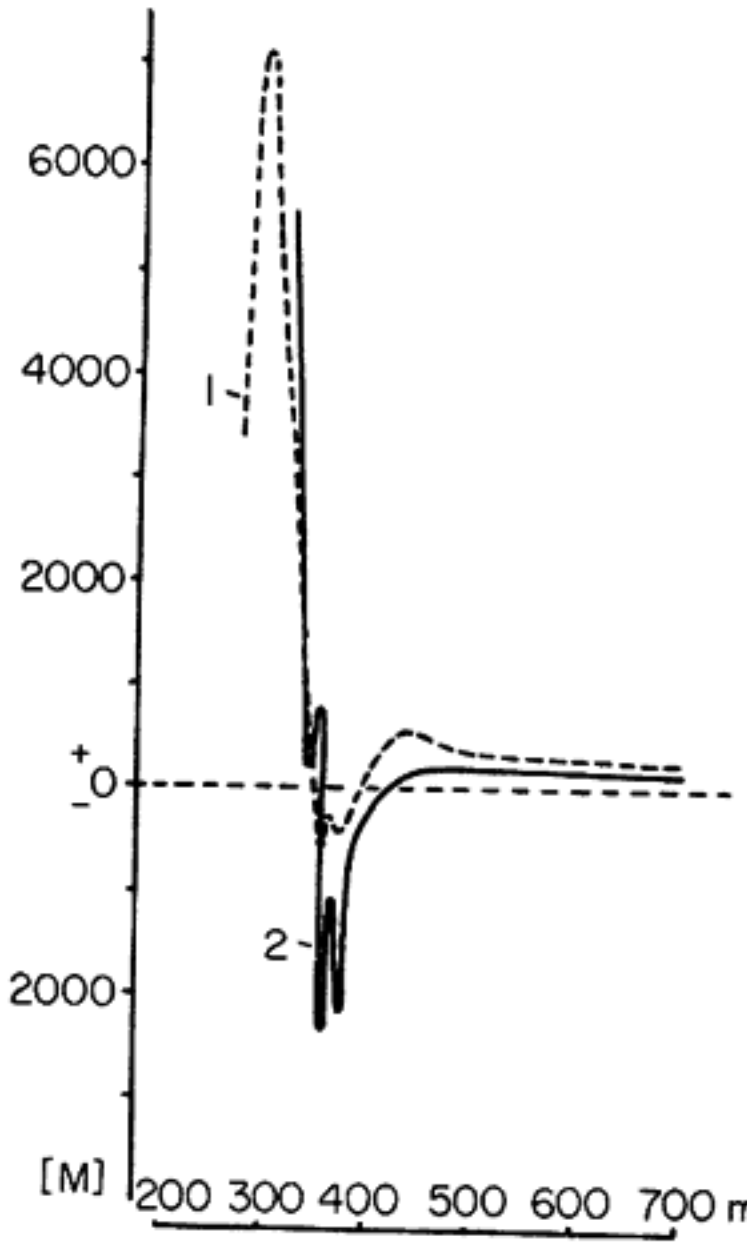


FIG. 3. Rotation-dispersion curves. 1: Testosterone (XIII); 2: (+)-$\Delta^{4,4a}$-*N*-methyl-octahydroquinolin-3-one(X).

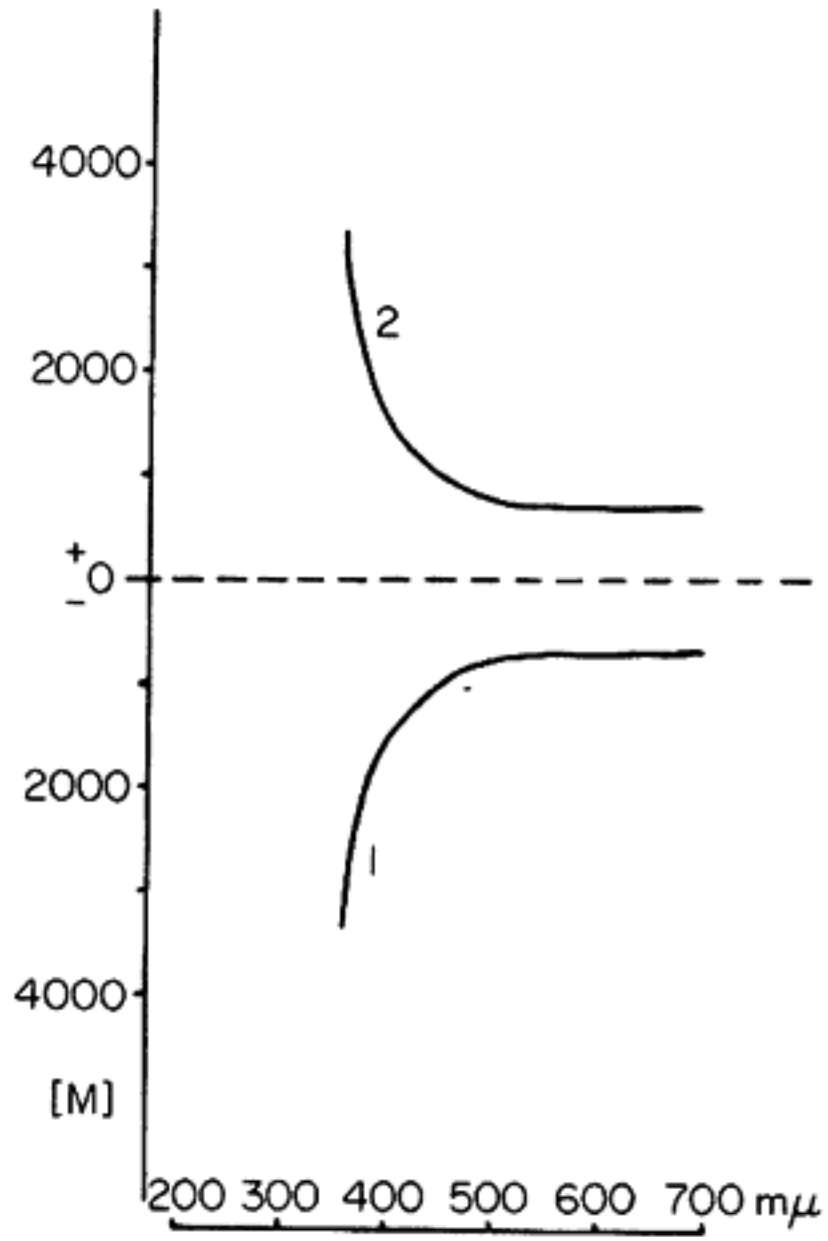


FIG. 4. Rotation-dispersion curves. 1: (−)-$\Delta^{1,10b}$-*N*-Methylhexahydrobenzo[*f*]quinolin-2-one; 2: (+)-$\Delta^{1,10b}$-*N*-methylhexahydrobenzo[*f*]quinolin-2-one (XI).

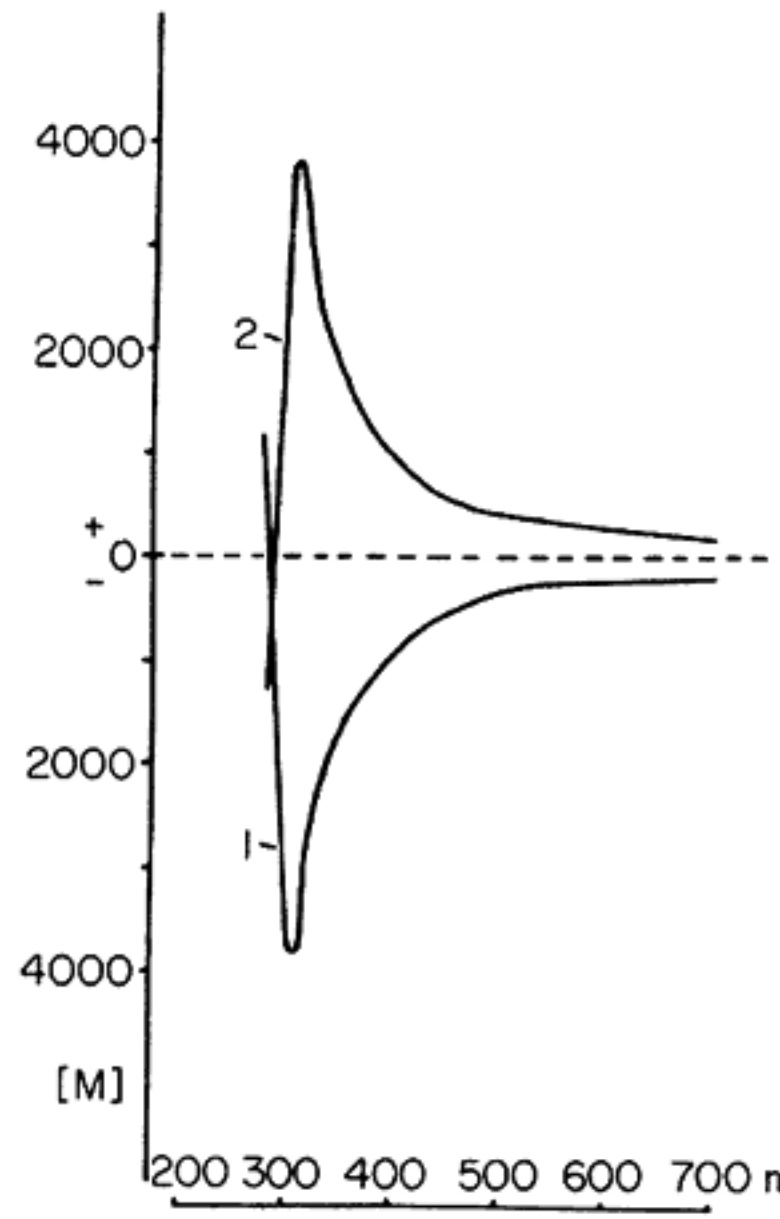
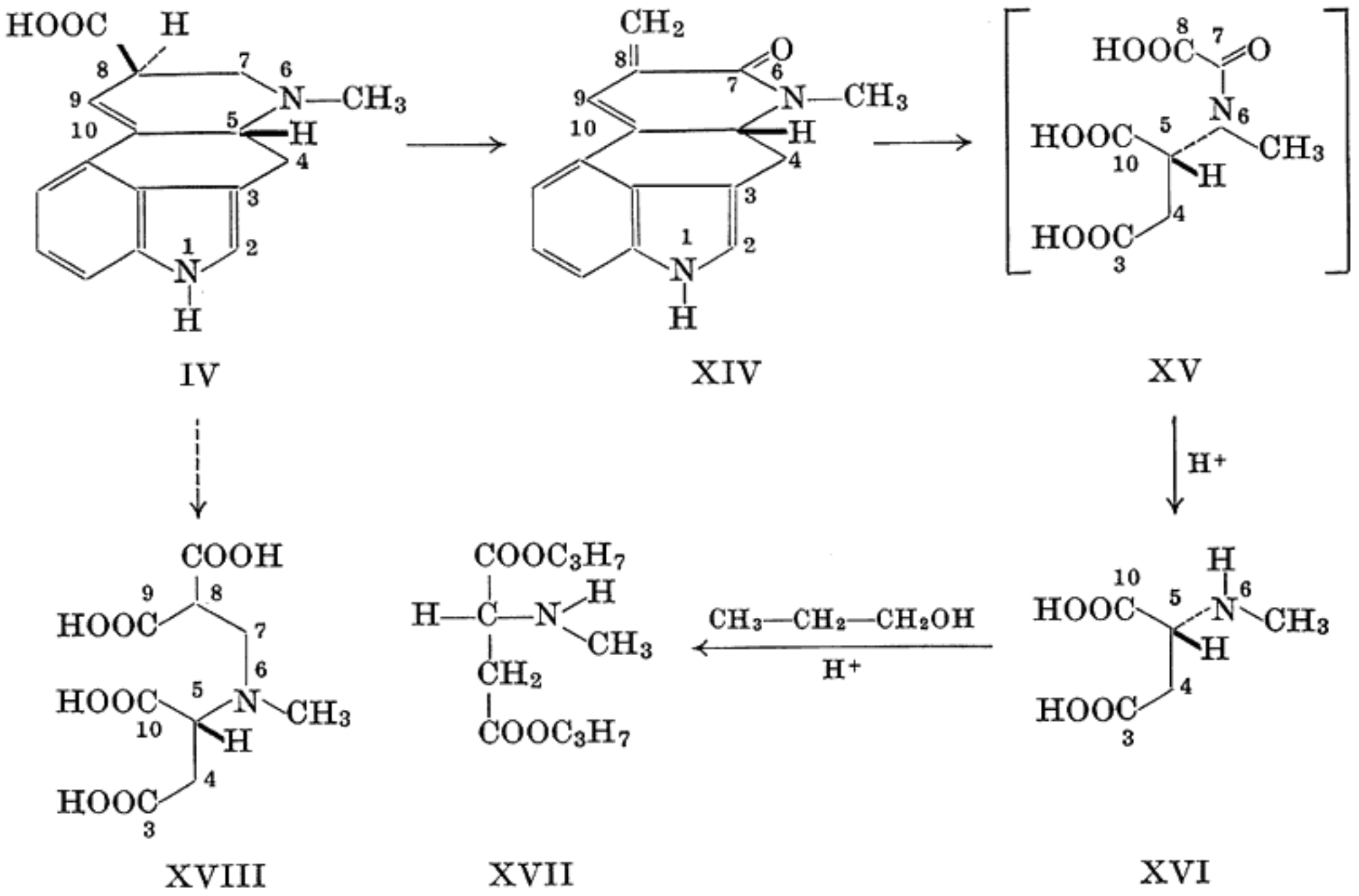


FIG. 5. Rotation-dispersion curves. 1: (−)-$\Delta^{1,10b}$-*N*-Methylhexahydrobenzo[*f*]quinolin-2-ol; 2: (+)-$\Delta^{1,10b}$-*N*-methylhexahydrobenzo[*f*]quinolin-2-ol (XII).

esterification of XVI with *n*-propanol, a yield of 4% of an optically active amino acid ester was obtained in pure form. This proved to be identical with authentic D-(+)-*N*-methylaspartic acid di-*n*-propylester (XVII). The natural lysergic acid thus has the (5R:8R) configuration depicted by formula IV.

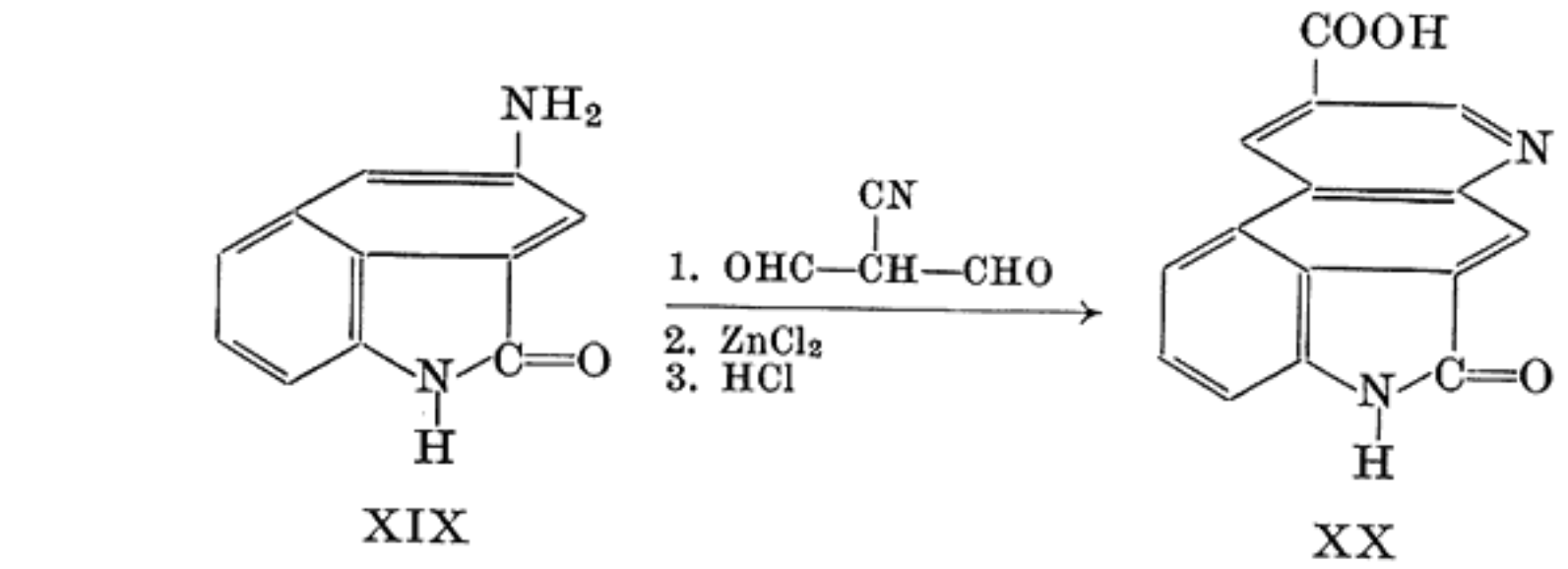


C. Syntheses in the Dihydrolysergic Acid Series

Numerous intermediate stages led to the total synthesis of lysergic acid. The syntheses by Jacobs and Gould in 1937 (16) of ergoline (I), a saturated tetracyclic ring system, constitute the first basic step. This was followed in 1945 by the synthesis of racemic dihydrolysergic acid by Uhle and Jacobs (48); in 1950, the optically active dihydrolysergic acids were synthesized by Stoll *et al.* (49); and finally Kornfeld *et al.* (50) synthesized natural lysergic acid in 1954.

4-Aminonaphthostyril (XIX), in which the rings A, B, and C of the ergoline system are already present, was used as starting material for the first synthesis of racemic dihydrolysergic acid (48). By condensing with cyanomalonic dialdehyde, cyclizing with zinc chloride, and saponifying the nitrile group with HCl, the ring structure (XX) of lysergic acid, containing a carboxyl group in the 8-position, was obtained. Catalytic hydrogenation of the chloromethylate of XX yielded tetrahydro-*N*-

methylcarboxylic acid (XXI) which, upon reduction with sodium and butanol, yielded a small quantity of racemic dihydrolysergic acid (XXII).



rac.-Dihydrolysergic acid

The naphthostyril derivative XXI was later produced by other processes (51, 52), thus clearing the way for further syntheses of dihydrolysergic acid. Compound XX was also produced by a further process,

rac.-Dihydronorlysergic acid

namely, by starting with 1-hydroxymethylene-1-phenyl-2-propanone as ring A and successively adding rings D, C, and B (53).

An improved synthesis of dihydrolysergic acid, which yielded the homogeneous racemates and furthermore led to the optically active dihydrolysergic acids, was effected via racemic dihydronorlysergic acids (54). As a starting material for this novel synthesis, Stoll and Rutschmann used the quinolone XXIII which had already been described by Gould and Jacobs (55).

To ensure a successful reaction, the butanol used must contain a trace of water so that the methyl ester group of XXIV is saponified before reduction to the corresponding alcohol occurs.

Compound XXV is a racemic mixture of three stereoisomers which, after esterification with methanol, may be resolved chromatographically to give racemic dihydronorlysergic acid-I methyl ester, racemic dihydronorisolysergic acid-I methyl ester, and racemic dihydronorisolysergic acid-II methyl ester.

