# RECENT INVESTIGATIONS ON ERGOT ALKALOIDS[1]

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As a result of the combined efforts of chemists and biologists, numerous fungi have, in the last few years, been brought into the forefront of scientific interest. From these low forms of life, extremely valuable therapeutic agents have been derived. These are the so-called "antibiotics," which are among the most powerful weapons available in the fight against infectious diseases. That fungi can provide useful remedies is, however, no new discovery. The fungus *Claviceps purpurea*, which produces the ergots seen in the ears of infected rye, has been employed on a purely empirical basis in popular medicine for several hundred years and has claimed the interest of numerous research workers for many decades.

This review will not deal in detail with the interesting history of ergot, an excellent account of which is given in George Barger's monograph *Ergot and Ergotism*, published in 1931, but will start with the most recent stage in the development of ergot research, that which began somewhere around the year 1920 with the isolation and preparation in a pure state of the first homogeneous ergot alkaloid, ergotamine. The idea that the active principles of ergot are alkaloids only began to find general acceptance about twenty-five years ago. Since then, the ergot alkaloids and the derivatives prepared from them synthetically have become valuable and, in some cases, indispensable remedies in the most varied fields of medicine.

The natural alkaloids of ergot which have so far been isolated are shown in table 1. Their classification into three groups—the ergotamine group, the ergotoxine group, and the ergobasine (ergonovine) group—is based upon differences in their chemical structure. As this table shows, the ergot alkaloids occur in pairs. The two alkaloids of a pair are stereoisomers and each readily undergoes rearrangement to the other. This isomerism is due to the isomerism between lysergic and isolysergic acids, the parent compounds from which all the alkaloids of ergot are derived. Whether existing independently or forming part of the alkaloid molecule, lysergic acid readily undergoes rearrangement to the isomeric isolysergic acid and *vice versa*. The natural levorotatory ergot alkaloids are derived from lysergic acid, whereas the isomeric dextrorotatory members of the pairs are derived from isolysergic acid. This isomerism is bound up with a number of interesting problems which will be discussed later. It is important to note that the natural levorotatory alkaloids have a powerful pharmacological action, whereas the corresponding dextrorotatory compounds possess only a fraction of the activity of their levorotatory isomers.

[1] Based on a lecture delivered before the Organic Colloquium at Harvard University on May 9, 1950.

Before considering the structure of the ergot alkaloids, attention should be directed to a few points in connection with the individual alkaloids listed in table 1. The first five pairs of alkaloids are presented in the chronological order of their discovery. The first is the alkaloid pair ergotamine–ergotaminine. Ergotamine (14) was isolated in crystalline form and subjected to chemical analysis as long ago as 1918. Not long afterwards, the observation was made that it could readily be converted into the strongly dextrorotatory but pharmacologically less active ergotaminine.

TABLE 1

*The natural alkaloids of ergot and their dextrorotatory isomers*

| NAME | FORMULA | $[\alpha]_D^{20}$ IN $CHCl_3$ | DISCOVERER |
|---|---|---|---|
| 1. Ergotamine group: | | | |
| Ergotamine | $C_{33}H_{35}O_5N_5$ | −155° | Stoll (1918) |
| Ergotaminine | | +385° | |
| Ergosine | $C_{30}H_{37}O_5N_5$ | −179° | Smith and Timmis (1936) |
| Ergosinine | | +420° | |
| 2. Ergotoxine group: | | | |
| Ergocristine | $C_{35}H_{39}O_5N_5$ | −183° | Stoll and Burckhardt (1937) |
| Ergocristinine | | +366° | |
| Ergokryptine | $C_{32}H_{41}O_5N_5$ | −187° | Stoll and Hofmann (1943) |
| Ergokryptinine | | +408° | |
| Ergocornine | $C_{31}H_{39}O_5N_5$ | −188° | Stoll and Hofmann (1943) |
| Ergocorninine | | +409° | |
| 3. Ergobasine group: | | | |
| Ergobasine | $C_{19}H_{23}O_2N_3$ | −44° | Dudley and Moir<br>Kharasch and Legault |
| Ergobasinine | | +414° | Stoll and Burckhardt<br>Thompson (1935) |

Preliminary experiments on the pharmacological properties of pure ergotamine carried out by Stoll, together with the investigations of Spiro (13) and the somewhat later and more detailed studies of Rothlin, showed that ergotamine in very small doses possesses the entire action of a good ergot preparation, a fact which was confirmed by the first clinical trials. It was found that in obstetrics and gynecology, the only field of application of ergot at that time, ergotamine could be employed with complete satisfaction in all the indications. It was thus clear that the specific active principles of ergot must be alkaloids, a fact which was of decisive importance for the further development of the chemistry and pharmacology of ergot. Nevertheless, until about 1925, and in some places still

later, the view was prevalent that the ergot alkaloids had given disappointing results when used clinically and that the therapeutic significance of ergot could not, therefore, be due to its alkaloid content. The very numerous pharmacological and clinical studies carried out with ergotamine accomplished valuable pioneer work, yet the view which is generally accepted today, that the specific active principles of ergot are alkaloids, only really took root after the discovery of ergobasine (ergometrine, ergonovine) in the middle of the 1930's.

The second pair of alkaloids in table 1, ergosine and its isomer ergosinine, was isolated by Smith and Timmis (12) in 1936, but neither alkaloid has yet been introduced into medicine.

Although there are a number of peculiar features connected with the discovery and chemical investigation of the three pairs of alkaloids comprising the ergotoxine group—ergocristine–ergocristinine, ergokryptine–ergokryptinine, and ergocornine–ergocorninine—it is only possible in this review to give a brief account of the research. In 1906, an apparently homogeneous but amorphous alkaloid preparation was isolated from ergot by Barger and Carr (1) in England and simultaneously by the Swiss pharmacist Kraft (11). The latter investigator designated the product "hydroergotinine," but the name *ergotoxine* is the one which has become universally accepted in the literature. As the result of various chemical and pharmacological investigations and considerations, it was shown that, although ergotoxine had in the meantime been obtained in a crystalline form, it was nevertheless not a homogeneous substance but a mixture of three isomorphous ergot alkaloids. One of these, ergocristine (16), had already been isolated in 1937, while the other two were previously unknown and were named ergokryptine and ergocornine (19).

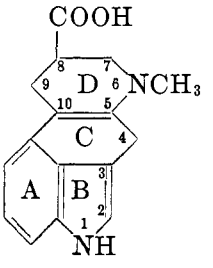
All the alkaloids of ergot, including ergobasine, contain either lysergic acid or isolysergic acid as the principal and characteristic constituent of the molecule. The alkaloids of the ergotamine and ergotoxine groups are polypeptides, the lysergic or isolysergic acid being joined to other amino acids. They thus occupy a special place among the vegetable alkaloids.

The last pair of alkaloids shown in table 1, ergobasine–ergobasinine, has a simpler structure, lysergic acid or isolysergic acid being combined merely with an aminoalcohol. Shortly after Jacobs (6) had established the composition of ergobasine—which is known in England as ergometrine and in America as ergonovine—its partial synthesis, the first to be achieved in the field of ergot chemistry, was accomplished by Stoll and coworkers.

The investigations on the constitution of the ergot alkaloids proceeded along two independent paths, being concerned, on the one hand, with the structure of the lysergic acid portion of the molecule and, on the other, with that of the basic side chain connected with it. While all the details regarding the structure of the lysergic acid portion have now been established with certainty, the constitution of the peptide portion is still being ardently investigated. A closely connected question is that of the linkage between the peptide portion and lysergic acid, regarding which no very definite information is yet available.

