THE ERGOT ALKALOIDS

XI. ISOMERIC DIHYDROLYSERGIC ACIDS AND THE STRUCTURE OF LYSERGIC ACID

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Lysergic acid is a substance which we have shown to be formed on hydrolysis of all of the known ergot alkaloids and must therefore occur as such or in the form of an isomer in each of these substances. From our degradation studies[1] it has also been possible to arrive at a probable structure for lysergic acid, as given in the accompanying formula, and which appears to explain all of the known properties and reactions of this substance. Most of these have already been discussed, except in connection with a special type of transformation which these alkaloids undergo and which remains to be explained—namely, the isomerization of ergotamine to ergotaminine and the change of ergotoxine (probably a similar isomerization in spite of the recorded analytical difference of 1 mole of H_2O)[2] into ergotinine and of ergometrine into ergometrinine.

From our present knowledge it appears certain that the center of such isomerization lies in the lysergic acid molecule and not in the other cleavage products of these alkaloids. Thus, Smith and Timmis have recently described[3] the isomer of ergometrine,

[1] Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, **111**, 455 (1935); **113**, 767 (1936); *Science*, **83**, 38 (1936).

[2] From the analyses of ergotoxine and its salts the formula $C_{35}H_{41}O_6N_5$ has been derived, but it is not certain that retention of solvent may not have contributed to the analytical results. The observed greater acidity of ergotoxine as compared with the more basic properties of ergotinine may again be merely an apparent effect. This question is being carefully investigated by us. (*Cf.* Soltys, A., *Ber. chem. Ges.*, **65**, 553 (1932).)

[3] Smith, S., and Timmis, G. M., *Nature*, **136**, 259 (1935).

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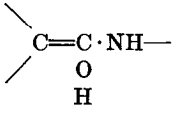
ergometrinine, as strongly dextrorotatory and apparently of the same dextrorotatory group as ergotinine and ergotaminine. This alkaloid obviously results from isomerization of ergometrine in solution. The methyl alcoholic solution of the latter has been shown to mutarotate,[4] becoming more dextrorotatory, which indicates partial transformation into such an isomer. There is no opportunity for such change to occur in the hydroxyisopropylamine portion of the molecule, thus leaving lysergic acid as the only center for such a change. Direct evidence for this we have been able to obtain in our hydrogenation studies.

In accordance with the proposed structural formula for lysergic acid, there are several possibilities which could be considered to explain its participation in the isomerization of the alkaloids. The asymmetric carbon atom, to which the carboxyl group is attached and which is joined in amide linkage in the alkaloids, could lose its asymmetry due to enolization



and since it is definitely known that other centers of asymmetry are present elsewhere in the alkaloid molecule, the result would be a mixture of epimers and not a racemic mixture. The individual epimers could be separated because of the difference in physical properties. This explanation has been excluded, however, since it has now been demonstrated that the double bond of lysergic acid is essential in the isomerization reaction.

It has been noted on a number of occasions that solutions of the alkaloids mutarotate, thus in the case of levorotatory ergotoxine by conversion into dextrorotatory ergotinine, and in that of levorotatory ergotamine because of change to dextrorotatory ergotaminine, and finally, as above stated, in the case of ergometrine (levorotatory in chloroform) because of change to the strongly dextrorotatory ergometrinine. Similarly, we have more recently found that lysergic acid methyl ester mutarotates on heating its methyl alcoholic solution, although the resulting transformation product could not be crystallized. On the other

[4] Kleiderer, E. C., *J. Am. Chem. Soc.*, **57**, 2007 (1935).

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hand, dihydrolysergic methyl ester did not change in rotation on boiling its methyl alcoholic solution. Likewise, dihydroergometrine could not be made to mutarotate. Thus, the double bond of lysergic acid must be essential for this change.

The subject has been investigated further from another angle. All of the alkaloids, whether of the levo or dextro series, which we have studied have been found to give the same lysergic acid on alkaline hydrolysis, which has in each case been confirmed by the preparation of the methyl ester. The question of its homogeneity will be discussed later. On the other hand, if the alkaloids were first hydrogenated (only in the case of dihydroergometrine was a crystalline alkaloid isolated) and then hydrolyzed, a striking result was obtained. The levorotatory alkaloids ergotoxine, ergotamine, and ergometrine gave in each case the same substance on alkaline hydrolysis, *viz. α-dihydrolysergic acid* ($[\alpha]_D = -110°$). On the other hand, the dextrorotatory alkaloids, ergotinine, ergotaminine, and also the dextrorotatory cleavage product, ergine (lysergic acid amide), when first hydrogenated and then hydrolyzed gave an isomeric cleavage product which, for reasons given further on, we have designated as *γ-dihydrolysergic acid* ($[\alpha]_D = +30°$).

Although in the operations with each series of substances the formation of still other isomeric dihydrolysergic acids is not excluded, none could be isolated. But the α derivative has appeared characteristic for the levo series and the γ derivative for the dextro series. The question remained as to whether such results could be conciliated with the structure for lysergic acid, which our degradation studies have led us to adopt. This will be seen to be possible in the later discussion.