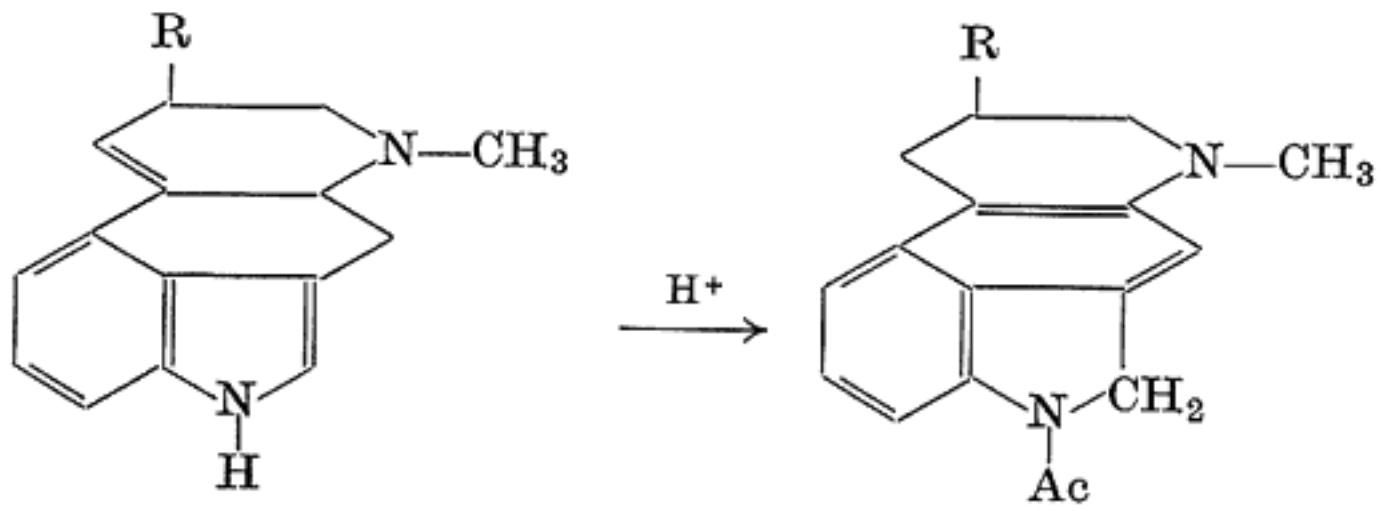
By reducing the tricyclic naphthostyril system to benz[*c*,*d*]indoline before addition of the D ring (56, 57), further variations for the synthesis of racemic dihydronorlysergic acids may be obtained.

The dihydronorlysergic acids were converted to the corresponding stereoisomer racemic dihydrolysergic acids by migration of the methyl radical. This migration was effected by heating the methyl esters of the dihydronorlysergic acids or by reduction in the presence of formaldehyde (49, 44, 58). By resolution of the resulting dihydrolysergic acid-I racemates in the form of the L-norephedride, Stoll *et al.* (49) succeeded in producing *d*-(−)-dihydrolysergic acid-I. This is the basic constituent of all the dihydrogenated natural ergot alkaloids.

D. Synthesis of Lysergic Acid

Various groups of research workers unsuccessfully attempted the synthesis of lysergic acid (59, 60, 61, 62, 63, 64, 65). Most of the attempts at synthesis failed because of the inability to introduce the double bond in the 9,10-position. This appears to be impossible when using the naphthostyril or benz[*c*,*d*]indoline system. The latter has a resonance energy which is approximately 20 kcal greater than that of the ergolene system of lysergic acid. Strong acidic reagents irreversibly rearranged lysergic acid derivatives XXVI to form benzindoline derivatives (XXVII) (56), which were crystallized in the form of their stable acyl compounds.

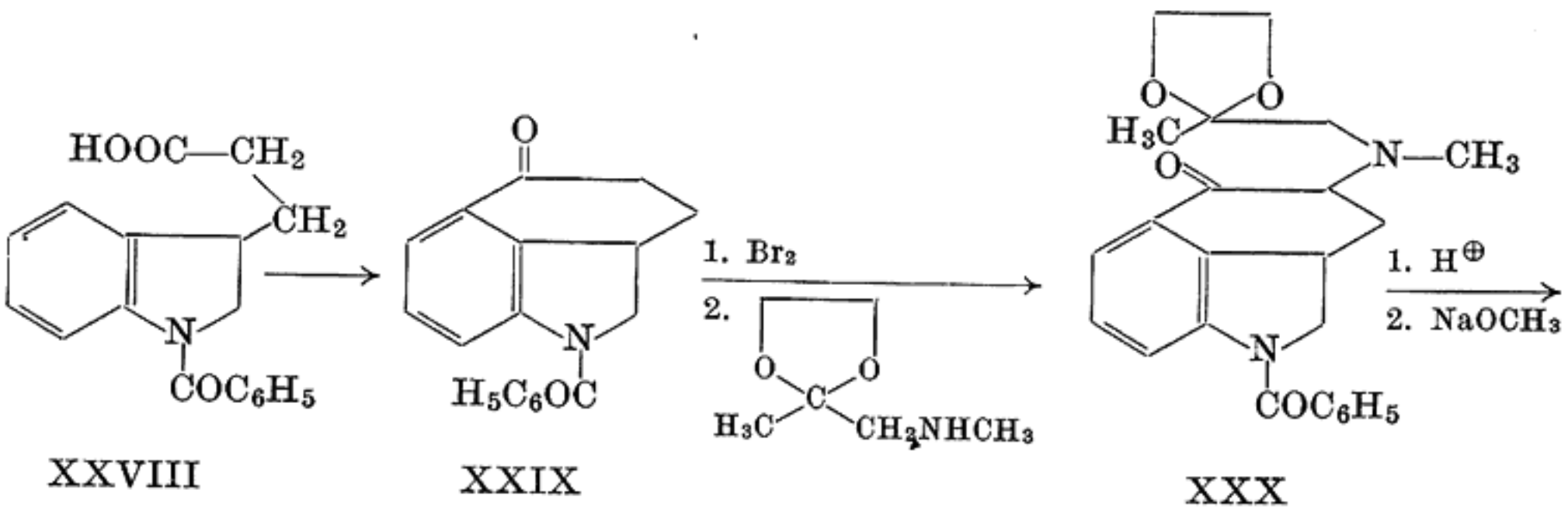
The production of lysergic acid via compounds of the type XXVII, for which syntheses were developed (56, 51), was thus not possible.



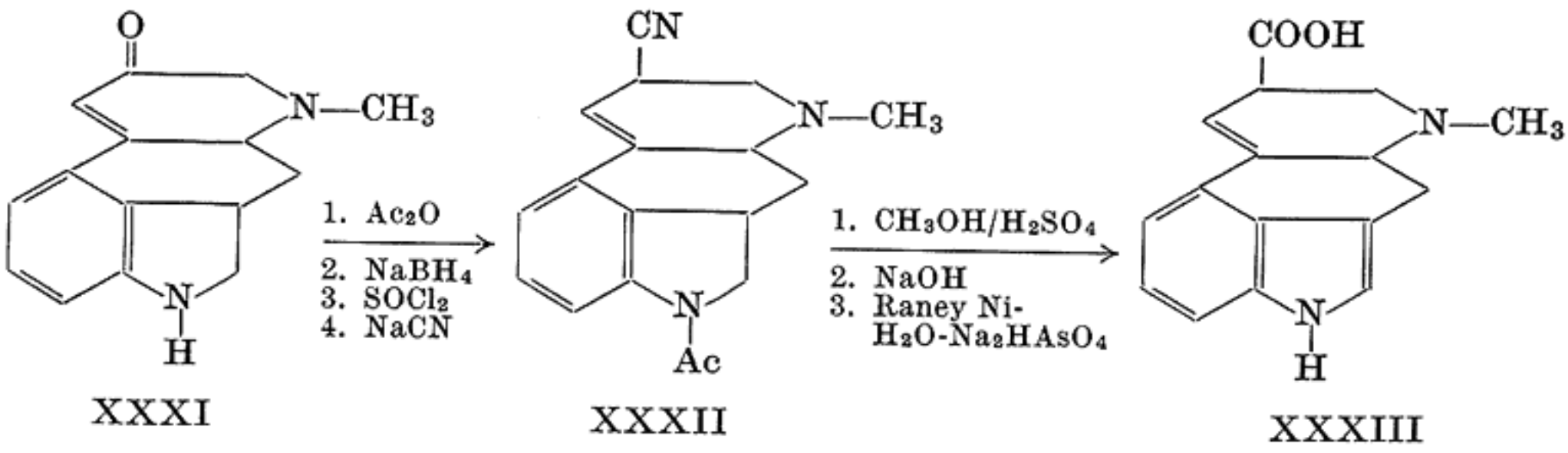
XXVI XXVII

R = COOH, $COOCH_3$, CH_2OAc

The first, and hitherto only, synthesis of lysergic acid was effected by the research group of Kornfeld *et al.* (50, 26). In this particular synthesis a *N*-acyl-2,3-dihydroindole derivative was used as starting material, thus allowing the formation of rings C and D by classical methods. Dehydrogenation of the 2,3-dihydroindole system to the indole system was only effected in the last stage so that the formation of the benz[*c*,*d*]-indoline system was prevented.



XXVIII XXIX XXX



XXXI XXXII XXXIII

rac.-Lysergic acid

N-Benzoylindolinyl-3-propionic acid (XXVIII) was condensed to form the tricyclic ketone XXIX via the acid chloride. The bromination

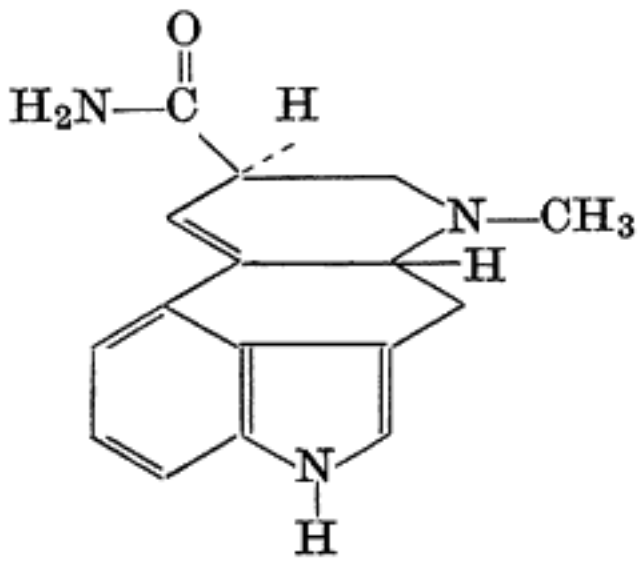
to the α-bromoketone was followed by the conversion with methylamineacetone ethylene ketal to form compound XXX. After acid hydrolysis to form the corresponding methylketone, this was cyclized with sodium methylate to give the tetracyclic, unsaturated ketone XXXI. The liberated secondary amino group was again protected by acetylation and the ketone then reduced with $NaBH_4$ to the secondary alcohol that was converted to the corresponding chloride in SO_2 solution with thionyl chloride. Conversion with sodium cyanide in liquid hydrocyanic acid yielded the nitrile XXXII which was converted by methanolysis to the corresponding ester. This was then subjected to alkaline saponification to form 2,3-dihydrolysergic acid. Dehydrogenating with deactivated Raney nickel in an aqueous solution in the presence of sodium arsenate yielded racemic lysergic acid (XXXIII).

As the resolution of the racemic lysergic acid into its optical antipodes and the synthesis of ergometrine had been described earlier by Stoll and Hofmann (25, 66), this meant that not only had the synthesis of *d*-lysergic acid been achieved but also the first total synthesis of an ergot alkaloid.

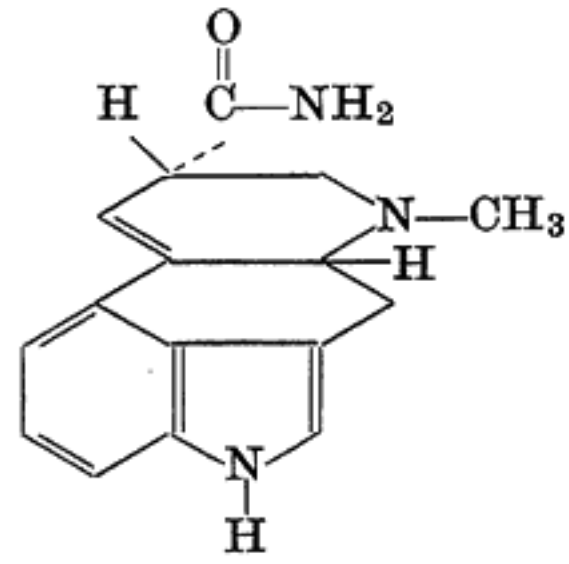
This synthesis has hitherto found no industrial application, as various steps are difficult to effect on a technical scale, especially since the dehydrogenation of 2,3-dihydrolysergic acid gives only a small yield.

IV. Simple Lysergic Acid Amides

A. Ergine-Erginine, $C_{16}H_{17}ON_3$ (267.3)



XXXIV
Ergine



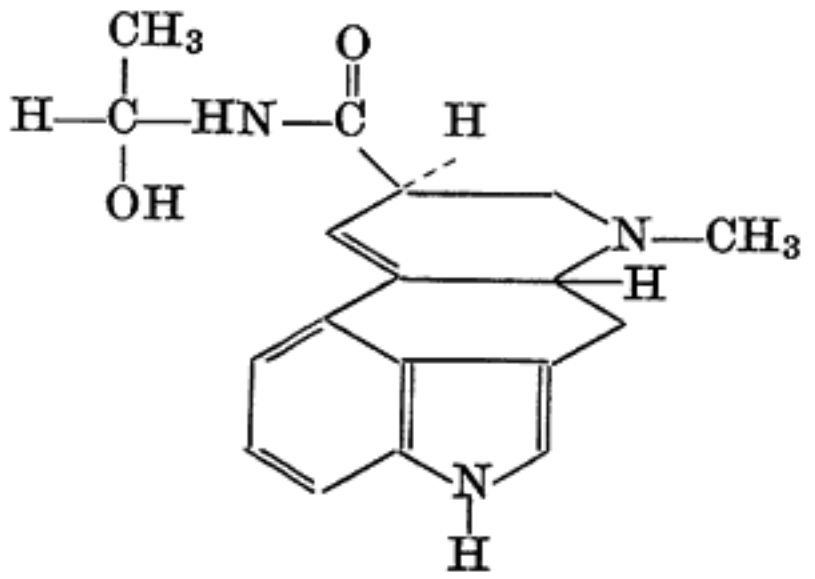
XXXV
Erginine

Ergine crystallizes from methanol in prisms, mp 242° (dec.), $[\alpha]_D^{20}$ 0° (±2°), $[\alpha]_{5461}^{20}$ +15° (±2°) (c = 0.5 in pyridine). Erginine is readily formed by rearrangement of ergine, e.g., by recrystallization of the latter from methanol. Long massive prisms containing 1 mole of methanol result; mp 132°–134° (dec.), $[\alpha]_D^{20}$ +480° (±2°), $[\alpha]_{5461}^{20}$ +608° (±2°) (c = 0.5 in pyridine).

Lysergic acid amide (XXXIV) and isolysergic acid amide (XXXV) which, for a long time, were only known as the hydrolysis products of ergot alkaloids (67, 18, 68), were recently isolated as the main constituents of the alkaloid mixture from ergot of *Paspalum distichum* L (69). They are thus also to be regarded as genuine ergot alkaloids. The term ergine, which was originally used for the first characteristic hydrolysis product of ergot alkaloids (67), before this was identified as isolysergic acid amide, is now correctly used in connection with lysergic acid amide. In accordance with the conventional nomenclature used in the case of ergot alkaloids, the isolysergic acid amide has been named erginine.

Recently, ergine and erginine were also isolated as main components, together with other alkaloids of the clavine group, from seeds of *Rivea corymbosa* (L.) Hall. f. and *Ipomoea tricolor* Cav. (70, 71). These seeds were used centuries ago by Central American indians as a magic drug under the name of "Ololiuqui." The occurrence of lysergic acid alkaloids in the plant family of Convolvulaceae is a completely unexpected phytochemical discovery as they had hitherto only been found in the lower fungi of the genus *Claviceps* but recently also in the genera *Aspergillus* and *Rhizopus* (72).

B. Lysergic Acid Methylcarbinolamide, $C_{18}H_{21}O_2N_3$ (311.4)



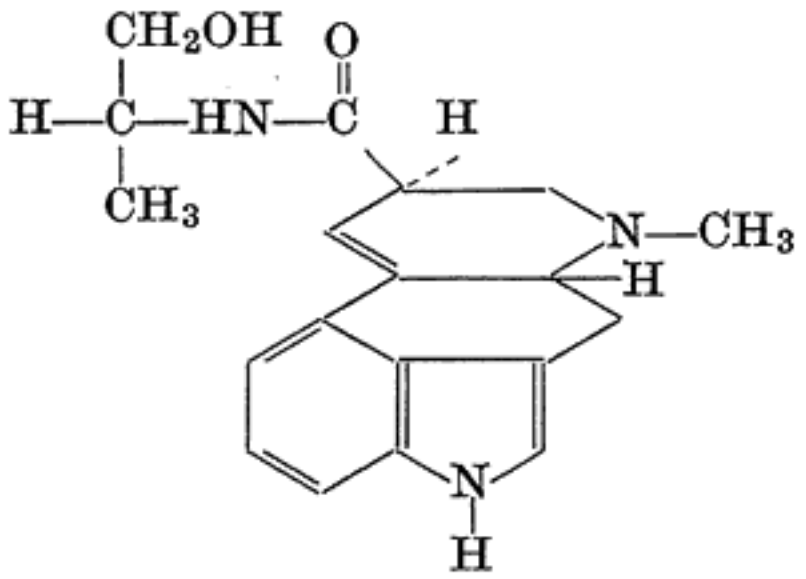
XXXVI

Lysergic acid methylcarbinolamide (XXXVI) crystallizes from chloroform in long prisms, mp 135° (dec.), $[\alpha]_D^{20}$ + 29° (c = 1.0 in dimethylformamide). The alkaloid, which was isolated together with ergine and erginine from saprophytic cultures of *Claviceps paspali* (69), easily decomposes in a weak acid solution to form ergine and acetaldehyde.

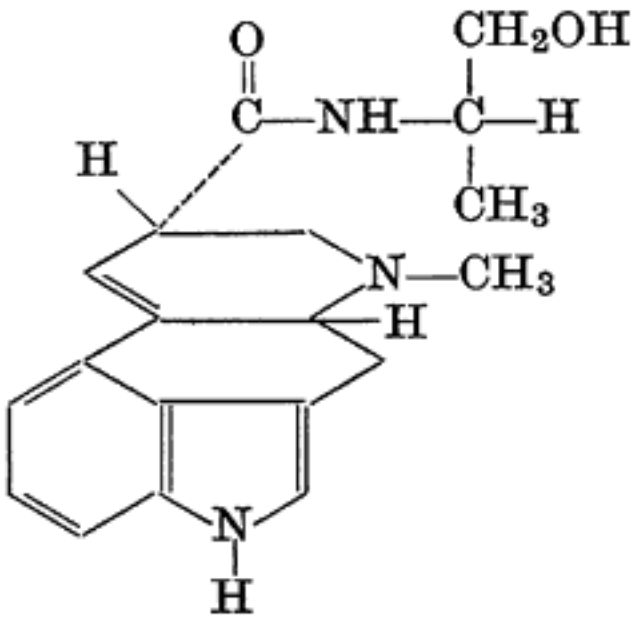
C. Ergometrine-Ergometrinine, $C_{19}H_{23}O_2N_3$ (325.4)

Ergometrine (XXXVII) crystallizes from ethyl acetate in massive tetrahedrons, mp 162° (dec.). From chloroform, in which the alkaloid is

difficultly soluble, it is obtained with 1 mole of crystalline solvent. Upon crystallization from acetone, dimorphism was observed (73). Aside from that form which melts at 162°, long needles having a mp of 212° (dec.) resulted; $[\alpha]_D^{20}$ +41°, $[\alpha]_{5461}^{20}$ +60° (c = 1.0 in ethanol).