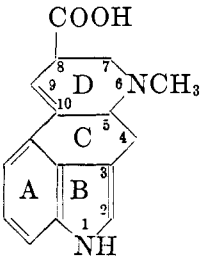
Fundamental knowledge regarding the structures of lysergic and isolysergic acids and of the individual components of the peptide portion is due to the in-

vestigations carried out by Jacobs and Craig at the Rockefeller Institute in New York City. Thus, from cleavage products obtained by the action of energetic reagents, Jacobs (3, 9) was able, as far back as 1938, to deduce formulas for lysergic acid and isolysergic acid which were in agreement with their reactions and with structural considerations.




I

Lysergic acid (Jacobs)




II

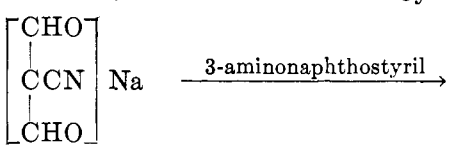
Isolysergic acid

In these formulas the following groups may be clearly recognized: an indole system (rings A and B), a naphthalene system (rings A and C), and an *N*-methylquinoline system (rings C and D). The difference between lysergic acid and isolysergic acid was attributed by Jacobs to a difference in the position of the double bond in ring D. This double bond is readily hydrogenated, giving rise to corresponding dihydro acids. Since, according to the above formulation, the dihydro acids exhibit asymmetric carbon atoms at positions 5, 8, and 10, it was to be anticipated that saturation of the double bond with hydrogen would lead to complicated racemic mixtures. This, in fact, proved to be the case. Bearing in mind these complications, Uhle and Jacobs (28) in 1945 carried out the total synthesis of a mixture of racemic dihydrolysergic acids and thus proved the correctness of the *skeleton* in their formula for lysergic acid. The following scheme illustrates the highly original synthesis employed by them:

$(C_2H_5O)_2CHCH_2Br \xrightarrow{KCN} (C_2H_5O)_2CHCH_2CN \xrightarrow[Na]{HCOOC_2H_5}$

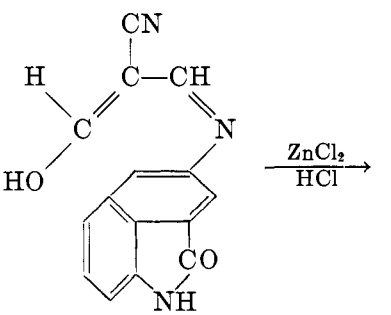
Bromoacetal

Cyanoacetal

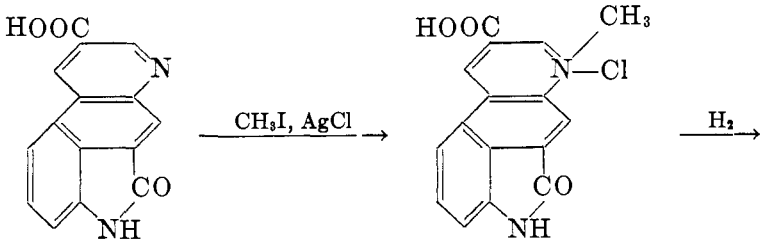



Sodium salt of cyanomalondialdehyde

3-aminonaphthostyril

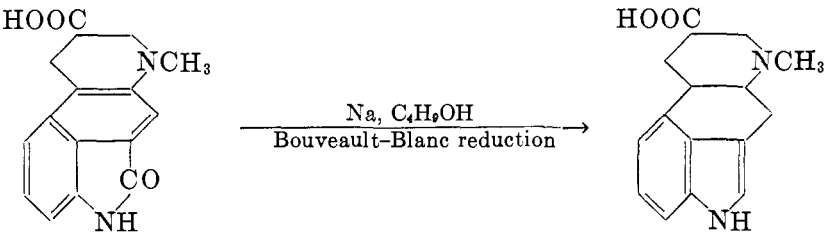



3-(2-Cyano-2-formyl-ethylideneamino)-naphthostyril




3′-Amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam

"Methochloride"




3′-Amino-*N*-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam

Dihydrolysergic acid

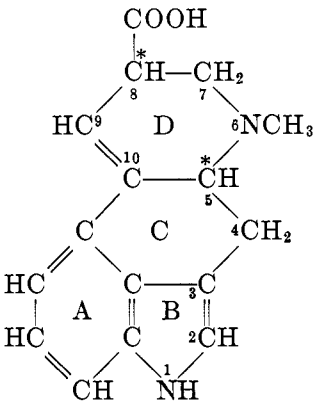
The starting point in this synthesis was bromoacetal, which was converted by means of potassium cyanide into cyanoacetal. This was subsequently treated with ethyl formate and sodium to give the sodium salt of cyanomalondialdehyde, which Uhle and Jacobs then reacted with 3-aminonaphthostyril. In this way they obtained 3-(2-cyano-2-formylethylideneamino)naphthostyril. On treatment with zinc chloride and hydrochloric acid, this compound yielded 3′-amino-5,6-benzoquinoline-3,7-dicarboxylic acid lactam, which was converted into the corresponding methochloride by means of methyl iodide and silver chloride. By catalytic hydrogenation of this methochloride, Uhle and Jacobs were able to obtain 3′-amino-*N*-methyl-1,2,3,4-tetrahydro-5,6-benzoquinoline-3,7-dicarboxylic acid lactam which, on treatment with sodium in boiling butanol, gave a very small yield of racemic dihydrolysergic acid.

The totally synthetic preparation obtained in this way proved to be identical with the product prepared by catalytic hydrogenation of the racemic lysergic acid of natural origin. In both cases the product obtained was a mixture of racemates.

After the ring system of lysergic acid and the nature and position of the substituents (carboxyl, methyl) had been established by Uhle and Jacobs by the total synthesis of dihydrolysergic acid, there remained two further questions of importance regarding the fine structure of lysergic acid still to be settled: (*1*) the position of the readily reducible double bond in ring D and (*2*) the mechanism of the reaction by which lysergic acid isomerizes to isolysergic acid and *vice versa*.

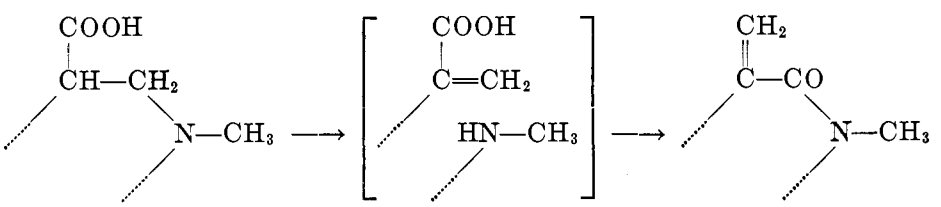
The hypothesis advanced by Jacobs that the double bond migrates from the 5,10-position to the 9,10-position during the isomerization of lysergic acid to isolysergic acid did not provide a satisfactory explanation for the process.

The results of recent investigations by Stoll and coworkers (22) furnished proof that the double bond is in the 9,10-position in both acids. Accordingly, lysergic acid and isolysergic acid have the following constitution:



Lysergic acid; isolysergic acid

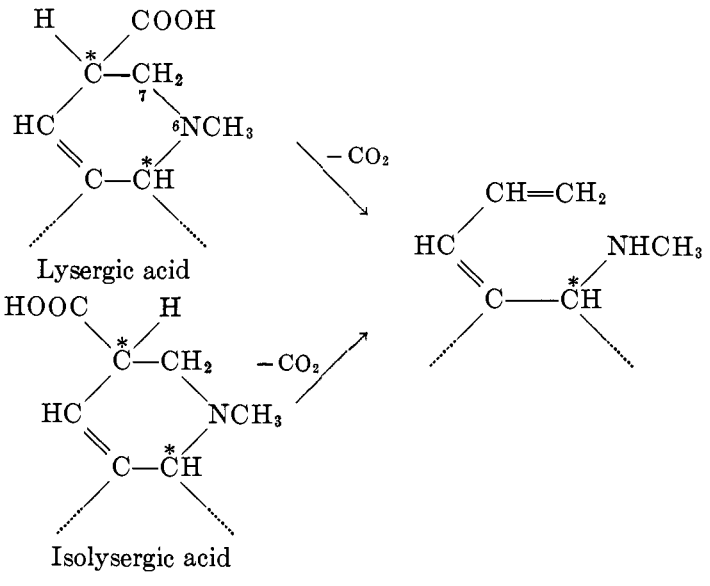
It would take too long to present in detail the experiments which have led to this conclusion. The main basis for the deductions was the finding that both lysergic acid and isolysergic acid react like β-aminocarboxylic acids on heating with acetic anhydride, i.e., with opening of ring D, and that subsequently lactam formation takes place between the secondary amino group and the carboxyl group:



Lysergic acid or isolysergic acid

"Lactam"

In these degradation experiments it was found that both lysergic acid and isolysergic acid gave rise to the same lactam. The position of the readily reducible double bond must therefore be the same in both acids. This conclusion is also in agreement with the results of decarboxylation experiments on lysergic acid and isolysergic acid, both compounds yielding the same product, as shown in the following scheme:




During this decarboxylation (22) not only is the carboxyl group split off, but the linkage between nitrogen atom 6 and carbon atom 7 is also broken. The

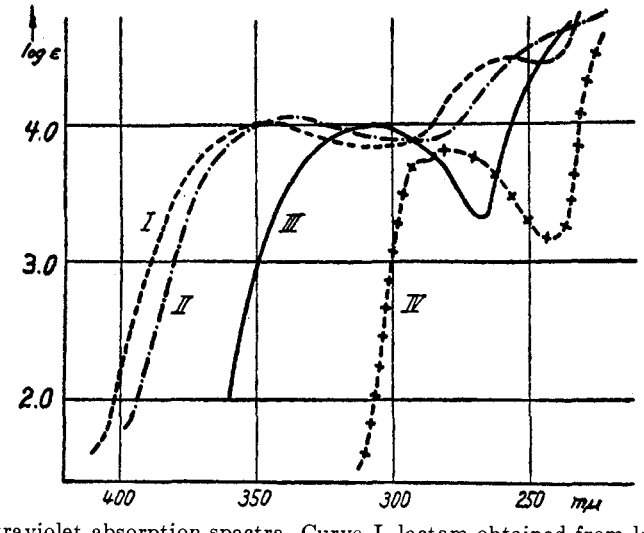
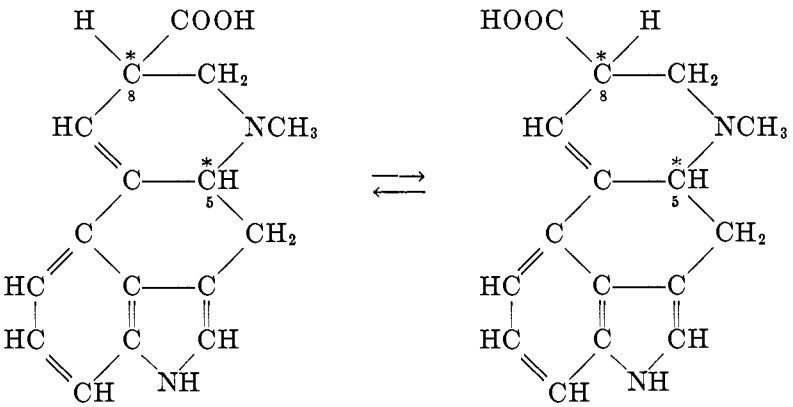



FIG. 1. Ultraviolet absorption spectra. Curve I, lactam obtained from lysergic acid or isolysergic acid; curve II, product obtained by the decarboxylation of lysergic acid or isolysergic acid; curve III, lysergic acid or isolysergic acid; curve IV, dihydrolysergic acid.

ultraviolet absorption spectrum of the decarboxylated product indicates clearly that the newly formed double bond between C-7 and C-8 is conjugated with the double bond already present, which must therefore be between carbon atoms

9 and 10. The chromophore system of this decarboxylation product is identical with that of the lactam just discussed, a fact which was confirmed by the agreement between the absorption spectra of the two compounds (see figure 1).

On the assumption that a double bond is present between carbon atoms 9 and 10, lysergic acid must have two asymmetric centers, one at C-5 and the other at C-8. That both lysergic acid and isolysergic acid possess a second asymmetric center in addition to that at C-8 was proved by the fact that the lactam previously discussed is *optically active*, although the asymmetric center at C-8 is no longer present. These facts also indicate that lysergic acid and isolysergic acid have the same configuration at C-5 and, since the double bond in ring D is situated in the same position, $\Delta^{9,10}$, in both acids, the only difference between them must be in the spatial arrangement of the substituents at C-8. Available evidence indicates that in lysergic acid the carboxyl group is nearer nitrogen atom 6 than it is in isolysergic acid. The following formulas illustrate these relationships:



Lysergic acid Isolysergic acid

As already mentioned, natural D-lysergic acid[2] and natural D-isolysergic acid have an identical configuration at C-5 and differ only in their configuration at C-8. Theoretically, however, either the D- or the L-configuration may be present at each of the two asymmetric carbon atoms 5 and 8. This may be represented schematically as follows:

| C-5 | | C-8 | |
|---|---|---|---|
| $D_5$ | $L_5$ | $D_8$ | $L_8$ |

By combining these four possibilities, the following four optically active isomers are obtained:

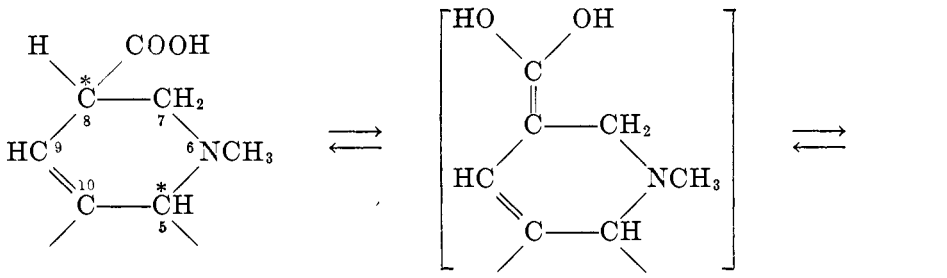
| $D_5D_8$ | $D_5L_8$ | $L_5L_8$ | $L_5D_8$ |
|---|---|---|---|
| I | II | III | IV |

[2] The small capitals D and L used in this publication refer to the *configurations* of the compounds in question. They give no information regarding the direction of the optical rotations, natural lysergic acid having been designated as D-lysergic acid.

I and III are optical antipodes and so are II and IV. On the other hand, I and II are diastereoisomers and the same relationship applies to III and IV. As can be gathered from this schematic representation, I and II and also III and IV agree in the configuration at C-5 and differ only in the configuration at C-8. Thus, either I and III are the two optical antipodes of lysergic acid while II and IV are the optical antipodes of isolysergic acid, or *vice versa*. Both possibilities must be taken into consideration, since the absolute configuration is not known either at C-5 or at C-8.

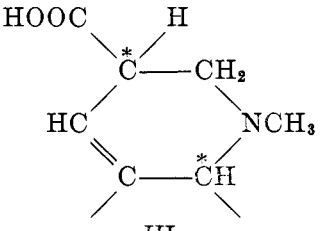
Practical experience with lysergic acid and isolysergic acid is in complete agreement with these theoretical considerations. Both natural D-lysergic acid and its optical antipode L-lysergic acid are known, as well as D-isolysergic acid and L-isolysergic acid. The two corresponding racemates have likewise been prepared.

These steric relationships having been elucidated, a simple explanation is available for the conversion of lysergic acid into isolysergic acid and *vice versa*. Enolization of the carboxyl group at position 8 leads to the intermediate formation of an acid enolate (II) which subsequently rearranges once more to the acid form, with the result that an alteration may take place in the configuration of the substituents at C-8.