XXXVII
Ergometrine



XXXVIII
Ergometrinine

In 1935 ergometrine was discovered in four different laboratories almost simultaneously and described under four different names (74, 75, 76, 77). Although the names ergometrine and ergobasine have remained in use in Europe, ergonovine was adopted in the USA as the official nomenclature for the specific uterotonic ergot alkaloid.

Ergometrinine crystallizes from acetone in the form of prisms, mp 196° (dec.), $[\alpha]_D^{20}$ +414°, $[\alpha]_{5461}^{20}$ +520° (c = 1 in chloroform). Only a small quantity of it occurs in the ergot drug together with ergometrine (78). However, it may easily be produced by rearrangement of ergometrine (79).

The relatively simple structure of ergometrine was elucidated by Jacobs and Craig, who showed that, upon alkaline hydrolysis, lysergic acid and L(+)-2-aminopropanol result (80). The synthesis of ergometrine from these two components was effected by Stoll and Hofmann (81, 66). This was the first synthesis of an ergot alkaloid. By use of *rac.*-isolysergic acid hydrazide, which could be resolved into its optical antipodes with di-(*p*-toluyl)tartaric acid (25), all eight theoretically possible stereoisomer forms of ergometrine were synthesized via the corresponding azides (66).

V. Peptide Alkaloids

A. Elucidation of Structure of the Peptide Portion

The majority of alkaloids produced from ergot fungi are peptides of lysergic acid. Upon hydrolysis they decompose to give lysergic acid, two

amino acids (one of which is always proline), one α-keto acid, and one equivalent of ammonia (82, 83, 84, 85, 13). L-Phenylalanine, L-leucine, and L-valine were found as variable amino acids, and pyruvic acid or dimethylpyruvic acid as α-keto acids. The amino acid proline, common to all peptide alkaloids, was obtained in the D-form upon acid hydrolysis or as L-proline under mild alkaline conditions. Table III gives a summary of the hydrolysis products.

The two alkaloid pairs yielding pyruvic acid have been named the ergotamine group after their most prominent representative. The three alkaloid pairs yielding dimethylpyruvic acid upon hydrolysis are known as the ergotoxine group. This nomenclature is due to the fact that, for numerous decades, mixtures of ergocristine, ergocryptine, and ergocornine, which contained varying proportions of these constituents, were assumed to be single homogeneous individuals and were named "ergotoxine" by Barger and Carr in 1906 (6). It was only in 1943 that Stoll and Hofmann succeeded in separating ergotoxine into its three components with the aid of di-*p*-toluyl-L-tartaric acid (10). In the "periodic system" of ergot alkaloids, the alkaloid corresponding to ergocornine and having valine as the second amino acid is still missing from the ergotamine group.

This alkaloid, which hitherto has not been found in nature, was, however, recently produced synthetically (169) (see Section V, B).

Recently a new alkaloid was discovered in the ergot of rye which, upon hydrolysis, yields α-keto butyric acid as α-keto acid, while the other cleavage products correspond to those of ergotamine and ergocristine. The new alkaloid, of which only a very small quantity is present together with ergotamine, was named ergostine whereas the isomer, which results from a transposition of said ergostine, was called ergostinine (175). This alkaloid pair forms the first representative of a further alkaloid group which, when using nomenclature analogous to that employed for the ergotamine and ergotoxine groups, could be called the ergostine group.

The α-keto acids are not present as such in the alkaloids as no free keto group can be detected. It was thus assumed that an α-hydroxy-α-amino acid group was present in the alkaloids, which would decompose to the corresponding α-keto acid and 1 equivalent of NH_3 (82, 86).

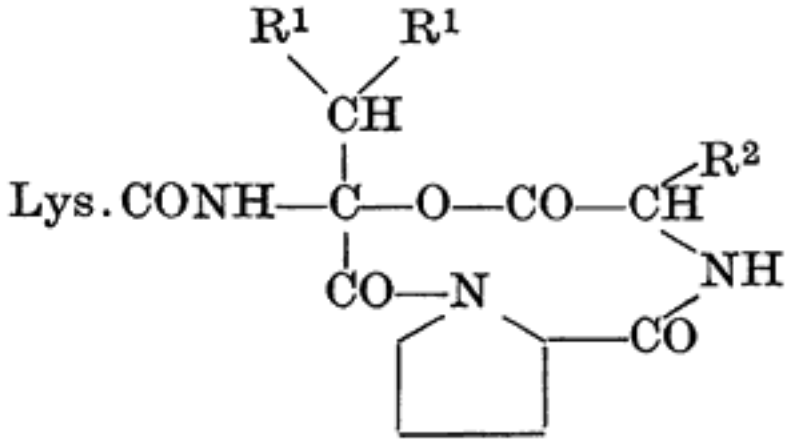
As neither a free carboxyl group nor a basic amino group could be detected in the peptide portion, a cyclic configuration of the various constituents had to be assumed. As somewhat milder alkaline hydrolysis yielded mainly lysergic acid amide instead of lysergic acid, it was obvious that an acid-amide linkage was present between the lysergic acid and the α-hydroxy-α-amino acid racidals. As a result of these

TABLE III

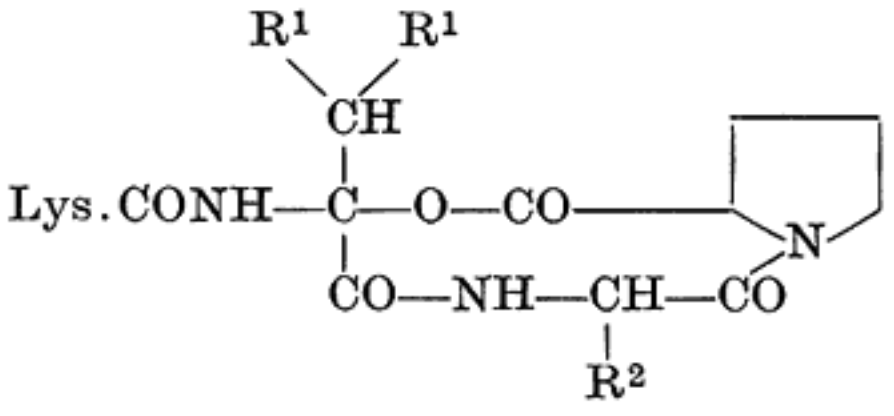
CLEAVAGE PRODUCTS RESULTING FROM HYDROLYTIC DEGRADATION OF ERGOT ALKALOIDS OF THE PEPTIDE TYPE

Lysergic acid (Isolysergic acid)	NH_3 Proline (D- or L-)	Pyruvic acid	L-Phenylalanine =	Ergotamine (Ergotaminine)	Ergotamine group
			L-Leucine =	Ergosine (Ergosinine)	
			L-Valine =	—	
		Dimethylpyruvic acid	L-Phenylalanine =	Ergocristine (Ergocristinine)	Ergotoxine group
			L-Leucine =	Ergocryptine (Ergocryptinine)	
			L-Valine =	Ergocornine (Ergocorninine)	

considerations, Jacobs and Craig (86) postulated structural formula XXXIX and Barger (87) postulated formula XL for the peptide alkaloids.



XXXIX



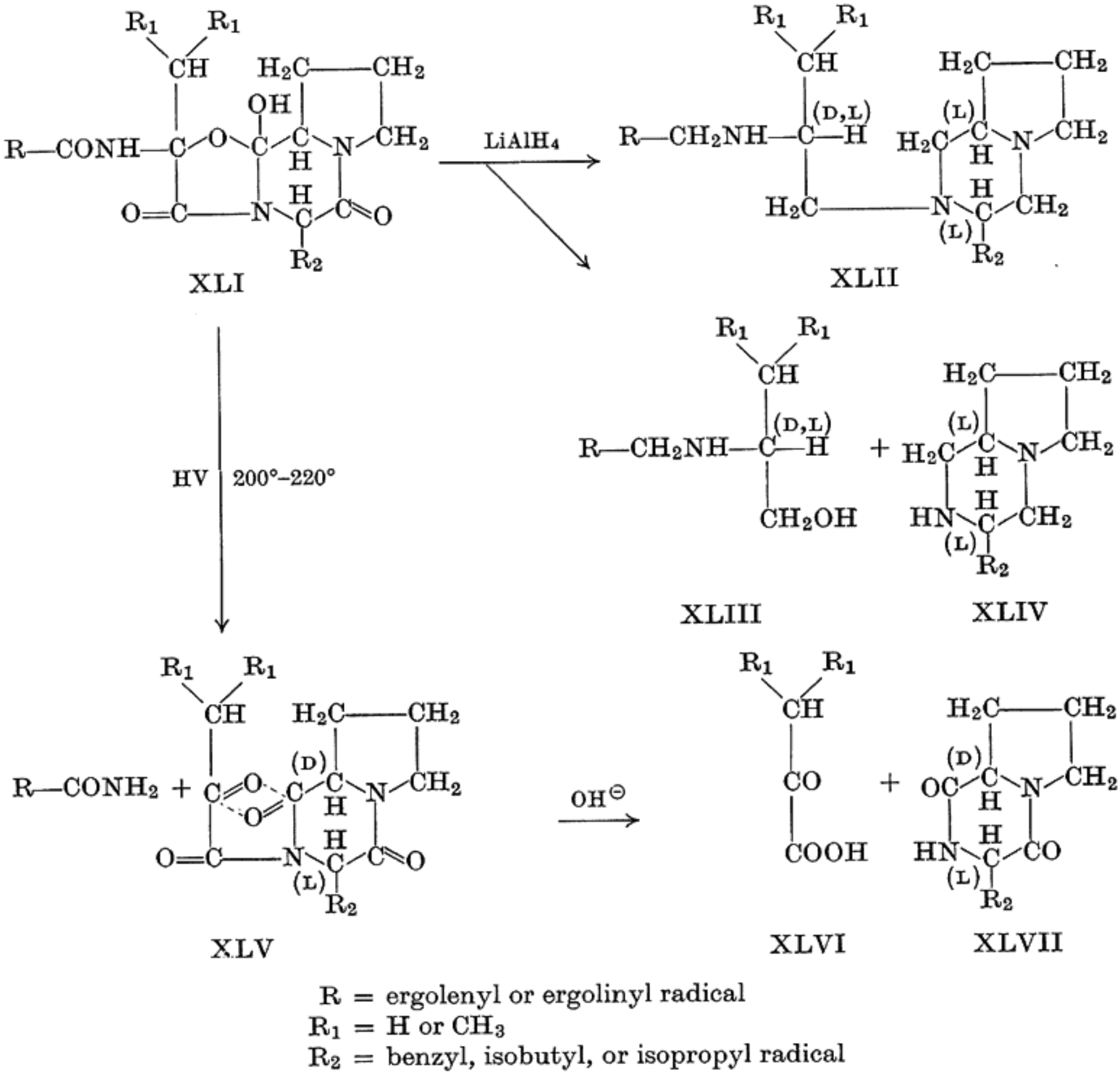
XL

These hypothetical structures (XXXIX and XL) differ only in the sequence of the amino acids. This was determined as a result of large cleavage products obtained by a partial hydrolysis of the alkaloids or their dihydro derivatives. Thus, for example, the cleavage of dihydroergotamine and of dihydroergocristine with hydrazine yielded, aside from dihydrolysergic acid hydrazide, propionyl-L-phenylalanyl-L-proline, or isovaleryl-L-phenylalanyl-L-proline (88). The structure of these compounds was confirmed by synthesis. The keto acid component was reduced by hydrazine to form the corresponding fatty acid. Upon mild hydrolysis with one equivalent of alkali in alcohol, however, the keto acid as such remained, and pyruvoyl-L-phenylalanyl-L-proline or dimethylpyruvoyl-L-phenylalanyl-L-proline (68) was obtained from the above-mentioned alkaloids. Thus it was that the sequence of the amino acids was found to be that depicted by formula XL. This, however, did not explain subsequent observations, all of which suggested that the peptide portion must necessarily contain a diketopiperazine ring. Cleavage with hydrazine and hydrolysis with one equivalent of alkali yielded, aside from the already mentioned acyl dipeptides, a considerable quantity of diketopiperazine, consisting of proline and the different amino acids, i.e., phenylalanylproline lactam in the case of ergotamine and ergocristine.

Even more informative were the results of (1) the reduction with lithium aluminum hydride and (2) the thermocleavage. These results are depicted by formulas XLI–XLVII (89).

It was to be expected that the lactone group in XL would be split with $LiAlH_4$ to form a primary and a tertiary hydroxyl function. Instead, however, the reduction products XLII, XLIII, and XLIV, the structure and configuration of which were confirmed by the synthesis, were obtained. In the case of the polyamines XLII, all the C and N atoms of

the relative alkaloids are still present, whereas all the oxygen has been removed by reduction.



XLI XLII XLIII XLIV XLV XLVI XLVII

The thermocleavage of the dihydro alkaloids yielded, aside from the dihydrolysergic acid amide, the corresponding pyruvoyl- or dimethyl-pyruvoyl-diketopiperazines (XLV). These products could later also be prepared by total synthesis, i.e., by cyclizing the corresponding acidic pyruvoyl- or dimethylpyruvoyl-peptides (90). Proline is present in the D form in compound XLV. Inversion must have occurred during the thermocleavage for, in the alkaloids, the proline radical has the L configuration, as may be seen from the isolation of XLII and XLIV. In XLV the carbonyl function of the α-keto acid radical cannot be detected chemically; obviously the capacity for reaction is impaired by its proximity to the neighboring lactam carbonyl group.

The above findings may be satisfactorily explained by ascribing

formula XLI to the peptide portion. In this formula the nine-membered lactam-lactone ring of XL is divided into a five- and a six-membered ring. The structure resulting from cyclizing and migration of a hydrogen atom from the nitrogen atom of an amide group to the oxygen atom of a neighboring lactone group was named the cyclol grouping. This name stems from Wrinch (91), who used it to characterize cyclic peptide structures which were, at that time, still hypothetical. The ortho-carboxylic acid form of proline is the basis of the novel amino acid grouping of the ergot alkaloids. One of the three hydroxyls has a lactone-like linkage, the other a lactam-like linkage, and the third is free. The last-mentioned hydroxyl still exhibits very weak acidic properties and is responsible for the solubility of the peptide alkaloids in strong aqueous sodium hydroxide solution.

Owing to the complete elucidation of the constitution of the compounds obtained by total reduction with $LiAlH_4$ and by thermocleavage, it was possible to propose structural formulas for the peptide alkaloids as early as 1951 (89). These formulas were confirmed by total synthesis of ergotamine after a further 10 years of intensive laboratory research (92).

B. The Synthesis of Ergotamine and Its Stereochemistry

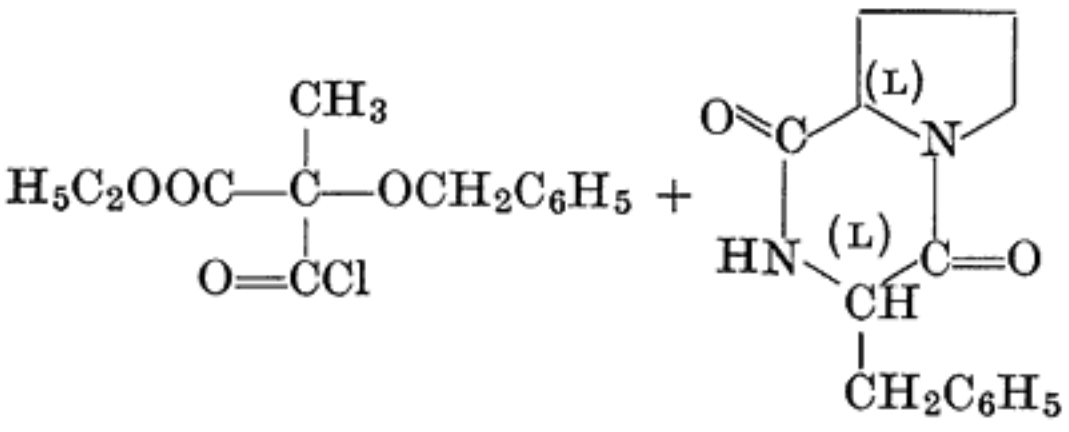
The major problem in the synthesis of the peptide portion of the ergot alkaloids was the assembly of the extremely labile α-hydroxy-α-amino acid grouping and the formation of the cyclol structure which was, at that stage, unknown in organic chemistry.

Extensive investigations on the production of α-hydroxy-α-amino acid derivatives were conducted by Shemyakin *et al.* (93, 94). They succeeded in incorporating derivatives of this type into di- and tripeptides but, owing to the labile nature of the α-hydroxy-α-amino acid group, all attempts at cyclization were unsuccessful.

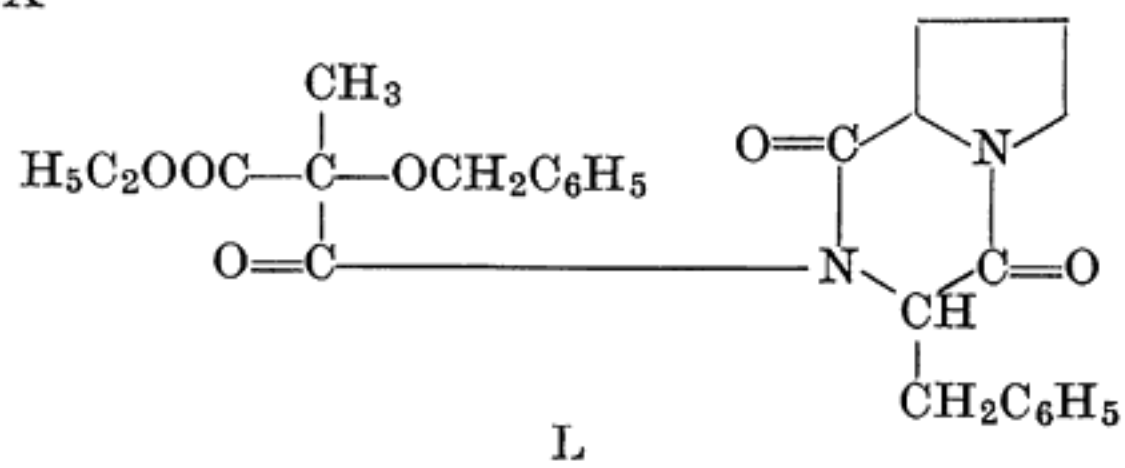
The reverse route, however, i.e., formation of the cyclol group followed by the introduction of the α-amino acid fraction, produced the desired compound (92). It was observed that cyclol formation occurred spontaneously if certain structural conditions were fulfilled and that the system underwent considerable stabilization upon cyclolization.

On this basis, Hofmann *et al.* synthesized the peptide portion of ergotamine via stages XLVIII–LIII and, by linking the resulting peptide portion with lysergic acid, synthetically produced this alkaloid (92).

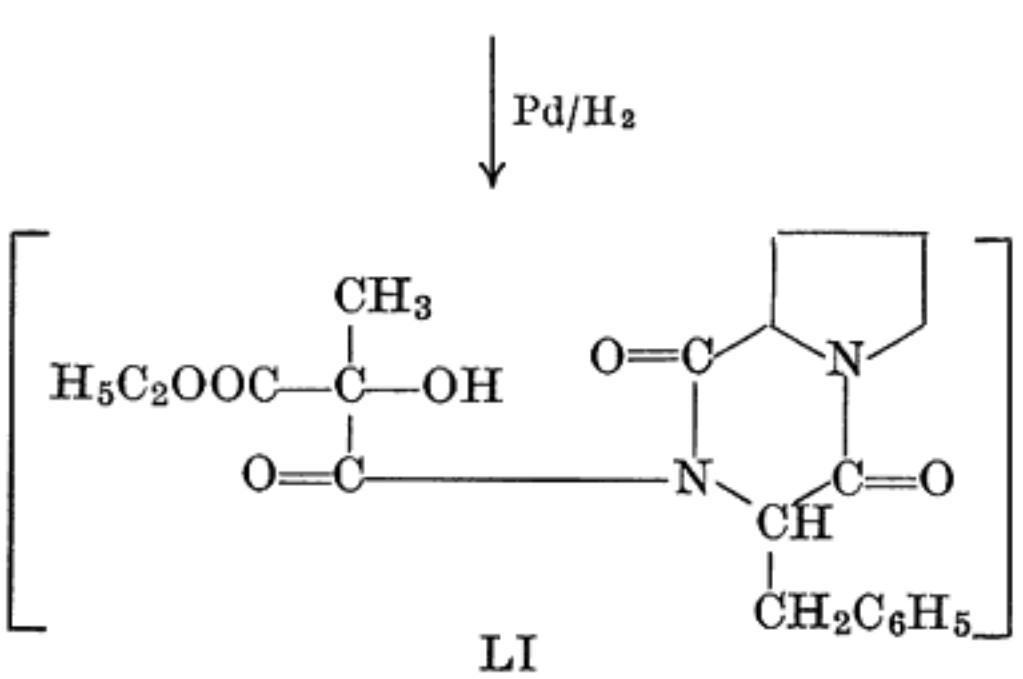
Methylbenzyloxymalonic acid ester, which may be produced from methylmalonic acid diethylester by bromination and conversion with



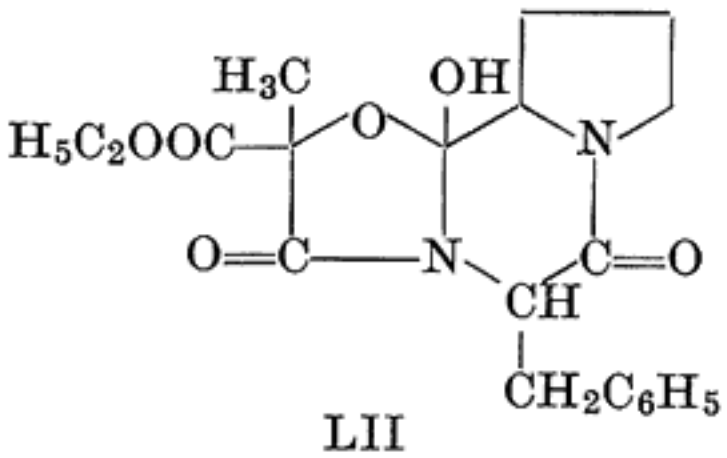
XLVIII XLIX



L



LI

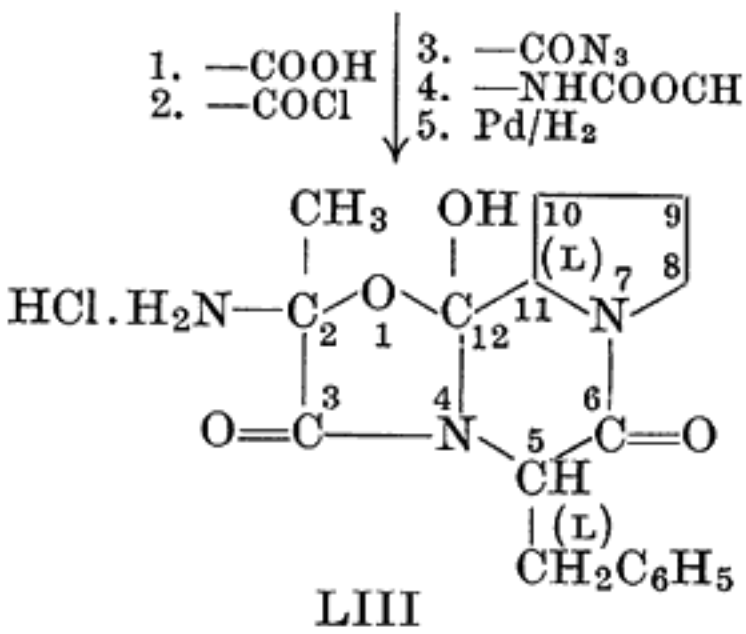


LII

a: mp 135°–136°
b: mp 202°–204°

1. —COOH
2. —COCl

3. —CON_3
4. —$NHCOOCH_2C_6H_5$
5. Pd/H_2



LIII

a: mp 180°–183°
b: mp 131°–133°

sodium benzylate, was used as a starting material for the production of the α-hydroxy-α-amino acid moiety. By saponification of one of the ester functions and subsequent treatment with thionyl chloride, the semiester acid chloride XLVIII resulted. This was reacted with L-phenylalanyl-L-proline lactam (XLIX) in pyridine to produce the acylated diketopiperazine (L). As compound XLVIII was in its racemic form, compound L consisted of a mixture of two diastereoisomer forms. The acyl radical of compound L, however, is easily split off again hydrolytically. For this

reason, compound L was immediately treated with palladium-hydrogen so as to remove the benzyl group. The resulting compound LI, having a free hydroxyl group, cyclized spontaneously to form the stable cyclol-carboxylic acid ester LII. The cyclol structure in LII was detected by the presence of an acid hydroxyl group and by analysis of the IR- and NMR-spectra. As compound LII was stable it could be resolved into the homogeneous stereoisomer forms by fractional crystallization. Two stereoisomers resulted, LIIa having a melting point of 135°–136° and LIIb having a melting point of 202°–204°. These compounds differ in their configuration at the C-2 atom (compare numbering in LIII). The occurrence of only two stereoisomer forms of LII shows that the cyclol formation, as a result of which a new center of asymmetry is formed at C-12, takes place stereospecifically. In both isomers the carbethoxy group was converted to the amino group by means of a Curtius degradation. Owing to the stability of the cyclol system, the ester could be saponified with sodium hydroxide solution to form the corresponding acid. This acid was reacted, in the form of the sodium salt, with oxalyl chloride to yield the acid chloride which, upon reaction with sodium azide, yielded the corresponding acid azide. A Curtius rearrangement of the azide, effected by heating with benzyl alcohol, yielded benzyl urethane which, upon hydrogenolytic cleavage, decomposed to form the amino cyclol LIII. Although compound LIII is not stable as a free base, it was crystallized in the form of its hydrochloride. The hydrochloride of the amino cyclol of the ester LIIa melts at 180°–183° and that of LIIb at 131°–133°. The entire peptide portion of ergotamine is present in compound LIII.

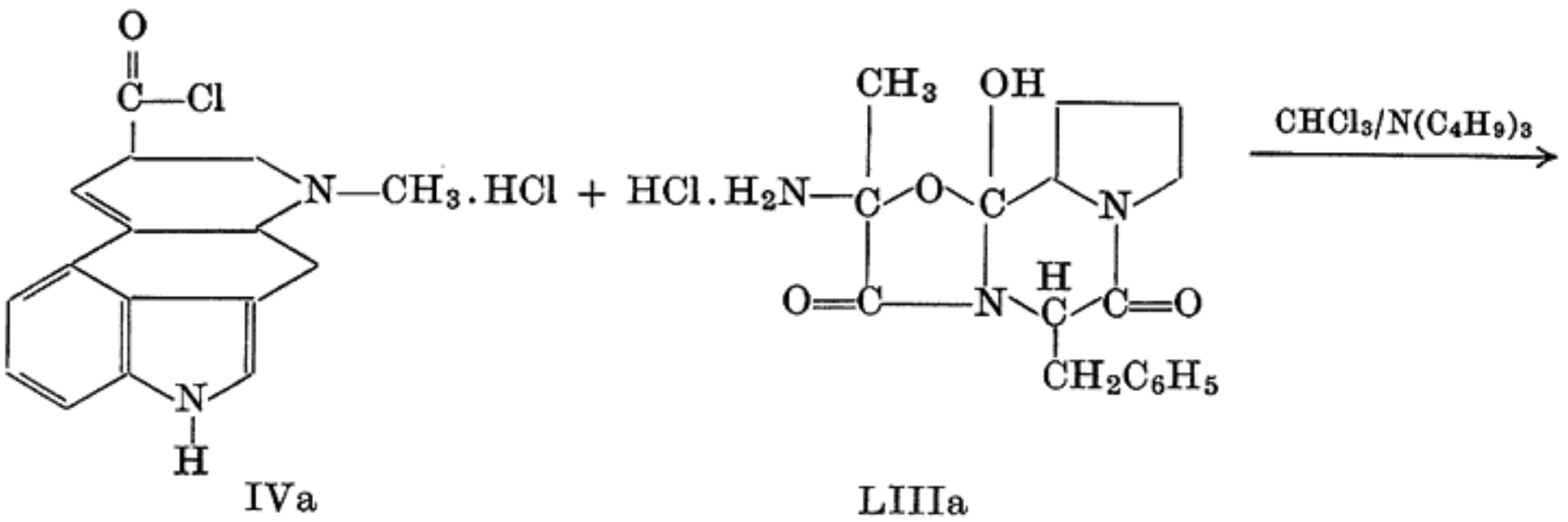
Conversion of isomer LIIIa with lysergic acid chloride hydrochloride (IVa) in chloroform, with the addition of tributylamine, yielded a compound whose chemical, physical, and pharmacological properties were identical with those of the natural alkaloid ergotamine. Thus, the total synthesis of this alkaloid was accomplished, lysergic acid having already been synthesized at an earlier date (50).

Acylation of compound LIIIb with IVa yielded an alkaloid (LIV) which is an isomer of ergotamine, differing therefrom only by the spatial arrangement at the C-2 atom of the peptide portion.

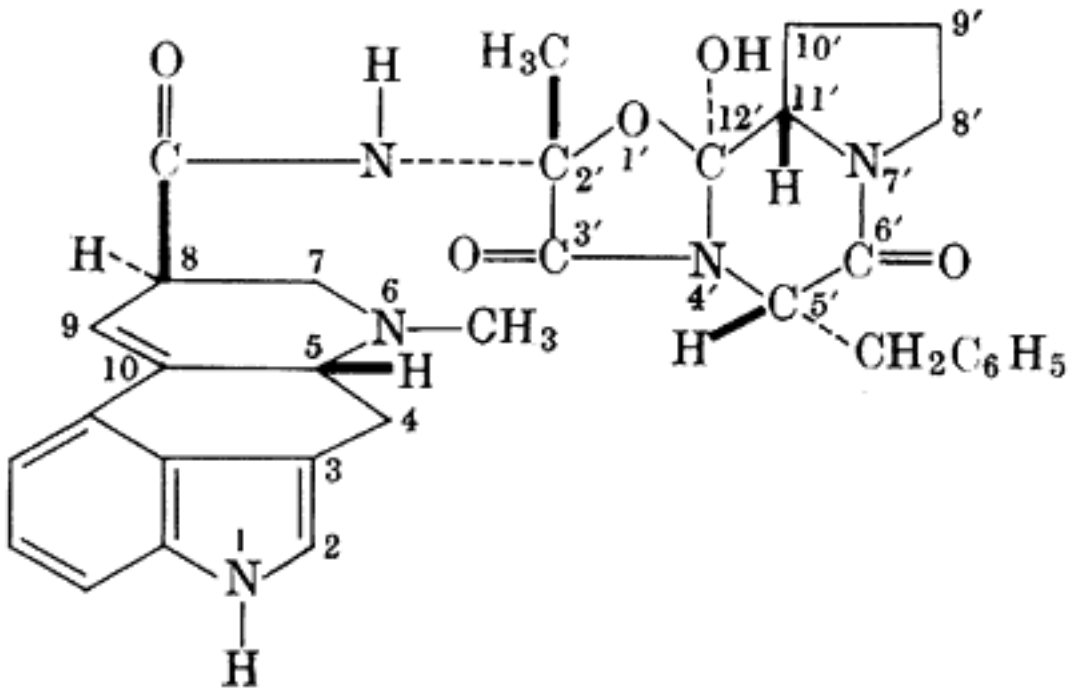
By means of a substantially similar process, ergosine as well as an alkaloid of the ergotamine group which had hitherto not been found in nature, viz., that alkaloid having *L*-valine as variable amino acid and which could be referred to as "ergovaline," were produced synthetically (175).

An improved process for the production of ergotamine (173) utilizes the optically active acid chloride of the methylbenzyloxymalonic

acid semiester (XLVIII) as starting material. As the absolute configuration of the corresponding optically active semiester had been elucidated (174), the absolute configuration at the C-2′ atom of the peptide portion



IVa LIIIa



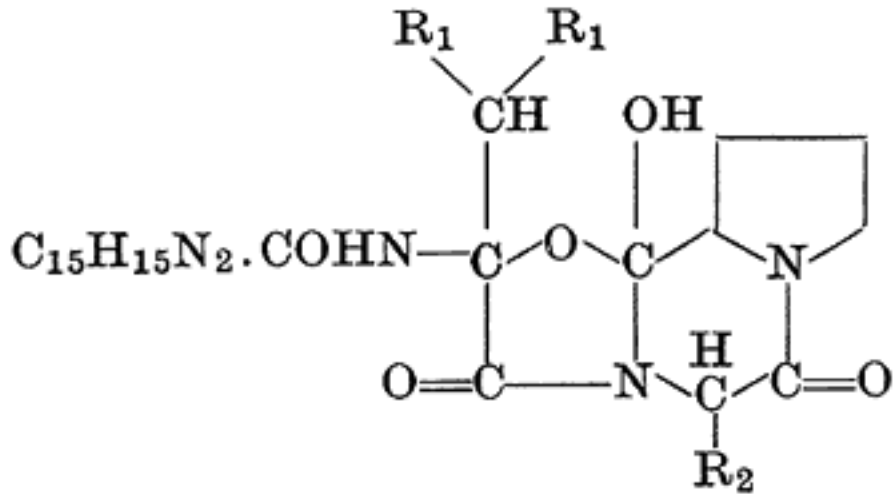
LIV
Ergotamine

of ergotamine is likewise known. Furthermore, with the aid of degradation reactions of intermediate products formed in the synthesis of the peptide portion, the configuration at the C-12′ atom could also be elucidated so that the absolute configuration is now known for all six centers of assymetry of ergotamine, as is shown by the formula LIV (173). The similar optical rotation values obtained could lead to the conclusion that the remaining ergot alkaloids of the peptide type exhibit the same stereochemistry as does ergotamine.

C. Characterization of the Ergot Alkaloids of the Peptide Type

A total of five alkaloid pairs of the peptide type, whose structures are depicted by formulas LIV–LVIII, have been isolated. A further alkaloid pair, ergosecaline and ergosecalinine, the structure of which has, as yet,

not been definitely elucidated, also appears to have a peptide character (95).



a: Lysergic acid radical (IV)
b: Isolysergic acid radical (V)

$R_1 = H; R_2 = CH_2C_6H_5$: ergotamine (LIVa), ergotaminine (LIVb)

$R_1 = H; R_2 = CH_2CH(CH_3)_2$: ergosine (LVa), ergosinine (LVb)

$R_1 = CH_3; R_2 = CH_2C_6H_5$: ergocristine (LVIa), ergocristinine (LVIb)

$R_1 = CH_3; R_2 = CH_2CH(CH_3)_2$: ergocryptine (LVIIa), ergocryptinine (LVIIb)

$R_1 = CH_3; R_2 = CH(CH_3)_2$: ergocornine (LVIIIa), ergocorninine (LVIIIb)

1. *Ergotamine-Ergotaminine*, $C_{33}H_{35}O_5N_5$ (581.7)

Ergotamine (LIVa) (13) crystallizes especially easily and typically from a 90% aqueous acetone solution in the form of truncated polyhedral prisms having the following composition:

$$C_{33}H_{35}O_5N_5 . 2CH_3COCH_3 . 2H_2O.$$

They disintegrate rapidly upon exposure to the atmosphere, mp 180° (dec.). From an 800-fold quantity of boiling benzene, long thin prisms are obtained, mp 212°–214° (dec.), $[\alpha]_D^{20}$ −160°, $[\alpha]_{5461}^{20}$ −192° (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ −12.7°, $[\alpha]_{5461}^{20}$ −8.6° (c = 1.0 in pyridine).

Salts of ergotamine. Ergotaminetartrate $(C_{33}H_{35}O_5N_5)_2 . C_4H_6O_6 . 2CH_3OH$, from methanol thick rhombic slabs, mp 203°, is the salt of ergotamine most used in pharmaceutical preparations (e.g., Gynergen, Bellergal) and this salt is the one which has been adopted by the pharmacopeias.

Ergotaminehydrochloride has a mp 212° (dec.); ergotaminehydrogen maleate, mp 195°–197° (dec.); ergotaminephosphate, mp 200° (dec.); ergotaminesulfate, mp. 207° (dec.); ergotaminemethanesulfonate, mp 210° (dec.).

Ergotamine was isolated from Swiss ergot by Stoll in 1918. It was the first chemically homogeneous and fully active ergot alkaloid and found widespread medical application. The great variety of clinical uses to which it is being put at present will be described in greater detail in the

last section of this article. The major portion of ergotamine is currently obtained from ergot cultivated in the Swiss midlands by artificial mechanical infection of rye cultures. A process (14, 13), developed by Stoll in as early as 1918, has been found especially effective for the industrial production of ergotamine.

Ergotaminine (LIVb) is very difficultly soluble in most solvents. Approximately 1500 parts of boiling methanol are required before it will dissolve and, upon cooling, it crystallizes in thin rhombic plates; mp 241°–243° (dec.); $[\alpha]_D^{20}$ +369°, $[\alpha]_{5461}^{20}$ +462° (c = 0.5 in $CHCl_3$); $[\alpha]_D^{20}$ +397°, $[\alpha]_{5461}^{20}$ +497° (c = 0.5 in pyridine).

As a result of the difficulty with which it dissolves, it crystallizes rapidly from the equilibrium set up between ergotamine and ergotaminine in hydroxyl-containing solvents. This leads to practically complete conversion of ergotamine to ergotaminine. On the other hand, the extreme difficulty with which ergotamine sulfate dissolves in glacial acetic acid may be used for the reversion of ergotaminine to ergotamine (13). As is the case with most of the isolysergic acid derivatives, ergotaminine is practically ineffective pharmacologically (96).