I
Lysergic acid

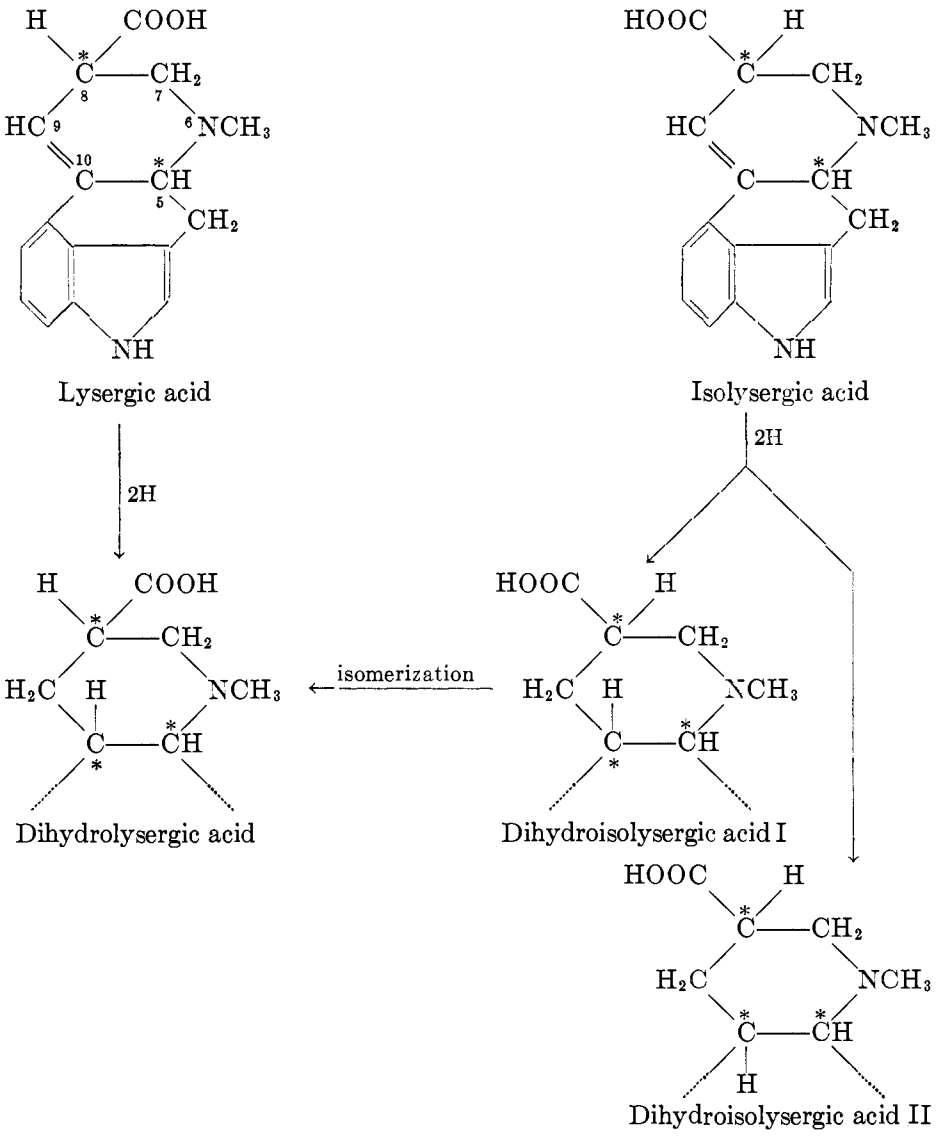
II
"Enolic form"



III
Isolysergic acid

These formulas also enable an explanation to be given for the observations regarding the catalytic hydrogenation of lysergic acid and isolysergic acid. With the saturation of the double bond in ring D, a new asymmetric center is produced at C-10 and both lysergic acid and isolysergic acid may therefore be expected *a priori* to yield two partial racemates. This in fact occurred, since hy-

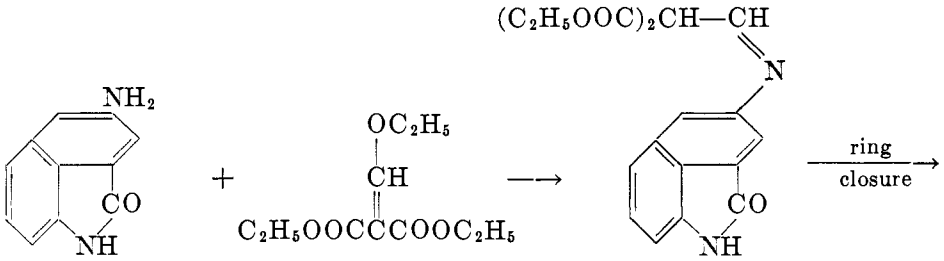
drogenation of isolysergic acid yielded two well-defined dihydroisolysergic acids, which were denoted by the Roman numerals I and II. Hydrogenation of lysergic acid, however, yielded only one dihydrolysergic acid. As may be seen from the following formulas, the isomerism between dihydroisolysergic acid I and dihydroisolysergic acid II is due to a difference in the spatial arrangement of the hydrogen atom at C-10. In the formulas depicted the orientations have been chosen arbitrarily.




As may be gathered from these formulas, the orientation of the hydrogen atom at C-10 in dihydrolysergic acid is the same as that in dihydroisolysergic acid I, the only difference between the two compounds being in the configuration at C-8.

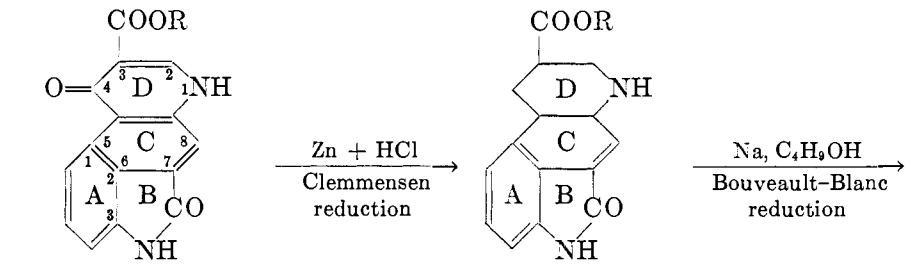
The synthesis of dihydrolysergic acid perforce gives rise to an optically inactive mixture which presumably contains the racemates of the three dihydro acids mentioned above. For purposes of comparison, natural lysergic acid was converted *via* the hydrazide to the racemates of isolysergic acid and lysergic acid, which were then subjected to catalytic hydrogenation to yield racemic dihydrolysergic acid and the racemic dihydroisolysergic acids I and II.

The next stage in the investigations concerned a synthesis of dihydronorlysergic acids (24), in which the nitrogen atom at position 6 carries no methyl group, and subsequent methylation of this nitrogen atom to yield the corresponding dihydrolysergic acids (25).

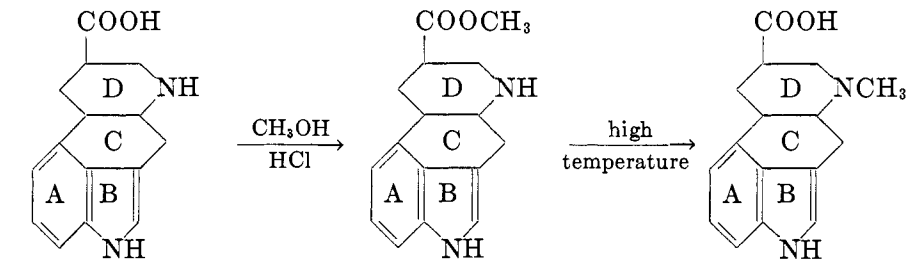



3-Amino-naphthostyril

Diethyl ethoxymethylene-malonate




3′-Amino-5,6-benzoquinolone(4)-3,7-dicarboxylic acid lactam ethyl ester




Dihydronorlysergic acid

Dihydronorlysergic acid methyl ester

Dihydrolysergic acid

The starting material for this synthesis was 3-aminonaphthostyril, which was condensed with diethyl ethoxymethylenemalonate according to the directions

given by Gould and Jacobs (5). Ring closure of the intermediate product so obtained yielded 3′-amino-5,6-benzoquinolone(4)-3,7-dicarboxylic acid lactam ethyl ester, which had also been previously prepared by Jacobs. With the aid of the Clemmensen reduction, the carbonyl group in position 4 of this ester was reduced to a $>CH_2$ group. The resulting compound was subjected to further reduction by the method of Bouveault–Blanc and, in this way, there was obtained a racemic mixture of the three acids: dihydronorlysergic acid, dihydronorisolysergic acid I, and dihydronorisolysergic acid II. The dihydronorlysergic acid was esterified with methanol and anhydrous hydrogen chloride to give dihydronorlysergic acid methyl ester. With the aid of a new type of rearrangement, involving migration of the methyl group, a conversion of this methyl ester into dihydrolysergic acid was effected. This reaction was carried out by heating the dihydronorlysergic acid methyl ester to a high temperature, whereupon the ester methyl group migrated to nitrogen atom 6. This reaction has been studied further and has been extended to other compounds, of which hygrinic acid and guvacoline may be mentioned as examples. In a similar manner, the methyl ester of dihydronorisolysergic acid I may also be converted to dihydrolysergic acid I.

The problems connected with the optical activity of these compounds were studied next. Thus, the synthetic, racemic dihydrolysergic acid was resolved into its optical antipodes, in this way accomplishing the first synthesis of D-dihydrolysergic acid which is derived from natural D-lysergic acid. This acid forms the parent substance of the dihydroalkaloids, dihydroergotamine, dihydroergocristine, dihydroergocornine, and dihydroergokryptine, which have now assumed considerable therapeutic importance.

The resolution of the racemic dihydrolysergic acid was accomplished in the following manner: The racemate was first converted to the methyl ester, which was then transformed into the hydrazide by means of anhydrous hydrazine. The racemic dihydrolysergic acid hydrazide was treated with nitrous acid, yielding racemic dihydrolysergic acid azide, which was allowed to react with L-norephedrine. As expected, the D-dihydrolysergic acid L-norephedride and the L-dihydrolysergic acid L-norephedride so obtained possess different chemical and physical properties and could be separated from one another by chromatography. In this way, the synthesis of D-dihydrolysergic acid L-norephedride as well as that of D-dihydrolysergic acid itself, which was obtained on alkaline hydrolysis, was accomplished for the first time. Data regarding some properties of these compounds are summarized in table 2.

Research on the fine structure of the basic fragment of the ergot alkaloid molecule, the peptide residue, has proved much less fruitful than in the case of the lysergic acid portion. It is true that forty years ago Barger and Ewins (2) had already shown that thermal decomposition of ergotoxine preparations yields the amide of dimethylpyruvic acid, while about fifteen years ago, Jacobs and Craig (7) were able to isolate from the alkaline cleavage of ergotinine and ergotamine not only lysergic acid but also two amino acids. One of these was proline in both cases, whereas the other differed according to the alkaloid. These in-

vestigations marked the first steps in elucidating the constitution of the peptide portion in alkaloids of the ergotamine type and subsequently led to extensive knowledge regarding the various units from which the peptide portions are built up in all the known alkaloids of ergot. The following cleavage products, for

TABLE 2

*Properties of synthetic dihydrolysergic acids and their* L-*norephedrides*

| SUBSTANCE | $[\alpha]_D^{20}$ | MELTING POINT |
|---|---|---|
| | | °C. |
| D-Dihydrolysergic acid L-norephedride | −114° | 240–241 |
| L-Dihydrolysergic acid L-norephedride | +107° | 252–253 |
| D-Dihydrolysergic acid | −120° | Above 300 (decomposition) |
| L-Dihydrolysergic acid | +120° | Above 300 (decomposition) |

TABLE 3

*Ergot alkaloids of the polypeptide type*

Structural units of all these alkaloids: lysergic acid radical, ammonia, D-proline

| | WITH PYRUVIC ACID: ERGOTAMINE GROUP | | WITH DIMETHYLPYRUVIC ACID: ERGOTOXINE GROUP | |
|---|---|---|---|---|
| | With lysergic acid | With isolysergic acid | With lysergic acid | With isolysergic acid |
| With L-phenylalanine | ergotamine ⇄ ergotaminine $C_{33}H_{35}O_5N_5$ | | ergocristine ⇄ ergocristinine $C_{35}H_{39}O_5N_5$ | |
| With L-leucine | ergosine ⇄ ergosinine $C_{30}H_{37}O_6N_5$ | | ergokryptine ⇄ ergokryptinine $C_{32}H_{41}O_5N_5$ | |
| With L-valine | | | ergocornine ⇄ ergocorninine $C_{31}H_{39}O_5N_5$ | |

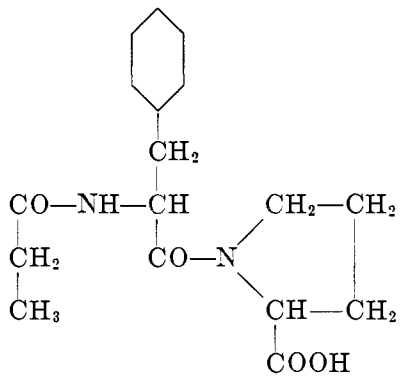
example, have been isolated from ergotamine:

| | | |
|---|---|---|
| Lysergic acid amide | $C_{16}H_{17}ON_3$ | |
| Pyruvic acid | $C_3H_4O_3$ | |
| L-Phenylalanine | $C_9H_{11}O_2N$ | |
| D-Proline | $C_5H_9O_2N$ | |
| $-3H_2O$ | $C_{33}H_{35}O_5N_5$ | Ergotamine |

As far back as 1938, Jacobs and Craig (8) demonstrated that the keto acid is not present as such in the ergotamine molecule but is formed from a precursor, the constitution of which is still unknown. A few years later, Stoll isolated from ergotamine L-phenylalanyl-D-proline lactam, which was the first large fragment of the peptide portion of this alkaloid to be obtained. His most recent investigations (23), which have been carried out mainly with the more stable dihydroalkaloids, have enabled some insight to be obtained into the structure of the peptide portion. In fact, it has proven possible to split off the *peptide residue*

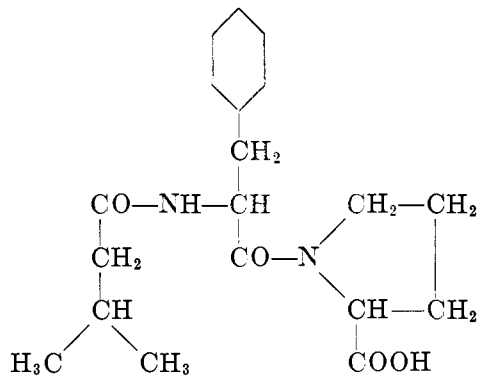
*as a whole* from practically all ergot alkaloids having a peptide structure, and the constitution of this peptide portion has been elucidated and its structure confirmed synthetically. Since, however, the peptide residue was split off by means of anhydrous hydrazine, the precursor of the keto acid was not obtained in its original form but as a reduced derivative. The products which were obtained from the dihydroalkaloids by cleavage with anhydrous hydrazine are shown in the following diagram:

*From dihydroergotamine*



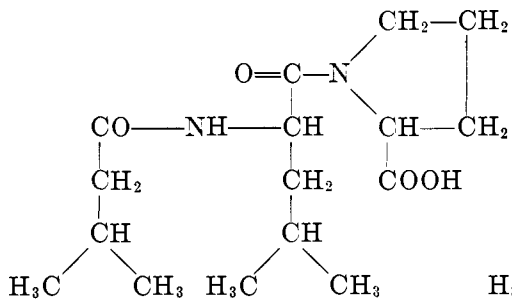
Propionyl-L-phenylalanyl-L-proline

*From dihydroergocristine*



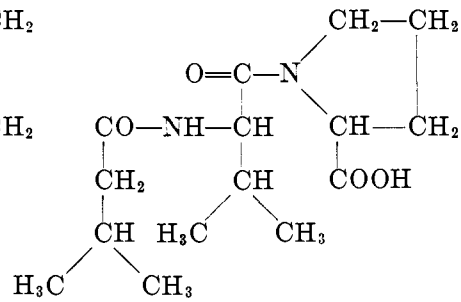
Isovaleryl-L-phenylalanyl-L-proline

*From dihydroergokryptine*



Isovaleryl-L-leucyl-L-proline

*From ergocornine*



Isovaleryl-L-valyl-L-proline

From this diagram it is very easy to see in which structural units the ergot alkaloids differ from one another. The lysergic acid portion of the molecule and the linkage between it and the peptide residue are the same in all the alkaloids. In the members of the ergotamine group the precursor of the keto acid, which is united directly with lysergic acid, possesses the carbon skeleton of propionic acid, whereas in the alkaloids of the ergotoxine group it is derived from isovaleric acid. This constitutes the only point of difference between ergotamine and ergocristine. In ergokryptine and ergosine, however, L-phenylalanine is replaced by L-leucine and in ergocornine by valine.

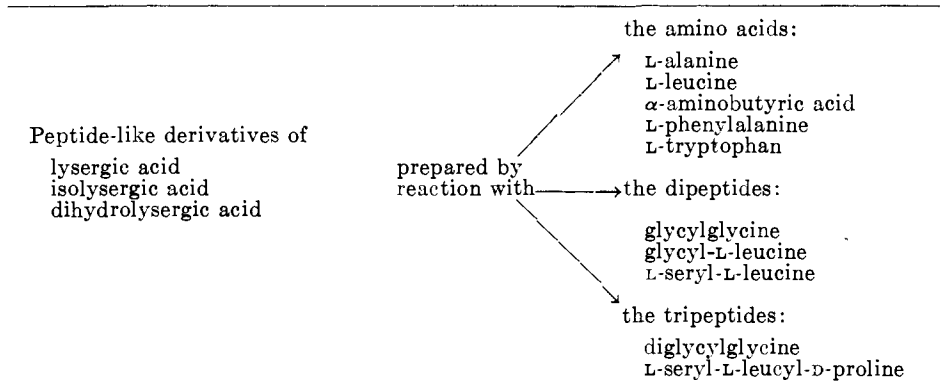
A summary of all the units from which the alkaloids of ergot of the polypeptide type are built up is provided by table 3. This shows, on the one hand, which

units are common to all the alkaloids and, on the other, the respects in which the alkaloids differ from one another.

In the natural alkaloids themselves, the peptide chain cannot be open since (*1*) it possesses no free carboxyl group and (*2*) its composition corresponds to one molecule of water less than would be required by the open chain, probably because the carboxyl group of proline has taken part in the formation of a lactone ring.

As has already been observed, no definite information regarding the nature of the linkage between lysergic acid and the peptide portion is available. Investigations in this direction are being continued and a considerable number of peptides (21) of lysergic acid, isolysergic acid, and the three isomeric dihydrolysergic acids have been synthesized *via* the hydrazides and azides. The amino acids and peptides used in the preparation of these partially synthetic derivatives are shown in the following diagram:

*Peptide-like, partially synthetic derivatives of lysergic acid, isolysergic acid, and dihydrolysergic acid*

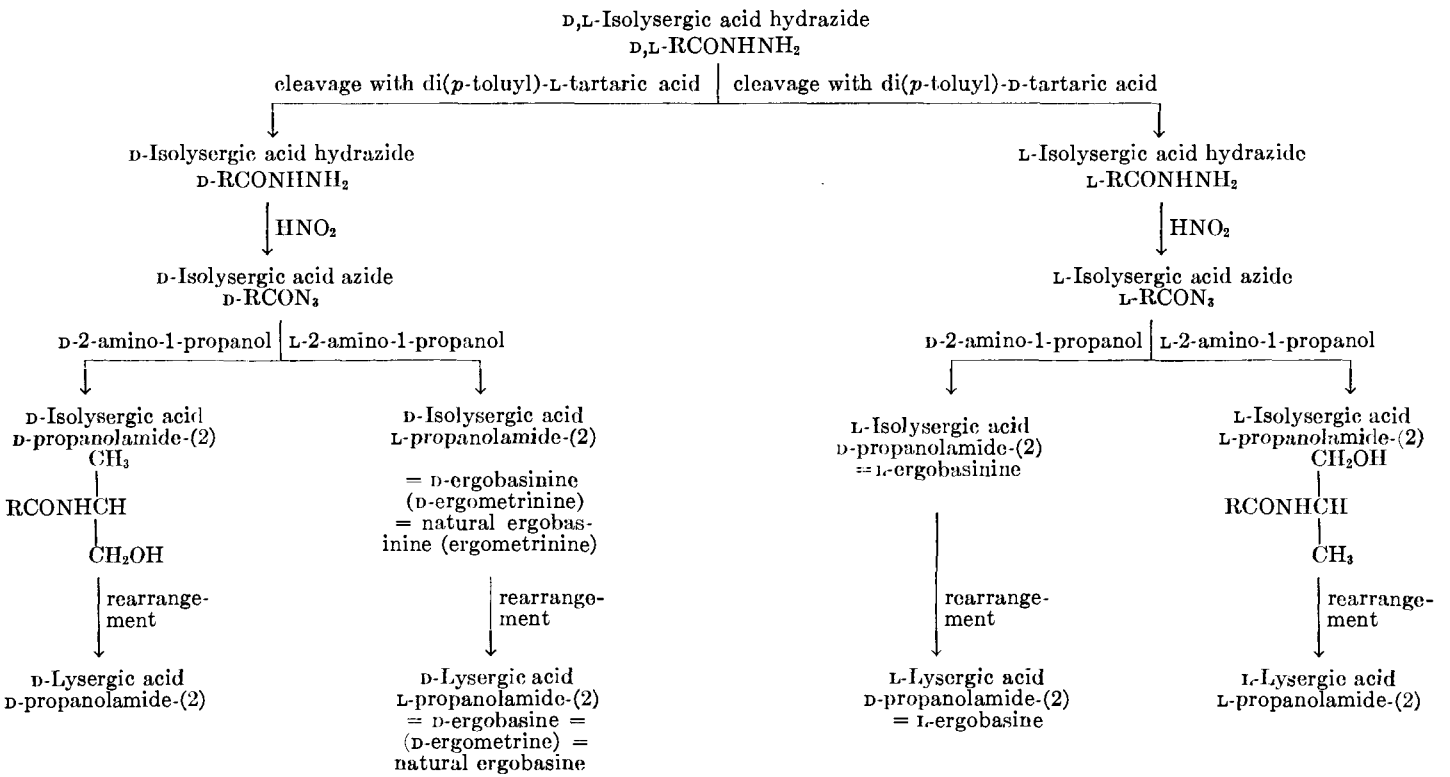



Unfortunately, none of these derivatives exhibited to an appreciable extent the sympathicolytic and adrenolytic action so characteristic of the natural polypeptides of the ergot alkaloids.

It was mentioned at the beginning of this review that, apart from the five pairs of alkaloids of the polypeptide type which have just been discussed, ergot also contains an alkaloid of simpler structure, consisting of lysergic acid combined merely with L-2-amino-1-propanol and known as ergobasine or ergonovine. In contrast to the ergot alkaloids of higher molecular weight, this compound is soluble in water and can consequently readily be separated from the other alkaloids.

Shortly after Jacobs and Craig (6) had elucidated the structure of ergobasine, Stoll and coworkers succeeded in accomplishing its partial synthesis, and this still remains the only synthesis (17, 18) of a natural alkaloid (4, 10, 15, 27) of ergot which has so far been achieved.