Long storage of ergotamine or ergotaminine at room temperature in acid solution or boiling for a short time causes rearrangements also of the peptide portion, and an equilibrium among ergotamine, aci-ergotamine, ergotaminine, and aci-ergotaminine is set up (97). The aci-isomers have an amphoteric nature and, unlike the alkaloids from which they stem, dissolve not only in dilute acids but also in dilute aqueous alkali solutions. Aci-ergotamine, $C_{33}H_{35}O_5N_5$, yields needles from methanol; mp 185°–187°, $[\alpha]_D^{20}$ −32° (c = 1.2 in pyridine). Aci-ergotaminine, $C_{33}H_{35}O_5N_5$, yields fine needles from methanol-ether, mp 203° (dec.), $[\alpha]_D^{20}$ +258° (c = 1.2 in pyridine). Pharmacologically speaking (96), the aci-isomers are only weakly active.

2. *Ergosine-Ergosinine*, $C_{30}H_{37}O_5N_5$ (547.6)

Ergosine (LVa) (98) crystallizes from ethyl acetate in rectangular plates; mp 220°–230° (dec.), $[\alpha]_D^{20}$ −183°, $[\alpha]_{5461}^{20}$ −220° (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ −8°, $[\alpha]_{5461}^{20}$ −1° (c = 1.0 in pyridine). Ergosine.HCl crystallizes from acetone in plates, mp 235° (dec.), ergosine.CH_3SO_3H crystallizes from methanol in clusters of needles, mp 217°–218° (dec.).

Ergosinine (LVb) crystallizes from acetone in the form of blunt prisms: mp 228° (dec.), $[\alpha]_D^{20}$ +420°, $[\alpha]_{5461}^{20}$ +522° (c = 1.0 in $CHCl_3$).

Ergosine and ergosinine, which were isolated from Iberian ergot by Smith and Timmis in 1937 (98), have so far found no medicinal application.

3. Ergocristine-Ergocristinine, $C_{35}H_{39}O_5N_5$ (609.7)

Ergocristine (LVIa) crystallizes from acetone in the form of prisms containing crystalline solvent and melting at 160°–175° (dec.); $[\alpha]_D^{20}$ $-183°$, $[\alpha]_{5461}^{20}$ $-217°$ (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ $-93°$, $[\alpha]_{5461}^{20}$ $-107°$ (c = 1.0 in pyridine). Ergocristine.HCl crystallizes from alcohol ether in long slabs; mp 205° (dec.); ergocristine.H_3PO_4 crystallizes from alcohol in hexagonal plates; mp 195° (dec.); ergocristine.$C_2H_5SO_3H$ crystallizes from acetone in the form of hexagonal slabs; mp 207° (dec.).

Ergocristine was isolated from Iberian ergot by Stoll and Burckhardt (99) in 1937 and later found by Stoll and Hofmann (10) to be a constituent of the alkaloid mixture known as ergotoxine (7). As a result of the strong sympathicolytic action of its dihydro derivative, it has found clinical application, e.g., as a component of Hydergin.

Ergocristinine (LVIb) crystallizes from alcohol in long thin prisms; mp 226° (dec.) (10); $[\alpha]_D^{20}$ $+366°$, $[\alpha]_{5461}^{20}$ $+460°$ (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ $+462°$, $[\alpha]_{5461}^{20}$ $+576°$ (c = 1.0 in pyridine).

4. Ergocryptine-Ergocryptinine, $C_{32}H_{41}O_5N_5$ (575.7)

Ergocryptine (LVIIa) crystallizes from a concentrated methyl alcoholic solution in truncated prisms; mp 212°–214° (dec.); $[\alpha]_D^{20}$ $-190°$, $[\alpha]_{5461}^{20}$ $-226°$ (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ $-112°$, $[\alpha]_{5461}^{20}$ $-133°$ (c = 1.0 in pyridine). Ergocryptine.H_3PO_4 crystallizes from 90% alcohol in hexagonal plates; mp 198°–200° (dec.); ergocryptine.$C_2H_5SO_3H$, prisms from alcohol-ether; mp 204° (dec.).

Ergocryptine was discovered by Stoll and Hofmann as a component of the ergotoxine complex (10). It is the main alkaloid in ergot of Japanese (100) and South American (101) wild grasses. Its dihydro derivative is used as a constituent of Hydergin.

Ergocryptinine (LVIIb) was produced by rearrangement of ergocryptine in boiling methyl alcohol (10). Thin prisms result; mp 240°–242° (dec.); $[\alpha]_D^{20}$ $+408°$; $[\alpha]_{5461}^{20}$ $+508°$ (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ $+479°$, $[\alpha]_{5461}^{20}$ $+596°$ (c = 1.0 in pyridine).

5. Ergocornine-Ergocorninine, $C_{31}H_{39}O_5N_5$ (561.7)

Ergocornine (LVIIIa) crystallizes from methanol in the form of polyhedra; mp 182°–184° (dec.); $[\alpha]_D^{20}$ $-188°$, $[\alpha]_{5461}^{20}$ $-226°$ (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ $-105°$, $[\alpha]_{5461}^{20}$ $-122°$ (c = 1.0 in pyridine). Ergocornine.H_3PO_4 crystallizes from 90% alcohol in the form of pointed prisms which combine to form clusters; mp 190°–195° (dec.); ergocornine.$C_2H_5SO_3H$, long needles from alcohol; mp 209° (dec.).

Ergocornine was first discovered by Stoll and Hofmann (10) upon

separation of the ergotoxine complex. It is used medically in the form of its dihydro derivative as a constituent of Hydergin.

Ergocorninine (LVIIIb) was obtained by isomerization of ergocornine (10). It crystallizes as pointed prisms from methanol; mp 228° (dec.); $[\alpha]_D^{20}$ +409°, $[\alpha]_{5461}^{20}$ +512° (c = 1.0 in $CHCl_3$); $[\alpha]_D^{20}$ +500°, $[\alpha]_{5461}^{20}$ +624° (c = 1.0 in pyridine).

VI. The Alkaloids of the Clavine Series

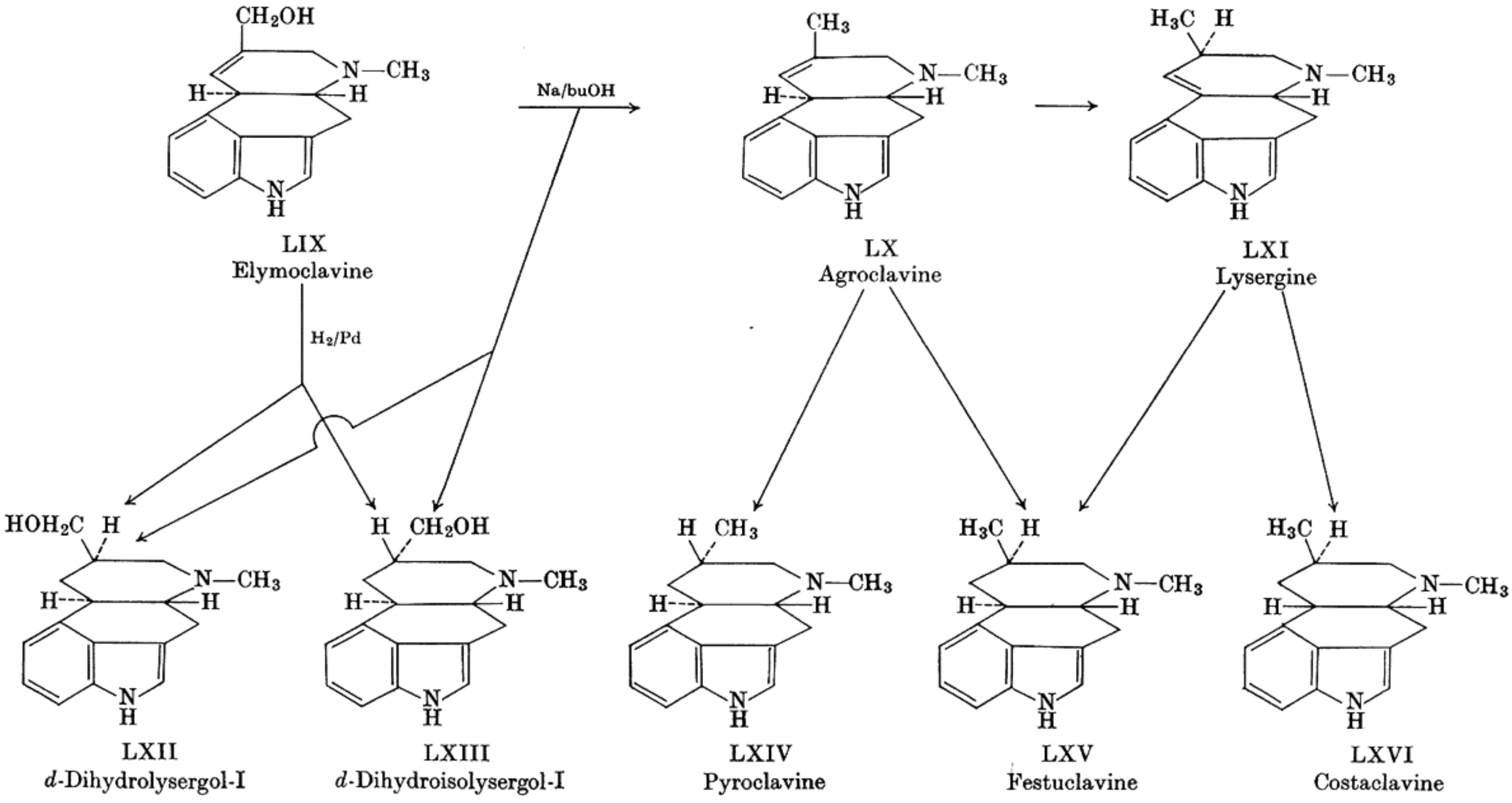
The first representatives of this second main group of ergot alkaloids, which differ from the classical lysergic acid alkaloids in that the carboxyl group of the lysergic acid has been reduced to the hydroxymethyl or methyl group, were discovered by Abe and collaborators in 1951 in Japan in the ergot of various species of grass growing in the Far East (100). These compounds were agroclavine, obtained from the ergot of *Agropyrum semicostatum* and elymoclavine from *Elymus mollis* ergot. All alkaloids of this type that were isolated later were given names ending in *-clavine* to show that they form part of the same structural group.

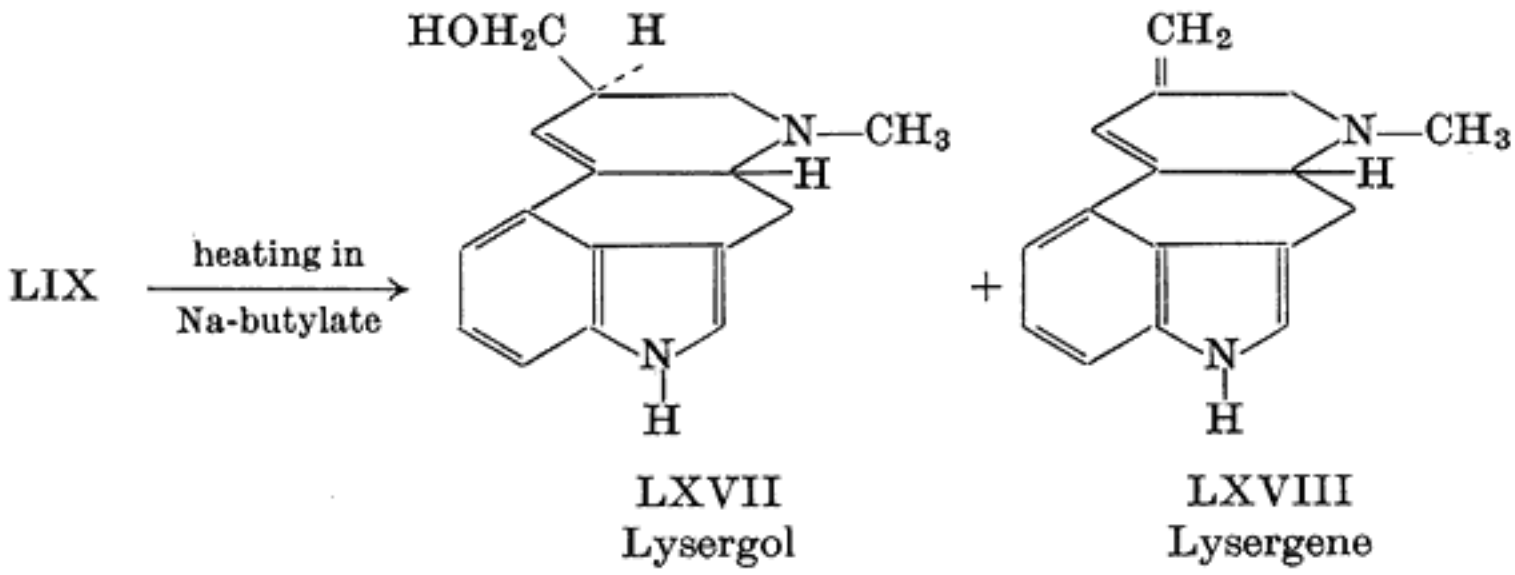
Recently, with the aid of the new, efficient methods of detection, e.g., paper and thin-layer chromatography, clavine alkaloids have also been found to occur in ergot obtained from rye. Furthermore, in 1960, Hofmann and Tscherter surprisingly found the occurrence of alkaloids of the clavine type in higher plants, i.e., in genera of the family of twining plants (Convolvulaceae) (70, 71).

A. Structural Relationships

The structural and configurative relationships between the alkaloids of the clavine group on the one hand, and the derivatives of lysergic acid alkaloids (LXII, LXIII) on the other, are shown by the illustrated formula scheme (LIX to LXVI).

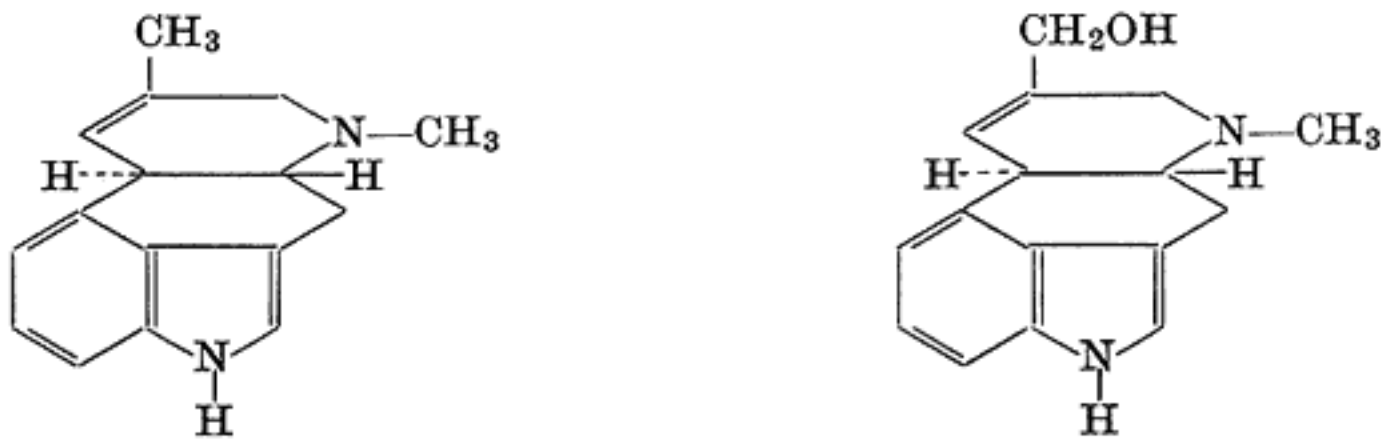
Catalytic hydrogenation of elymoclavine (LIX) (102) yielded a mixture of *d*-dihydrolysergol-I (LXII) (103) and *d*-dihydroisolysergol-I (LXIII) (103). It has the same ring system and the same configuration at the C-5 and C-10 atoms as *d*-dihydrolysergic acid. Reduction of compound LIX with sodium in butanol yielded a mixture of agroclavine (LX), lysergine (LXI), pyroclavine (LXIV), festuclavine (LXV), and costaclavine (LXVI) in addition to *d*-dihydrolysergol-I (LXII) and *d*-dihydroisolysergol-I (LXIII) (104, 105).


CH2OH
N—CH3
H
H
N
H
LIX
Elymoclavine
Na/buOH
H2/Pd
CH3
LX
Agroclavine
H3C H
LXI
Lysergine
HOH2C H
LXII
d-Dihydrolysergol-I
H CH2OH
LXIII
d-Dihydroisolysergol-I
H CH3
LXIV
Pyroclavine
H3C H
LXV
Festuclavine
H3C H
LXVI
Costaclavine



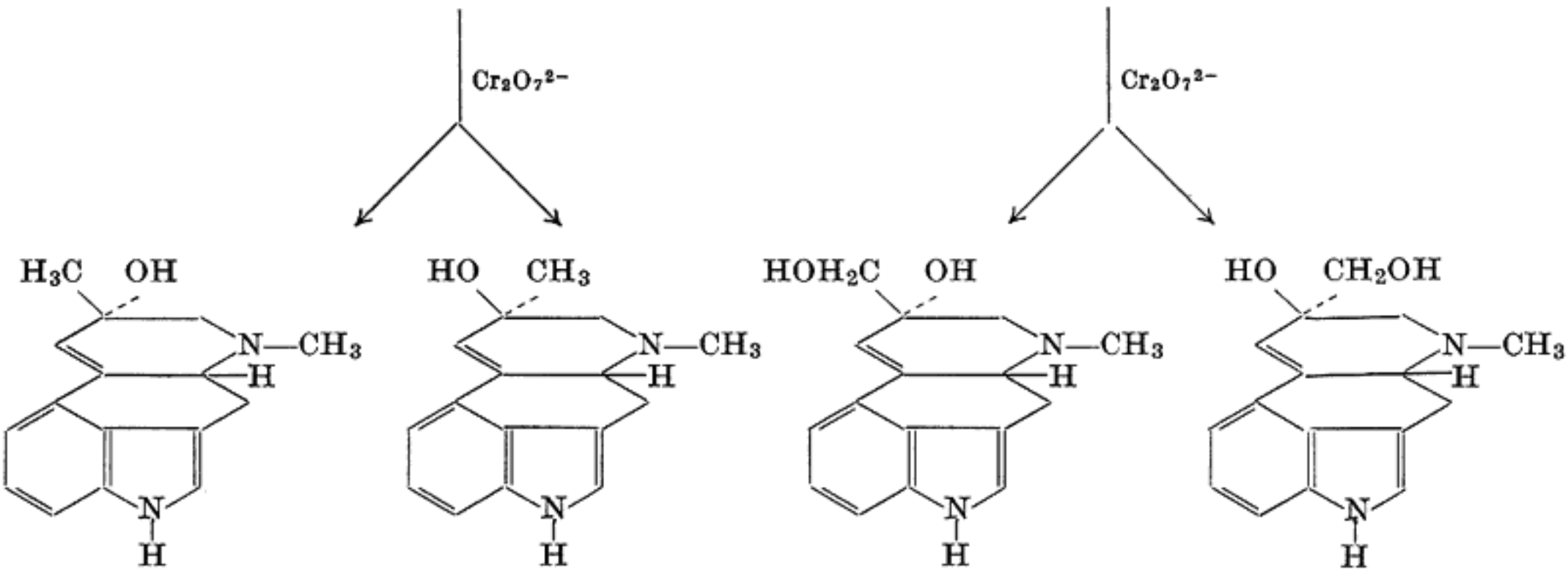
LXVII
Lysergol

LXVIII
Lysergene



LX
Agroclavine

LIX
Elymoclavine



LXIX
Setoclavine

LXX
Isosetoclavine

LXXI
Penniclavine

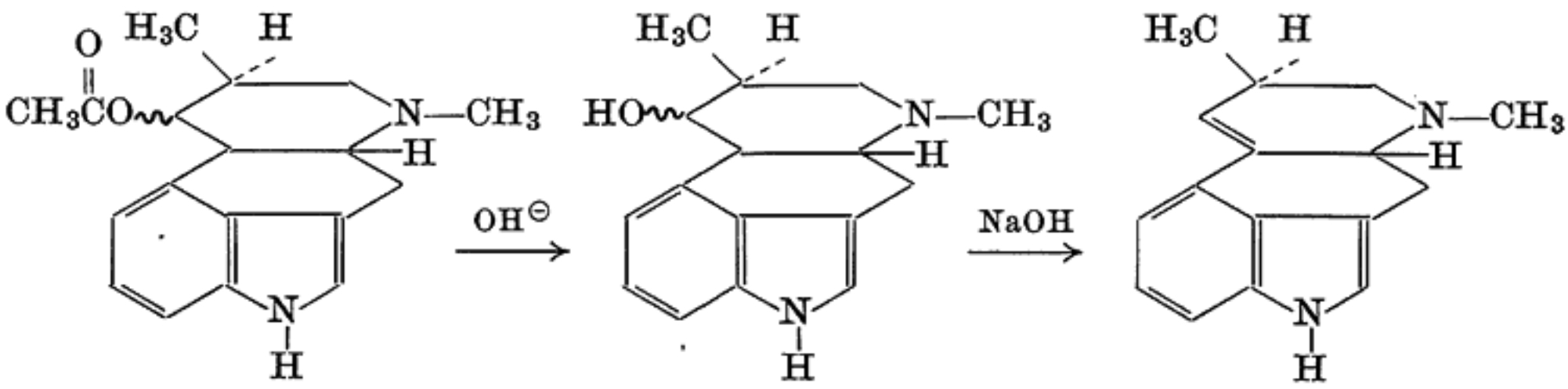
LXXII
Isopenniclavine

The position of the isolated double bond in agroclavine, for which the 7-8 or 8-9 position came into consideration, was determined from the fact that agroclavine gave nearly the same pK value as its dihydro derivatives (106). Heating of agriclavine in a sodium butylate solution produced only lysergine, whereas the same treatment in the case of elymoclavine yielded a mixture of lysergol (LXVII) and lysergene (LXVIII) (105).