Since lysergic acid, isolysergic acid, and the aminoalcohol each exist in two optically active forms, eight isomeric amides are theoretically possible; all of these have been prepared and characterized. The partial synthesis of these


D,L-Isolysergic acid hydrazide
D,L-RCONHNH2
cleavage with di(p-toluyl)-L-tartaric acid
cleavage with di(p-toluyl)-D-tartaric acid
D-Isolysergic acid hydrazide
D-RCONHNH2
HNO2
D-Isolysergic acid azide
D-RCON3
D-2-amino-1-propanol
L-2-amino-1-propanol
D-Isolysergic acid D-propanolamide-(2)
CH3
RCONHCH
CH2OH
rearrangement
D-Lysergic acid D-propanolamide-(2)
D-Isolysergic acid L-propanolamide-(2)
= D-ergobasinine (D-ergometrinine) = natural ergobasinine (ergometrinine)
rearrangement
D-Lysergic acid L-propanolamide-(2) = D-ergobasine = (D-ergometrine) = natural ergobasine
L-Isolysergic acid hydrazide
L-RCONHNH2
HNO2
L-Isolysergic acid azide
L-RCON3
D-2-amino-1-propanol
L-2-amino-1-propanol
L-Isolysergic acid D-propanolamide-(2) = L-ergobasinine
rearrangement
L-Lysergic acid D-propanolamide-(2) = L-ergobasine
L-Isolysergic acid L-propanolamide-(2)
CH2OH
RCONHCH
CH3
rearrangement
L-Lysergic acid L-propanolamide-(2)

compounds was accomplished in the following stages: Cleavage of natural ergot alkaloids of the peptide type with hydrazine hydrate provides a good yield of racemic isolysergic acid hydrazide, which can be separated through the di(*p*-toluyl)tartaric acid salt into the homogeneous optically active components, the hydrazides of D-isolysergic acid and L-isolysergic acid. On treatment with nitrous acid, the hydrazides are converted into the corresponding azides. These react similarly to acyl halides and, on condensation with the two homogeneous, opti-

TABLE 4

*The eight isomers of ergobasine*, $C_{19}H_{23}O_2N_3$

| NAME | DECOMPOSITION POINT | $[\alpha]_D^{20}$ | TYPICAL CRYSTALLINE FORM |
|---|---|---|---|
| | °C. | | |
| D-Lysergic acid L-propanolamide-(2) (D-ergobasine) | 162 | +90° (in water) | Well-formed tetrahedra from ethyl acetate; |
| L-Lysergic acid D-propanolamide-(2) (L-ergobasine) | 162 | −89° (in water) | soft needles from benzene; very sparingly soluble molecular compound with 1 $CHCl_3$ |
| D-Isolysergic acid L-propanolamide-(2) (D-ergobasinine) | 196 | +414° (in $CHCl_3$) | From acetone in large transparent prisms |
| L-Isolysergic acid D-propanolamide-(2) (L-ergobasinine) | 196 | −415° (in $CHCl_3$) | |
| D-Lysergic acid D-propanolamide-(2) | 220 | −11° (in pyridine) | From methanol on dilution with benzene in |
| L-Lysergic acid L-propanolamide-(2) | 220 | +10° (in pyridine) | elongated flat prisms |
| D-Isolysergic acid D-propanolamide-(2) | 195 | +353° (in $CHCl_3$) | From acetone in massive prisms; perchlorate |
| L-Isolysergic acid L-propanolamide-(2) | 195 | −351° (in $CHCl_3$) | from 95 per cent alcohol in short prisms and polyhedra |

cally active 2-amino-1-propanols yield the four amides of isolysergic acid listed in table 4. On isomerization these are transformed into the corresponding derivatives of lysergic acid, one of which is natural ergobasine, D-lysergic acid L-propanolamide-(2). Some of the properties of the eight isomers are summarized in table 4.

Attention should be called particularly to the fact that corresponding antipodes possess precisely opposite optical rotations.

The crystalline forms of these eight isomers are shown in figure 2. From these photographs it may be clearly seen that the crystalline form of one member of any particular pair of isomers is the mirror image of that of the other.

The same process as was used for the synthesis of ergobasine has made possible the preparation of a whole series of homologous and analogous compounds (18). Moreover, these substances have been tested both on animals and in man, and interesting connections between the structures of the partially synthetic compounds and their pharmacodynamic actions have been established. A few of these compounds are summarized in table 5.

The most striking result which can be seen from table 5 is that only the derivatives of natural D-lysergic acid are active, whereas the corresponding compounds obtained from L-lysergic acid are entirely without activity. On the other

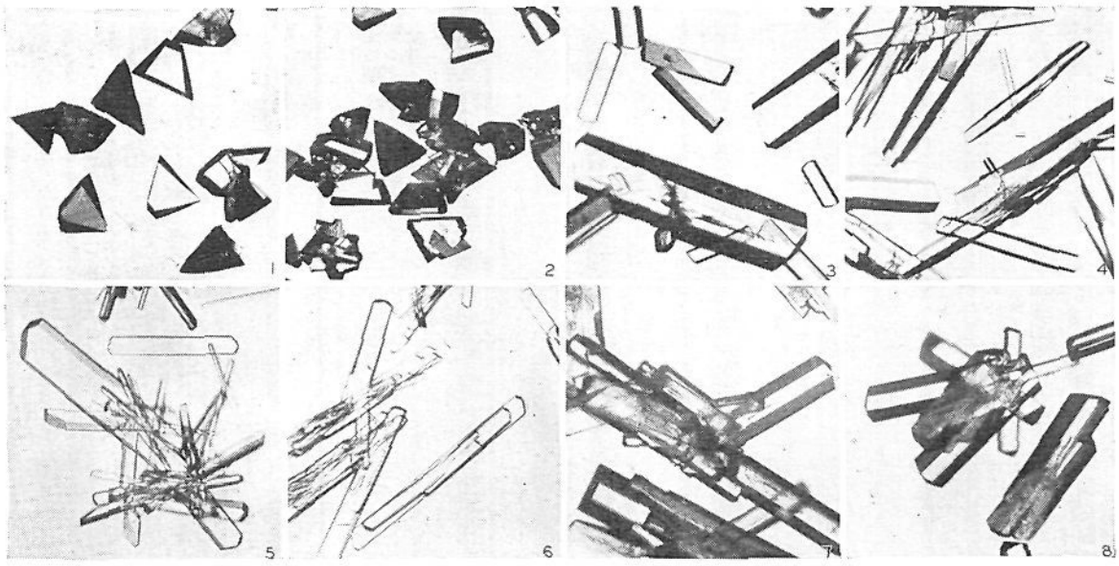


FIG. 2. The eight isomers of ergobasine

| | |
|---|---|
| 1 | D-Lysergic acid L-propanolamide-(2) or D-ergobasine (D-ergonovine) |
| 2 | L-Lysergic acid D-propanolamide-(2) or L-ergobasine (L-ergonovine) |
| 3 | D-Isolysergic acid L-propanolamide-(2) or D-ergobasinine |
| 4 | L-Isolysergic acid D-propanolamide-(2) or L-ergobasinine |
| 5 | D-Lysergic acid D-propanolamide-(2) |
| 6 | L-Lysergic acid L-propanolamide-(2) |
| 7 | D-Isolysergic acid D-propanolamide-(2) |
| 8 | L-Isolysergic acid L-propanolamide-(2) |

hand, it makes no difference whatever to the activity whether the alcohol combined with lysergic acid is L- or D-2-amino-1-propanol. If the activity of ergobasine is taken as 1, then the activity of norergobasine is 0.3 and that of methylergobasine 1.5, whereas the activity of isopropylergobasine is again 0.3.

The last member of the series, lysergic acid diethylamide, likewise exerts a powerful action on the uterus but, at the same time, exhibits a remarkable effect on the human psyche (26). Even when administered orally, the very small dose of 30–50 $\gamma$ is sufficient to cause marked psychic changes combined with hallucinations and colored vision. Similar phenomena are produced by mescaline but only in a dosage 2000 to 3000 times as great. These are only a few examples of the interesting pharmacological actions which have been observed with the partially synthetic derivatives of D-lysergic acid.

The action of the ergot alkaloids is influenced to a very large extent by *the double bond in ring D* of lysergic acid which, as already explained, is assumed to be in the 9,10-position. If this bond is saturated by catalytic hydrogenation, all the natural ergot alkaloids lose entirely their action on the uterus. On the other hand, the dihydroalkaloids of the polypeptide type exhibit a greatly enhanced

TABLE 5

*Uterine action of ergobasine (ergonovine) and other lysergic acid amides*

| NO. | COMPOUNDS | ACTIVITY ON RABBIT UTERUS *in situ* |
|---|---|---|
| | **Isomers of ergobasine** | |
| 1..... | D-lysergic acid L-propanolamide-(2) (D-ergobasine, natural ergobasine) | 1.0 |
| 2..... | L-Lysergic acid D-propanolamide-(2) (L-ergobasine) | 0.0 |
| 3..... | D-Lysergic acid D-propanolamide-(2) | 1.0 |
| | **Homologs of ergobasine** | |
| 4..... | D-Lysergic acid ethanolamide (norergobasine) | 0.3 |
| 5..... | D-Lysergic acid (+)-butanolamide-(2) (methylergobasine) | 1.3 |
| 6..... | D-Lysergic acid (+)-4-methylpentanolamide-(2) (isopropylergobasine) | 0.3 |
| | **Phenylergobasines** | |
| 7..... | D-Lysergic acid D-norephedride | 0.05 (approx.) |
| 8..... | D-Lysergic acid L-norephedride | 1.0 |
| 9..... | L-Lysergic acid L-norephedride | 0.0 |
| 10..... | D-Lysergic acid D-nor-ψ-ephedride | 0.4 |
| | **Various derivatives of ergobasine** | |
| 11..... | D-Lysergic acid 1,3-dihydroxypropanamide-(2) (hydroxyergobasine) | 0.7 |
| 12..... | D-Lysergic acid L-*N*-benzylpropanolamide-(2) (*N*-benzylergobasine) | 0.01 (approx.) |
| 13..... | D-Lysergic acid L-ephedride (*N*-methylphenylergobasine) | 0.3 |
| 14..... | D-Lysergic acid diethylaminoethylamide | 0.05 (approx.) |
| 15..... | D-Lysergic acid diethylamide | 0.7 |

sympathicolytic action, manifest by a pronounced antagonism to adrenaline, while their toxicity is greatly reduced in comparison with the natural products.

The alkaloids of the lysergic acid series yield only one dihydro derivative, whereas each of the alkaloids derived from isolysergic acid yields two derivatives corresponding to the dihydroisolysergic acids I and II. The dihydroalkaloids which have been prepared (20) are summarized in tables 6 and 7, together with some of their characteristic properties.

So far the only alkaloids which have attained therapeutic importance are those derived from D-dihydrolysergic acid. How great the influence of saturating the double bond in ring D can be, may be illustrated by means of the following example. Ergotamine is a powerful oxytocic, characterized by a very strong and protracted constrictory action on the uterus. Dihydroergotamine not only lacks this oxytocic action, but in cases where excessive uterine tonus is liable to hinder the normal progress of parturition, it is even able to bring about relaxation of the uterus or to restore the normal tone.

TABLE 6

*Dihydro derivatives of the natural levorotatory alkaloids of ergot*

| COMPOUND | MELTING POINT (DECOMPOSITION) | $[\alpha]_D^{20}$ (IN PYRIDINE) | TYPICAL CRYSTALLINE FORM |
|---|---|---|---|
| | °C. | | |
| Ergotamine group: | | | |
| Dihydroergotamine, $C_{33}H_{37}O_5N_5$ | 239 | −64° | From 90 per cent aqueous acetone in horizontally truncated polyhedral prisms |
| Dihydroergosine, $C_{30}H_{39}O_5N_5$ | 212 | −52° | From ethyl acetate in pointed prisms and polyhedra |
| Ergotoxine group: | | | |
| Dihydroergocristine, $C_{35}H_{41}O_5N_5$ | 180 | −56° | From acetone in massive hexagonal plates |
| Dihydroergokryptine, $C_{32}H_{43}O_5N_5$ | 235 | −41° | From ethyl alcohol in massive plates and polyhedra |
| Dihydroergocornine, $C_{31}H_{41}O_5N_5$ | 187 | −48° | From ethyl alcohol in massive plates, usually hexagonal |
| Ergobasine group: | | | |
| Dihydroergobasine, $C_{19}H_{26}O_2N_3$ | 230 | −145° | From benzene in needles |

Hydrogenation of the natural alkaloids of the polypeptide type, besides leading to the disappearance of the oxytocic action which, in many indications, is undesirable, also results in a considerable enhancement of the adrenosympathicolytic action, a property already inherent in the natural compounds. As a result there is now a considerable prospect that a number of important diseases, such as hypertension, peripheral vascular disorders, and angina pectoris, which were previously outside the field of indications of the ergot alkaloids, may be treated successfully with the dihydro derivatives.

From these observations it will be apparent that, on the one hand, there are now available for use in the old fields of obstetrics and gynecology preparations such as ergobasine and, more especially, the partially synthetic methylergobasine

which possess an exclusively oxytocic action, while, on the other hand, there are also available the dihydroalkaloids, which are able to influence many of the functions controlled by the autonomic nervous system in such a way that they help to reëstablish normal equilibrium. The vast amount of new knowledge

TABLE 7

*Dihydro derivatives of the dextrorotatory alkaloids of ergot*

| COMPOUND | MELTING POINT (DECOMPOSITION) | $[\alpha]_D^{20}$ (IN PYRIDINE) | TYPICAL CRYSTALLINE FORM |
|---|---|---|---|
| | °C. | | |
| Dihydroergotaminine I, $C_{33}H_{37}O_5N_5$ | 236 | +97° | From alcohol in hexagonal leaflets |
| Dihydroergotaminine II, $C_{33}H_{37}O_5N_5$ | 206 | −7° | From acetone in rectangular plates |
| Dihydroergosinine I, $C_{30}H_{39}O_5N_5$ | 234 | +108° | From alcohol in long needles |
| Dihydroergosinine II, $C_{30}H_{39}O_5N_5$ | 223 | +3° | From acetone in fine needles |
| Dihydroergocristinine I, $C_{35}H_{41}O_5N_5$ | 248 | +109° | From alcohol in polyhedra |
| Dihydroergocristinine II, $C_{35}H_{41}O_5N_5$ | 175 | +13° | From acetone in hexagonal or octagonal plates |
| Dihydroergokryptinine I, $C_{32}H_{43}O_5N_5$ | 268 | +126° | From methylene chloride–methanol in long prisms |
| Dihydroergokryptinine II, $C_{32}H_{43}O_5N_5$ | 226 | +26° | From methylene chloride–petroleum ether in spear-shaped needles |
| Dihydroergocorninine I, $C_{31}H_{41}O_5N_5$ | 264 | +147° | From chloroform–alcohol in long needles |
| Dihydroergocorninine II, $C_{31}H_{41}O_5N_5$ | 180 | +32° | From methylene chloride in massive hexagonal plates |
| Dihydroergobasinine I, $C_{19}H_{25}O_2N_3$ | 211 | +8° | From ethyl acetate–methanol in leaflets |
| Dihydroergobasinine II, $C_{19}H_{25}O_2N_3$ | 212 | +45° | From acetone in massive obliquely truncated prisms |

which has been gained by the most recent chemical and pharmacological investigations on the ergot alkaloids has also enabled their therapeutic applications to be better differentiated and more clearly defined, with the result that a number of new and more refined tools have been placed at the disposal of the physician.

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