The correctness of these deductions was confirmed by the extensive investigations of Schreier (107).

The structures of setoclavine (LXIX), isosetoclavine (LXX), penniclavine (LXXI), and isopenniclavine (LXXII) were, for the major part, obtained from the oxidative formation of these alkaloids from agroclavine (LX) and elymoclavine (LIX).

Oxidation of compound LX with potassium dichromate in dilute sulfuric acid yielded a mixture of setoclavine and isosetoclavine (108) which has the same UV-spectrum as lysergic acid. The double bond in the 8-9 position of compound LX has shifted to the 9-10 position. As a result of the tertiary character of the hydroxyl group, the pK values, and chromatographic behavior, the structure depicted by LXIX was attributed to setoclavine and that of LXX to isosetoclavine. Similarly, elymoclavine yielded the isomeric pair, penniclavine and isopenniclavine (109, 108). The structures depicted by LXXI and LXXII were deduced for these alkaloids which contain a glycol grouping.



LXXIII
Fumigaclavine A

LXXIV
Fumigaclavine B

LXI
Lysergine

Deacetylation caused fumigaclavine A (LXXIII) to be converted to fumigaclavine B (LXXIV). The ease of deacetylation, as well as the IR-bands at 1241 and 1725 cm^{-1}, indicated the presence of an ester group in compound LXXIII. Heating of compound LXXIV with NaOH caused water to be split off and resulted in the formation of lysergine (LXI). The configurations at the C-9 and C-10 atoms of compounds LXXIII and LXXIV have not, as yet, been elucidated. The negative optical rotation suggests a *trans*-linkage of rings C and D (72).

Chanoclavine (LXXV) (108) is the only known ergot alkaloid in which the D ring of the ergoline system is open. LXXV easily forms an *O*,*N*-

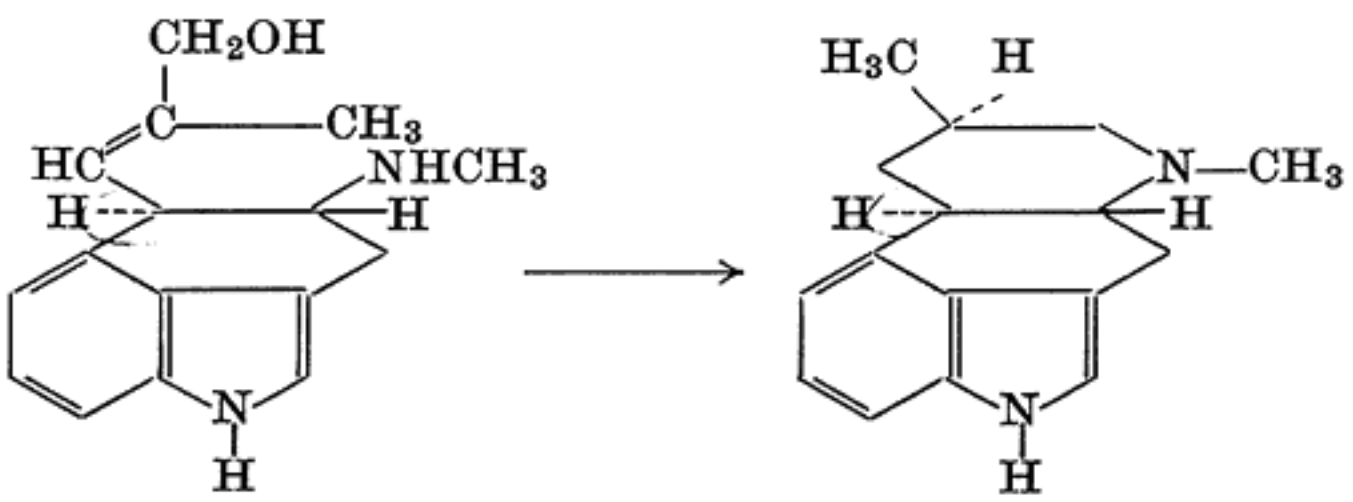


TABLE IV

THE CLAVINE ALKALOIDS

Alkaloid	Formula	mp (solvent) (°C)	[α]	Source; ergot of:	Reference
Agroclavine	$C_{16}H_{18}N_2$ vb[a]	205–206 (acetone)	$[\alpha]_D^{20}$ −182° pyridine 0.5	*Agropyrum semicostatum*	110
				A. ciliare Fr.	111
			$[\alpha]_D^{20}$ −155° $CHCl_3$ 0.9	*Pennisetum typhoideum* Rich.	112
Elymoclavine	$C_{16}H_{18}ON_2$ vb	245–249 (methanol)	$[\alpha]_D^{20}$ −152° pyridine 0.9	*Elymus mollis* Tri.	100
				Pennisetum sp.	112
				Rivea corymbosa (L.) (seed) Hall.f.	71
Molliclavine	$C_{16}H_{18}O_2N_2$ g	253 (methanol)	$[\alpha]_D^{17}$ +30° pyridine 0.2 $[\alpha]_{5461}^{17}$ +42° pyridine 0.2	*Elymus mollis*	113
Lysergine	$C_{16}H_{18}N_2$ vb	286 (methanol, ethyl acetate)	$[\alpha]_D^{20}$ +65° pyridine 0.5	*Agropyrum* sp.	114
				ex elymoclavine	104
				ex agroclavine	104
				ex lysergene	107
Lysergol	$C_{16}H_{18}ON_2$ b	253–255 (ethanol)	$[\alpha]_D^{20}$ +54° pyridine 0.3 $[\alpha]_{5461}^{20}$ +87° pyridine 0.3	*Rivea corymbosa* *Elymus* sp.	71 114, 115
Lysergene	$C_{16}H_{16}N_2$ g	247–249	$[\alpha]_D^{20}$ +504° pyridine 0.4	ex elymoclavine	104, 107
				Elymus sp.	114, 115
Setoclavine	$C_{16}H_{18}ON_2$ g	229–234 (acetone, methanol)	$[\alpha]_D^{20}$ +174° pyridine 1.0 $[\alpha]_{5461}^{20}$ +232° pyridine 1.0	*Pennisetum typhoideum* *Elymus mollis*	108 109
Isosetoclavine	$C_{16}H_{18}ON_2$ g	234–237 (methanol)	$[\alpha]_D^{20}$ +107° pyridine 0.5 $[\alpha]_{5461}^{20}$ +147° pyridine 0.5	*Pennisetum* sp. Japanese grasses	108 116

Penniclavine	$C_{16}H_{18}O_2N_2$ g	222—225 (acetone)	$[\alpha]_D^{20}$ +151° pyridine 0.5 $[\alpha]_{5461}^{20}$ +201° pyridine 0.5	*Pennisetum typhoideum* Japanese grasses Rye	108, 112 109 117
Isopenniclavine	$C_{16}H_{18}O_2N_2$ g	163–165 (water)	$[\alpha]_D^{20}$ +146° pyridine 0.7 $[\alpha]_{5461}^{20}$ +198° pyridine 0.7	*Pennisetum* sp.	108
Festuclavine	$C_{16}H_{20}N_2$ vb	242–244 (methanol)	$[\alpha]_D^{20}$ −110° pyridine 0.5 $[\alpha]_{5461}^{20}$ −128° pyridine 0.5 $[\alpha]_D^{20}$ −70° $CHCl_3$ 0.5 $[\alpha]_{5461}^{20}$ −83° $CHCl_3$ 0.5	*Agropyrum* and *Phalaris* spp. *Aspergillus fumigatus* Fres. ex agroclavine	111 72 104, 107, 118
Pyroclavine	$C_{16}H_{20}N_2$ vb	204 (methanol, benzene, ethyl acetate)	$[\alpha]_D^{20}$ −90° pyridine 0.2 $[\alpha]_{5461}^{20}$ −105° pyridine 0.2	ex ML. from festuclavine ex agroclavine	116 104, 107
Costaclavine	$C_{16}H_{20}N_2$	182 (ethyl acetate)	$[\alpha]_D^{20}$ +44° pyridine 0.2 $[\alpha]_{5461}^{20}$ +59° pyridine 0.2	*Agropyrum* spp. ex agroclavine and elymoclavine	116 104
Fumigaclavine A	$C_{18}H_{22}O_2N_2$	84–85 (methanol-H_2O)	$[\alpha]_{5461}^{22}$ −56.7° methanol 1.5	*Aspergillus fumigatus*	72
Fumigaclavine B	$C_{16}H_{20}ON_2$	244–245 and 265–267 (ethanol-H_2O)	$[\alpha]_{5461}^{22}$ −113° pyridine 0.6 $[\alpha]_{5461}^{22}$ −6.3° methanol 1.2	*Aspergillus fumigatus*	72
Chanoclavine	$C_{16}H_{20}ON_2$ vb	220–222 (methanol, acetone)	$[\alpha]_D^{20}$ −240° pyridine 1.0 $[\alpha]_{5461}^{20}$ −294° pyridine 1.0	*Pennisetum typhoideum* Ergots *Rivea corymbosa*	108 116, 119, 120 71
N-acetylchanoclavine		226–228	$[\alpha]_D^{20}$ −80° pyridine 0.5		
O,N-diacetylchanoclavine		174–175	$[\alpha]_D^{20}$ −55° pyridine 0.9		

[a] Keller's color reactions: g = green; b = blue; vb = violet-blue.

diacetyl derivative in which the N atom in the 6 position is acetylated. The configuration of LXXV was deduced by comparison with festuclavine (LXV), a small yield of which is obtained by catalytic hydrogenation of chanoclavine.

B. The Clavine Alkaloids

Table IV (p. 764) contains chemical and physical data and indications on the source of the clavine alkaloids.

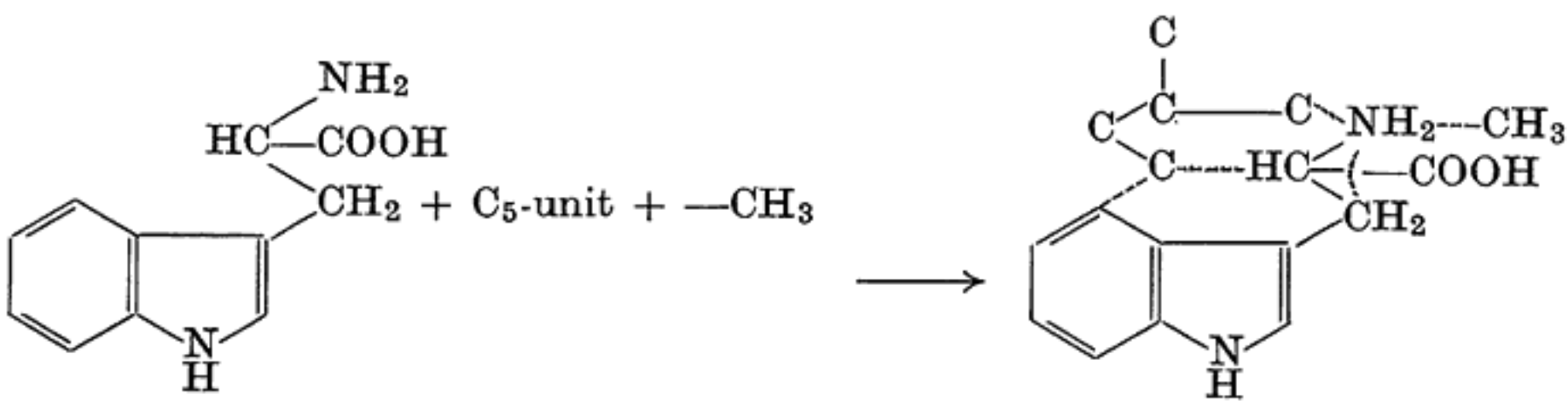
VII. Biogenesis of the Ergot Alkaloids

In all hypotheses relating to the biogenesis of the ergoline-lysergic acid moiety of ergot alkaloids, it was assumed that tryptophan constituted a main structural element. This assumption was later shown by experiment to be correct.

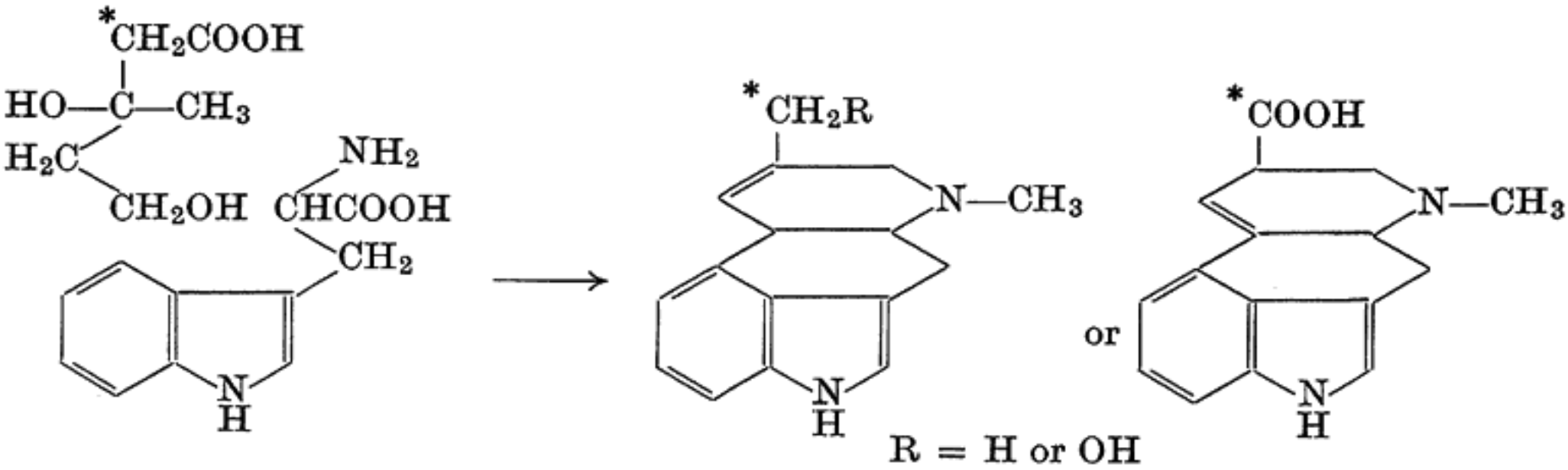
Injection of D,L-tryptophan-β-C^{14} into the internodes of rye plants yielded ergot alkaloids whose lysergic acid portion was radioactive (121). Upon the addition of D,L-tryptophan-β-C^{14} to saprophytic cultures of an ergot strain producing clavine alkaloids it was found that 10–39% was assimilated. It was further found that the addition of pyridoxalphosphate increased the yield. Experiments with tryptophan-$C^{14}OOH$, on the other hand, yielded practically inactive alkaloids, from which it may be deduced that the carboxyl group of the tryptophan is not incorporated in the ergoline structure (122). A large quantity of D,L-tryptophan-β-C^{14} was also found to be assimilated in the case of a *Claviceps* strain producing lysergic acid alkaloids (123). By incorporation of D-tryptophan labeled with tritium, it was proved that the unphysiological D-form of this amino acid was also utilized by the fungus (124). It was also possible to incorporate indole-2-C^{14} into the ergot alkaloids. Tryptamine-β-C^{14}, however, is not utilized. Thus, it is improbable that decarboxylation of tryptophan occurs prior to its incorporation into the alkaloid molecule. An assimilation of 1.35% for L-methionine-methyl-C^{14} shows that the *N*-methyl group of the ergot alkaloids is derived from methionine via a transmethylation reaction (125).

In saprophytic cultures of the *Pennisetum* ergot fungus, only tryptophan, deuterated in the 5 or 6 position, was used for the synthesis of the clavine alkaloids without loss of the deuterium. Deuterium in the 4 position was lost. These experiments showed that the hypotheses, according to which 5-hydroxytryptophan would be an intermediate stage in the biosyntheses (126, 127), could not be correct (128).

Various hypotheses were forwarded concerning the nature of the structural element which was required in biosynthesis in addition to the tryptamine portion (127, 126, 129, 130). The following experiments show that, aside from tryptophan, an isoprenoidal 5-C compound participates in the formation of the ergoline structure. This was first postulated by Mothes (121).



Mevalonic acid, the precursor of the active isoprene, was used in the incorporation studies. Both mevalonic acid-2-C^{14} and mevalonic acid-2T or -4T were utilized by the fungus for the synthesis (131, 132). By means of a stagewise degradation of radioactive alkaloids formed with the aid of mevalonic acid-2-C^{14} and localization of the C^{14}, it could be shown that mevalonic acid is incorporated into the molecule in the manner depicted by the accompanying reaction scheme (133, 134, 135).



The addition of mevalonic acid-1-C^{14} to a pyroclavine- and festuclavine-producing fungus strain yielded inactive alkaloids which, in agreement with the scheme, showed that the carboxyl group of the mevalonic acid is not incorporated. Lowering of the assimilation of mevalonic acid-2-C^{14} by the addition of dimethylallylpyrophosphate or isopentenylpyrophosphate supported the assumption that mevalonic acid enters the alkaloid molecule via one of these activated isoprene radicals. This was confirmed by the incorporation of deuterated isopentenylpyrophosphate in alkaloids of the clavine type in saprophytic cultures of a *Claviceps* strain (128).

Experiments with alkaloids labeled with C^{14} showed that, in saprophytic cultures, agroclavine is converted into elymoclavine, penni-

clavine, and isopenniclavine, whereas only penniclavine and isopenniclavine are produced by labeled elymoclavine. Labeled penniclavine and isopenniclavine on the other hand caused no formation of elymoclavine or agroclavine. The biogenesis thus appears to consist of a progressive hydroxylation (136).

VIII. Derivatives of Ergot Alkaloids

The potent and versatile pharmacological activity of natural ergot alkaloids prompted investigations on the relationship between their chemical structure and physiological action. It also caused the natural alkaloids to be modified chemically and the resulting variations of pharmacological and therapeutic action to be studied.

A. Lysergic Acid and Dihydrolysergic Acid Derivatives of the Acid Amide Type

The azide process, employed in the first partial synthesis of ergometrine (81, 66), was used in the production of a great number of lysergic acid and dihydrolysergic acid derivatives of the acid amide type. Aside from the homologs and analogs of ergometrine, resulting from the condensation of isolysergic acid azide with the corresponding amino alcohols (66, 137), many unsubstituted mono and dialkyl amides of lysergic acid and dihydrolysergic acid (138, 139, 140, 141), as well as cycloalkylamides and a great number of derivatives of the peptide type, in which the lysergic acid or dihydrolysergic acid is linked with amino acids or with di- or tripeptides, were produced (142, 143).

In the last few years, further processes for the partial synthesis of ergometrine and other lysergic acid derivatives of the amide type have been discovered.

In accordance with the method of Garbrecht (144), the lithium salt of lysergic acid is converted in dimethylformamide solution with SO_3 to form the mixed lysergic acid sulfuric acid anhydride which reacts with primary or secondary amines to give a good yield of the corresponding lysergic acid amides.

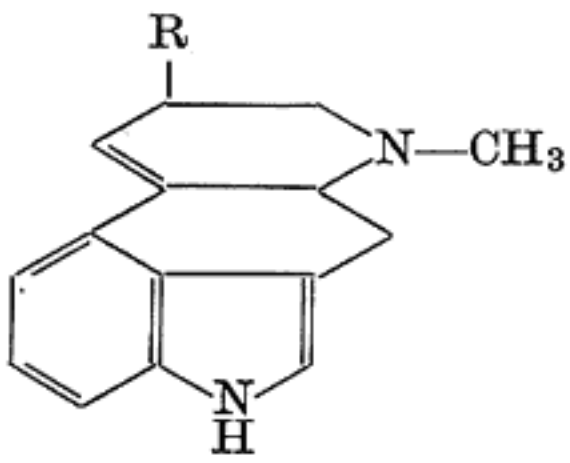
Similarly, the process according to Pioch (145) is effected via a mixed anhydride, namely, via the mixed lysergic acid trifluoroacetic anhydride. In this case, however, the yields of lysergic acid amide are usually not as good as in the SO_3 process.

A further process, which is used on a technical scale and which, like the azide method, had its origin in the SANDOZ laboratories, employs lysergic acid chloride hydrochloride as the activated form (146, 92). Furthermore, the method developed in peptide chemistry, using *N*,*N*′-carbonyldiimidazole as condensation agent (147), may be used to produce acid amides of lysergic acid and dihydrolysergic acid (148).

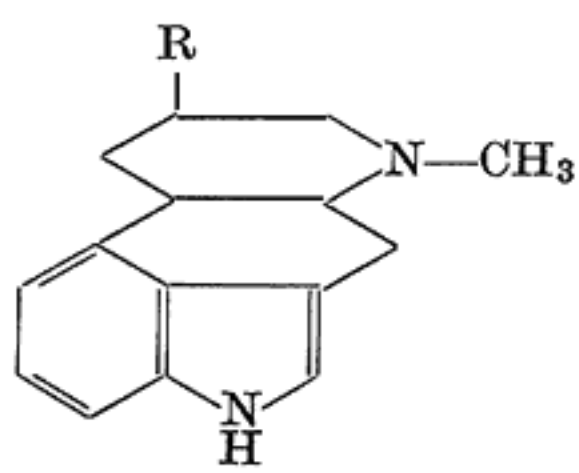
Of all these derivatives, two compounds have found medical application. D-Lysergic acid (+)-butanolamide(2), which is the next highest homolog of ergometrine, finds wide application in obstetrics, under the name of Methergine, owing to its uterotonic action and ability to arrest post partum hemorrhage. *d*-Lysergic acid diethylamide, which is characterized by its exceptional hallucinogenic and psycholytic action, has become known in experimental psychiatry as LSD 25 or under the trade name of Delysid and is also used as a drug aid in psychotherapy.

B. Amino and Carbamic Acid Derivatives of 6-Methylergolene and 6-Methylergoline

The isomeric 6-methyl-8-amino-ergolenes (LXXVIa) and ergolines (LXXVIIa) were produced by a modified Curtius degradation of *d*-lysergic acid azide, of *d*-isolysergic acid azide, or of the isomeric *d*-dihydrolysergic acid azides (149).



LXXVI



LXXVII

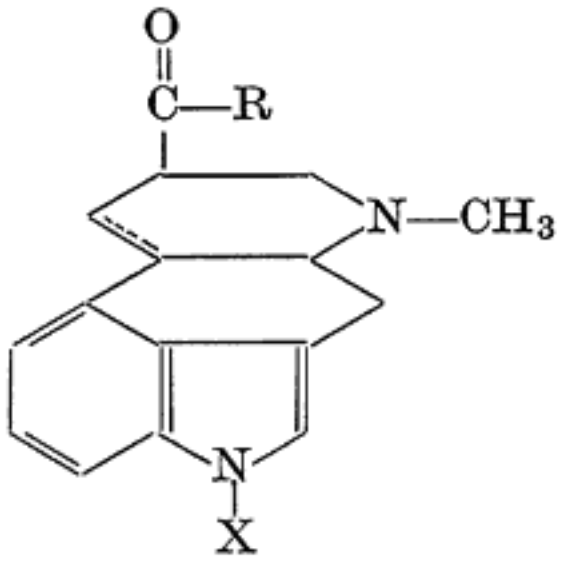
a: R = NH_2
b: R = NHCOOR′
c: R = NHCON(R″)(R‴)

Conversion of the corresponding isocyanates, resulting from the heating of the azides in benzene, with alcohols of general formula R′OH, yielded the carbamic acid esters LXXVIb (150), and with amines R″R‴NH, the urea derivatives LXXVIc and LXXVIIc (151, 152).

C. Substitutions in the Ring System of Lysergic Acid

Positions 1 and 2 of the ring structure of lysergic acid are especially reactive and various substituents may be introduced.

In derivatives of lysergic acid and dihydrolysergic acid, in which the carboxyl group has an ester-like or acid amide-like substituent, the indole nitrogen atom could be acetylated with ketene (LXXVIIIa and b) substituted with the hydroxymethyl radical (LXXVIIIc) using formaldehyde, by the dialkylaminomethyl radical (LXXVIIId) by means of a Mannich reaction (153), or by the cyanoethyl radical (LXXVIIIf) by the alkaline catalyzed addition of acrylonitrile (154).



LXXVIII

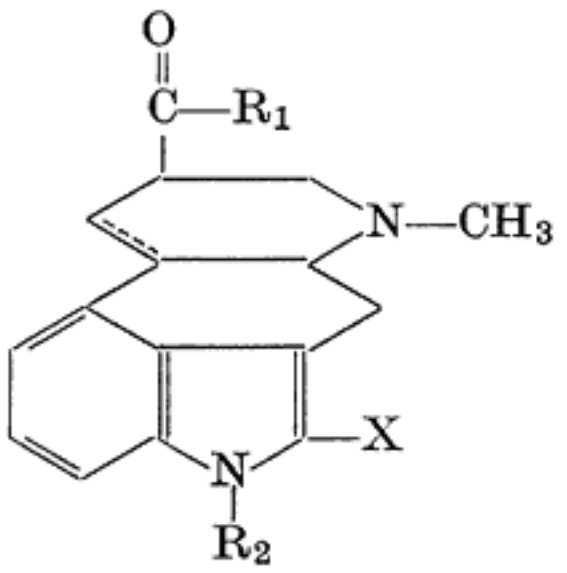
a: X = $COCH_3$
b: X = $COCH_2COCH_3$
c: X = CH_2OH
d: X = $CH_2N(alkyl)_2$
e: X = alkyl, benzyl
f: X = CH_2CH_2CN

The hydrogen atom at the indole nitrogen atom of lysergic acid derivatives was furthermore replaced by the methyl group and by larger alkyl radicals, e.g., ethyl, propyl, allyl, and benzyl radicals (LXXVIIIe). The alkylation is effected in liquid ammonia by reaction with the corresponding alkyl halides (155) and can be carried out most advantageously with the free carboxylic acids (156, 148). The *N*-methyllysergic acid butanolamide is a highly active serotonin antagonist and is widely used in the form of Deseril to cure stubborn headaches.

Derivatives of lysergic acid or dihydrolysergic acid, in which the 1 position is free or substituted with an alkyl radical, may be halogenated in the 2 position with bromino- or iodosuccinimide, *N*-2,6-trichloro-4-nitroacetanilide, and similar mild reagents (157) to compounds LXIX, a–c.

Halogenated lysergic acid and dihydrolysergic acid derivatives may easily be differentiated from the starting materials containing no

halogen since the van Urk color reaction, which is based on the condensation of *p*-dimethylaminobenzaldehyde with the free 2 position of the indole compounds (158), is negative in the case of halogenated derivatives.

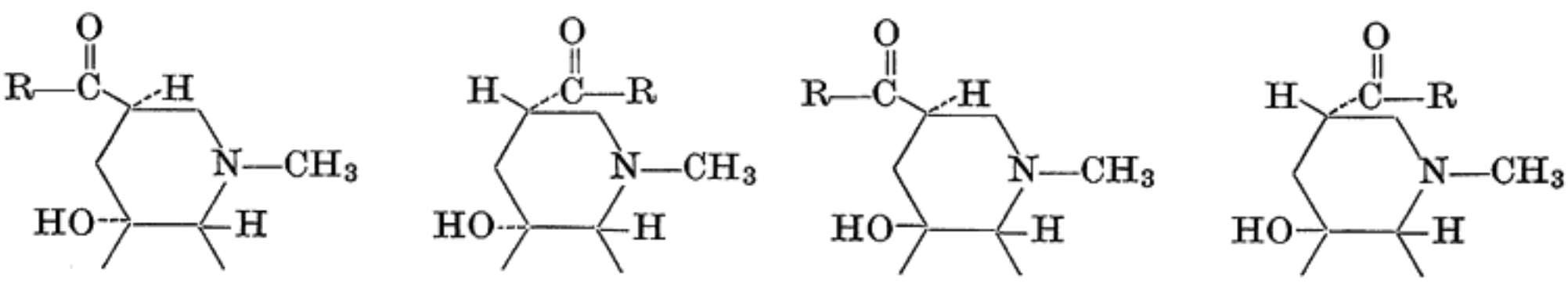


LXXIX

a: X = Cl
b: X = Br
c: X = J

Saturation of the double bond in the 9-10 position by catalytic hydrogenation has been discussed in Section III, B.

One molecule of water could also be added at the double bond in the 9-10 position. This reaction is effected in an acid aqueous solution of the alkaloids under intense irradiation with UV-light. The structures and configurations of the so-called lumi derivatives are depicted by formulas LXXX–LXXXIII (159, 160, 161, 162, 163, 164).



LXXX
Lumi-lysergic acid-I derivative

LXXXI
Lumi-isolysergic acid-I derivative

LXXXII
Lumi-lysergic acid-II derivative

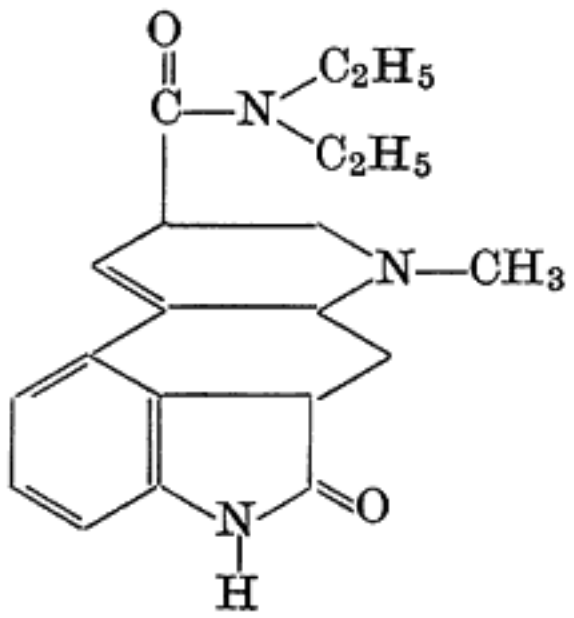
LXXXIII
Lumi-isolysergic acid-II derivative

By reduction with zinc dust in hydrochloric acid, the lysergic acid derivatives may be hydrogenated selectively in the 2-3 position and dehydrogenated with mercuric acetate in glacial acetic acid to form the starting materials (165).

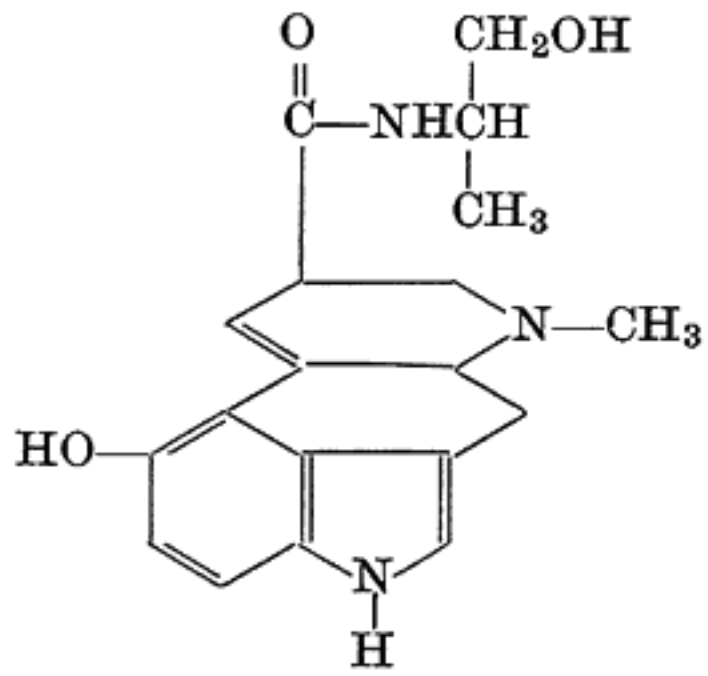
D. Biological Oxidation of Lysergic Acid Derivatives

d-Lysergic acid diethylamide is converted with a microsome preparation, obtained from guinea pig liver, to 2-oxo-2,3-dihydro-*d*-lysergic acid

diethylamide (LXXXIV). The constitution of this compound was ascertained by its partial chemical synthesis from *d*-lysergic acid diethylamide (166,167).



LXXXIV



LXXXV

On the other hand, ergometrine and *d*-lysergic acid diethylamide are secreted by the rat through the gall in the form of glucuronides of hydroxy derivatives (168). The hydroxyergometrine LXXXV isolated was found to be identical with the 12-hydroxyergometrine obtained by oxidation of 2,3-dihydroergometrine with potassium nitrosodisulfonate (169).

IX. The Pharmacology and Therapeutic Use of Ergot Alkaloids and Their Derivatives

The literature on pharmacological and clinical investigations of the ergot alkaloids and their derivatives is very comprehensive. There have already been more than one-thousand reports on lysergic acid diethylamide (LSD 25) (66), which was prepared only 20 years ago; the publications on the pharmacological and clinical effects of ergotamine (13, 14), which was isolated in 1918, are far greater in number. In this review it will therefore not be possible to go into details; it will be based on a schematic representation provided by Cerletti (170) and further elaborated by Hofmann (171).

The pharmacodynamic properties of the ergot alkaloids cover a relatively broad spectrum of activity which can be classified as in the accompanying tabulation (see next page).

All natural ergot alkaloids possess these six principal effects to a greater or lesser degree. The vasoconstrictor effect and the contractile effect on the smooth muscle of the uterus are the most important peripheral effects. The latter accounts for the classical indication of the ergot alkaloids in obstetrics where they are used to treat post partum hemorrhage and to accelerate uterine involution in the puerperium. The wide-

Direct peripheral effects (on smooth muscles)	(1) Uterine contraction (2) Vasoconstriction
Indirect peripheral (humoral) effects	(3) Serotonin antagonism (4) Adrenergic blockade
Central nervous effects	(5) Bulbomedullary components: Vomiting, bradycardia, inhibition of the vasomotor center, and of the baroceptive reflexes (6) Mesodiencephalic components: Syndrome of ergotropic excitation with mydriasis, hyperglycemia, and hyperthermia

spread and successful use of ergotamine to mitigate migraine attacks is due to its tonifying effect on the smooth muscle of the blood vessels.

The neurohumoral effects of the ergot alkaloids are manifested in an antagonism to adrenaline and noradrenaline on the one hand and to 5-hydroxytryptamine (serotonin) on the other. The adrenolytic effect accounts for the use of the ergot alkaloids in internal medicine for the treatment of sympathetic overexcitation. The antagonism of the natural alkaloids to serotonin was discovered only in recent years, as it is not present to a marked degree. However, as will be shown subsequently, certain derivatives exhibit a marked and specific antagonism to serotonin.

The effects of the ergot alkaloids on the central nervous system are very diverse as sites of action are situated in the vasomotor center and the cardiac inhibitory center in the medulla oblongata as well as in the sympathetic structures of the diencephalon, particularly the hypothalamus. The inhibition of the vasomotor center and of the baroceptive reflexes and the stimulation of the vagal nuclei are responsible for the vasodilator, hypotensive, and bradycardic effects, especially in the case of the peptide type of alkaloid. Some also have a stimulating effect on the vomiting center.

Most ergot alkaloids stimulate the sympathetic structures of the mesencephalon and diencephalon, particularly the hypothalamus, leading to a syndrome of excitation with mydriasis, hyperglycemia, tachycardia, etc. This syndrome may be closely related to the psychotomimetic effects of certain alkaloid derivatives, e.g., lysergic acid diethylamide.

Considerable quantitative shifts in the pharmacodynamic effects can be produced by chemical changes in the periphery of the lysergic acid

moiety of the ergot alkaloids. The six principal effects remain intact but some are so markedly modified that they are practically no longer manifest, whereas others are so enhanced that they determine the character of action of the substance and at the same time restrict its range of action. Cerletti (170) made a graphic representation of the activity spectra of the various ergot alkaloids, making use of the symbols

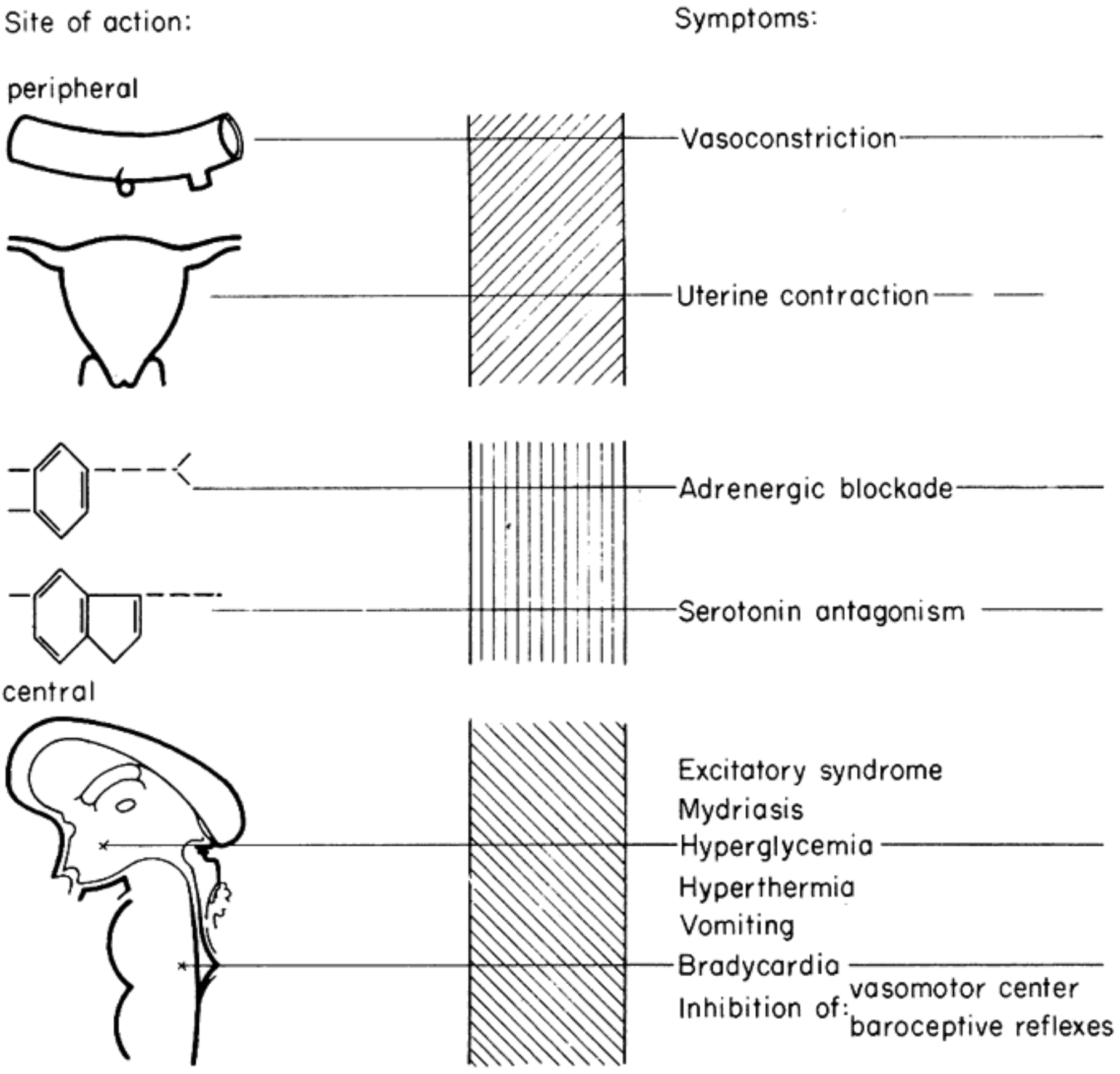


FIG. 6. Activity spectra of ergot alkaloids.

illustrated in Fig. 6. If the relative dosage scale is recorded on the ordinate and the principal effects are entered on the abscissa in a series 1–6 from left to right, more or less comparative diagrams are obtained (Fig. 7) which clearly show the quantitative differences in the various activity ranges for the individual substances. Figure 7a depicts the spectrum of activity of ergotamine. This possesses the typical effect of the ergot alkaloids in a well-balanced manner. Ergotamine exerts a full-strength contractile effect on the uterus and on the smooth muscle of the vessels,

reduces adrenergic activity, and elicits central effects by inhibiting the vasomotor centers. The stimulation of higher nervous structures is less pronounced and occurs only after the administration of toxic doses. Based on this spectrum of activity, ergotamine is an excellent hemostatic in obstetrics while it is also used in internal medicine and neurology as a sympathicolytic for the treatment of sympathicotonic conditions

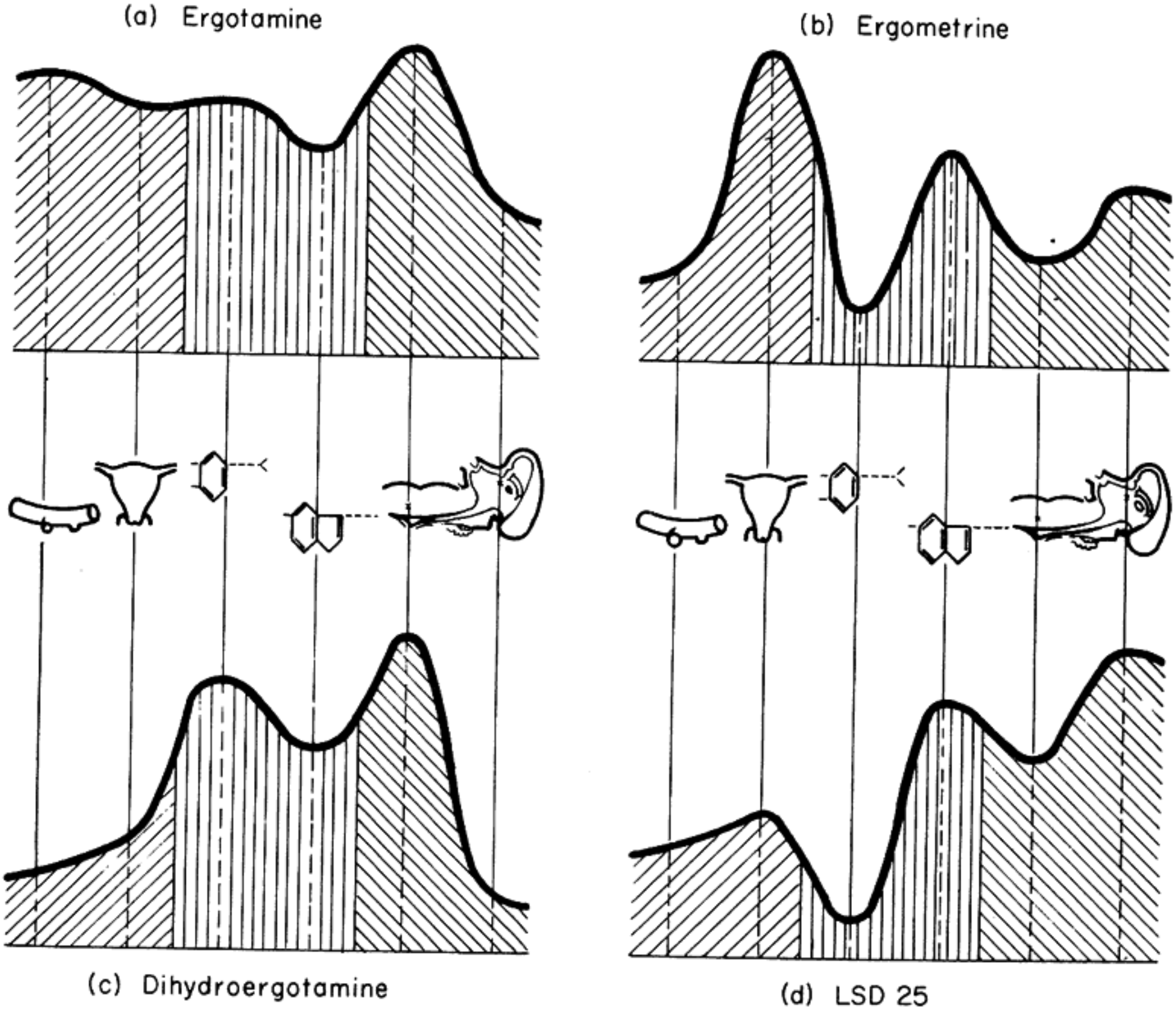


FIG. 7. Comparative diagrams showing the quantitative differences of activity of various ergot products.

and as a vasoconstrictor in migraine and related vascular headaches. The single therapeutic dose in the form of ergotamine tartrate is 0.25–1.0 mg.

The other natural polypeptide alkaloids, e.g., the alkaloids of the ergotoxine group (ergocristine, ergokryptine, and ergocornine) have a spectrum of activity similar to that of ergotamine but their toxic effects are more pronounced. For this reason they have not attained the clinical importance of ergotamine.

The activity spectrum of ergometrine (Fig. 7b) is quite different from that of ergotamine (Fig. 7a). It exerts a marked uterotonic effect, whereas its adrenolytic action is practically insignificant and the central nervous effects are only manifest after high doses. Ergometrine is therefore used mainly in obstetrics. In recent years it has been demonstrated that ergometrine exerts a pronounced antiserotonin effect.

Partial synthesis of a great number of ergometrine analogs, in which the amino-propanol moiety is replaced by other amino alcohols or by simple primary and secondary amines, results in significant shifts in the pharmacodynamic profile; these shifts are especially evident quantitatively, but also qualitatively.

Substitution of the propanolamine moiety in ergometrine by butanolamine yields methylergometrine, which exerts a greater effect than the natural alkaloid on smooth muscle and is therefore used on a large scale under the name Methergin as a uterotonic and hemostatic in obstetrics for the management of the third stage as well as in gynecology.

Lysergic acid diethylamide (LSD 25), trade name Delysid, which is partly synthetic, exhibits a quite unexpected type of effect as can be seen from Fig. 7d where comparison is made with ergometrine. LSD 25 possesses a clear-cut uterotonic effect but exerts practically no adrenolytic effect although it is a potent antagonist of serotonin. This product elicits marked excitation of central nervous structures. In minimal doses it elicits mydriasis, hyperthermia, and hyperglycemia. This syndrome of central excitation is closely related to the psychotomimetic effects of LSD 25, which has become of considerable importance in experimental psychiatry and has given a substantial impetus to modern psychopharmacology. The most striking effects of LSD are colored vision and hallucinations. LSD 25 is still regarded as an experimental tool in psychotherapy and its use as an adjuvant in psychoanalysis meets a growing interest. Active doses usually range from 30 to 150 μg.

Hydrogenation of the double bond in position 9-10 of the lysergic acid moiety results in fundamental changes in the pharmacodynamic action, as a comparison of the activity spectra of ergotamine (Fig. 7a) and dihydroergotamine (Fig. 7c) makes evident. The vasoconstrictor and uterotonic effects of the dihydrogenated derivative have been markedly attenuated, as has the stimulation of central structures, so that these effects are hardly elicited by therapeutic doses. On the other hand the adrenolytic effect and the central inhibition of the vasomotor centers are markedly enhanced. This is manifested clinically in vasodilatation, hypotension, and a certain sedative action.

These properties are still more marked in the case of the hydrogenated derivatives of the ergotoxine alkaloids. A combination of dihydro-

ergocristine, dihydroergokryptine, and dihydroergocornine in equal proportions has been widely used under the name Hydergine for the treatment of peripheral and cerebral vascular disorders and of essential hypertension.

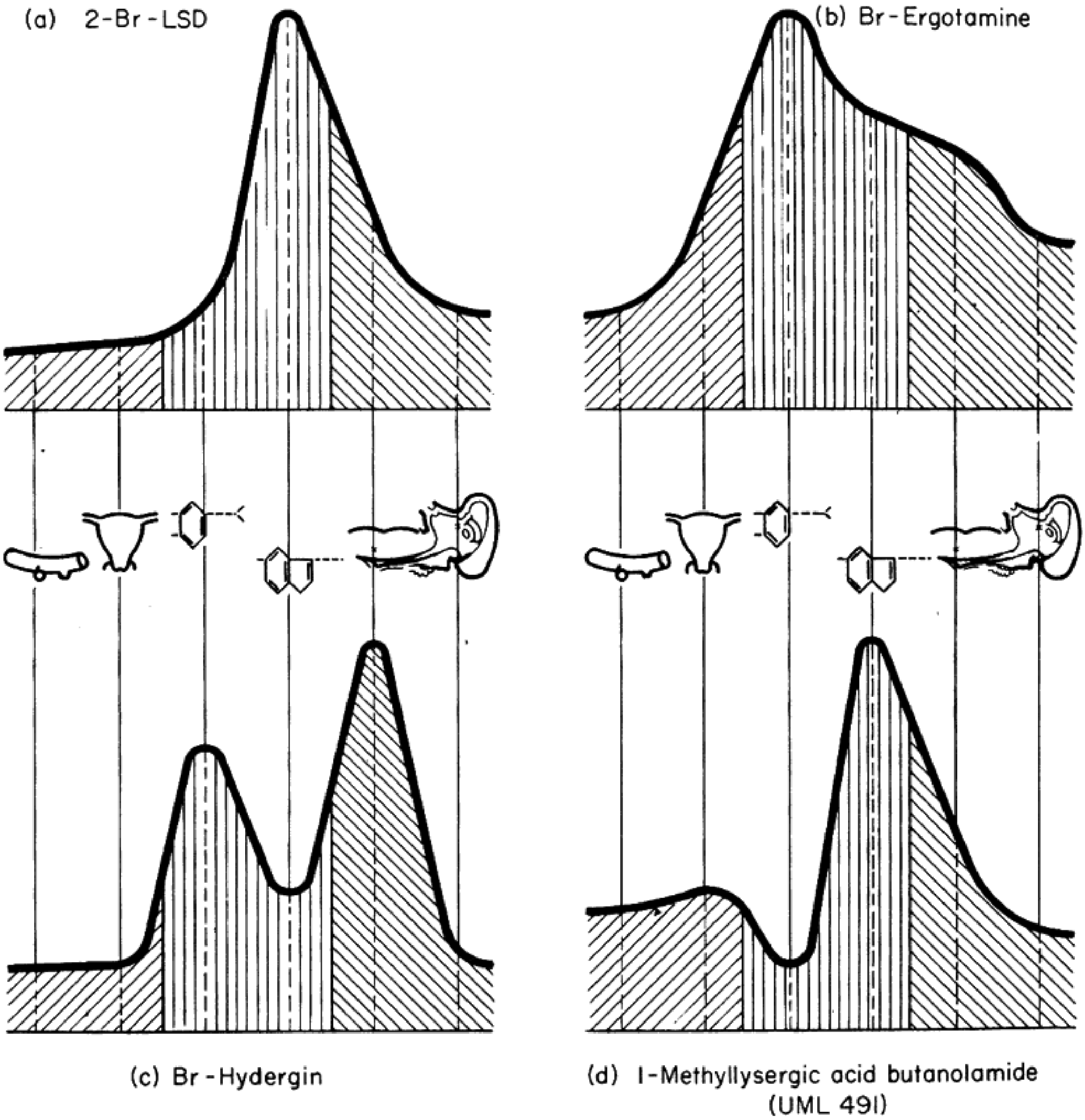


FIG. 8. Comparative diagrams showing the activity of ergot substances made by substitutions in the indole nucleus.

Substitutions at the nitrogen and in position 2 of the indole portion of lysergic acid have a striking influence on pharmacodynamic properties. Many such substitution products have been prepared and pharmacologically investigated. The activity spectra of four such substances (Fig. 8) demonstrate how very diverse the effects of ergot substances can be made by substitutions in the indole nucleus.

Bromination of LSD 25 yields 2-bromolysergic acid diethylamide which exerts practically no psychotomimetic effect (Fig. 8a); the central excitation syndrome is reduced, whereas the antiserotonin effect remains intact, but the effect on smooth muscle is practically absent. This compound is almost as potent as LSD 25 in antagonizing serotonin but does not elicit hallucinogenic effects.

Bromination of ergotamine to yield 2-bromoergotamine (Fig. 8b) enhances the adrenolytic effect and reduces the oxytocic effect to such a degree that it cannot be demonstrated, e.g., on the rat uterus. The vasoconstrictor, hypertensive, and central effects of bromoergotamine are also weakened, resulting in significantly lower toxicity.

The introduction of bromine in the hydrogenated derivatives of the ergotoxine alkaloids (Hydergine) reduces their adrenolytic properties, but the central hypotensive effects remain intact (Fig. 8a). The other central effects, particularly the emetic effect, and toxicity are decreased.

Methylation at the indole nitrogen group specifically enhances the serotonin antagonism exhibited by all ergot alkaloids. For example, 1-methyl-LSD and 1-methyl-2-bromo-LSD exhibit antiserotonin activity several times greater than that of their nonmethylated parent compounds.

The same phenomenon is observed when ergotamine is methylated. It is still more marked when ergometrine or methylergometrine (Methergin) is methylated at the indole nitrogen. 1-Methyl-D-lysergic acid propanolamide is 2.5 times more active than lysergic acid diethylamide (LSD 25) in antagonizing serotonin; 1-methyl-D-lysergic acid butanolamide (Deseril, Sansert) is, depending on the test employed, 4–6 times more powerful than LSD 25 as a serotonin antagonist and is therefore the most potent serotonin antagonist so far discovered (Fig. 8d). This antagonism is very specific; Deseril (Sansert) inhibits serotonin-induced potentiation of barbiturates but has no effect on phenothiazine-induced potentiation. On the other hand the oxytocic effect of Deseril is 15–20 times weaker than that of Methergin. Concurrently, the toxicity of the 1-methyl compound is markedly decreased. 1-Methyl-D-lysergic acid butanolamide does not exert any significant adrenolytic effect; it does not possess the vasoconstrictor and pressor properties so typical of the natural ergot alkaloids. As it also lacks psychotomimetic effects, it can be used in far higher doses than methylergometrine or LSD 25.

As investigations in recent years have shown that serotonin may play an important role as a transmitter substance, Deseril will undoubtedly contribute to the elucidation of the functions of serotonin in the organism. Investigations have already shown that it exerts very beneficial effects in the preventive treatment of migraine and other vascular headaches

and that it offers promising results in the treatment of rheumatic disorders and certain symptoms in the carcinoid syndrome. However, several years will be required before the therapeutic range of 1-methylmethylergometrine can be definitely established.

All ergot alkaloids which have so far been used therapeutically are lysergic acid derivatives. Representatives of the second main group, the clavine alkaloids, have also been found to be pharmacodynamically active, but as yet, none has been found to exert effects that can be utilized in therapy. The uterotonic and sympatholytic actions are less prominent in their pharmacological spectra of activity but, for example, elymoclavine and agroclavine have a pronounced central excitatory action which is attributed to their stimulation of sympathetic centers (172).

The ergot alkaloids, especially those containing the lysergic acid radical, occupy a special position among the indole alkaloids not only by virtue of their origin and their peptide structure, but also by virtue of the diversity of pharmacodynamic properties which is not often found among plant bases. Relatively slight chemical modifications yield derivatives in which the properties present in the natural substances are so selectively enhanced that new types of drugs for more closely defined ranges of indications are obtained. The ergot alkaloids have proved not only to be highly interesting natural substances from the chemical point of view but also a veritable treasure house for new types of drugs.

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