A further point has been the study of lysergic acid. Attempts to show that this acid as obtained from the various alkaloids is a mixture have convinced us of its homogeneity. Its properties appeared to remain constant on repeated recrystallization, even after recrystallization as the hydrochloride. The methyl ester, obtained in a yield up to 90 per cent, has also given no evidence of being a mixture. On the other hand, when lysergic acid is catalytically reduced, a definite mixture resulted from which both α- and γ-dihydrolysergic acids were isolated. Although it is remotely possible that lysergic acid may after all be a mixture of

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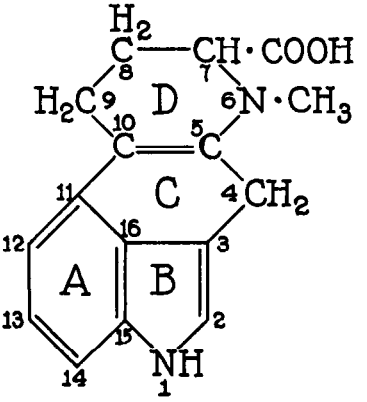
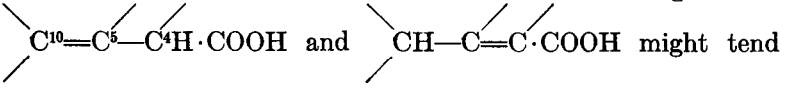
acids belonging to each series of alkaloids, another interpretation appears much more probable; *viz.*, that new centers of asymmetry are produced by its hydrogenation with production of isomeric dihydrolysergic acids. This last interpretation we accept for the purposes of the argument.

Although evidence for the position of the carboxyl group is still lacking, this position appears to be restricted definitely to Ring C or Ring D. At present, it is assumed to be in Ring D, as given in the accompanying formula, and for convenience of discussion



we have assigned also numbers to the individual ring atoms. Position (4) for the carboxyl group, as presented in our previous paper,[5] appears less likely because of the stability of dihydrolysergic acid which can be sublimed at 300° without appreciable decomposition. Again, with the carboxyl group at position (4) and the double bond between (4) and (5) or (5) and (10) (or (10) and (9)), as indicated by the ultraviolet absorption spectra,[6] only one center of asymmetry could exist in either case, at (10) or at (4). Because of a more rigid configuration of the triad carbon atoms (4), (5), and (10), due to their occurrence in a ring (C) and not in an open chain, it might be expected that the shift of the double bond in either direction between the configurations



might tend

[5] Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, **113**, 771 (1936).
[6] Jacobs, W. A., Craig, L. C., and Rothen, A., *Science*, **83**, 166 (1936).

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to proceed with production of asymmetry at the carbon atom left by the double bond. Nevertheless, during the formation of lysergic acid under the conditions of alkaline hydrolysis, partial, if not total, racemization would be expected since each of the possible centers of asymmetry, carbon atoms (4), (5), and (10), can be involved during the shift of the double bond, and there would be no fixed center of asymmetry elsewhere in the molecule.

Position (7) for the carboxyl group appears more plausible. In this case, the configuration at carbon atom (7) could be maintained constant throughout and need play no rôle in the isomerism of the two series of alkaloids. The isomerism could be due (*a*) to epimerization on carbon atom (10) caused by shift of the double bond from between (4) and (5) to between (5) and (10) and back again to (4) and (5), or it could be caused (*b*) by a shift so that the double bond is fixed in one series between positions (4) and (5) and in the other between (5) and (10) (or (9) and (10)). If it is assumed that the first of these possibilities, (*a*), occurs with epimerization on carbon atom (10) with the double bond between (4) and (5), then the following isomers would be expected on hydrogenation. With the fixed configuration on carbon atom (7) of d^7 throughout these would be in the case of one series of alkaloids

$$d^7,\ d^{10},\ d^5, \text{ and } d^7,\ d^{10},\ l^5$$

and in the case of the other series

$$d^7,\ l^{10},\ d^5, \text{ and } d^7,\ l^{10},\ l^5$$

Thus, opportunity would be given for the production of different dihydrolysergic acids from each series of alkaloids.

If such an explanation for the isomerism of the alkaloids is accepted, the double bond in the case of lysergic acid, however, must be assumed to occupy rather the position between carbon atoms (5) and (10), perhaps because of the polar character of the free carboxyl group at (7). This would permit the simultaneous formation from this acid of two isomeric dihydrolysergic acids (α and γ) such as, for example, $d^7,\ d^{10},\ d^5$ and $d^7,\ l^{10},\ l^5$, which, as above noted, are individually characteristic as products of each series of alkaloids. If the double bond were between carbon atoms (4) and (5) in lysergic acid, with fixed configuration at (10), then the conditions would be identical with what has been assumed

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in the case of the alkaloids, and α- and γ-dihydrolysergic acid should not be simultaneously produced from it. Even if the double bond of lysergic acid were assumed to have a degree of lability between positions (5), (10) and (10), (9) with epimerization at (5), then all of the above four isomers would be simultaneously expected, thus giving opportunity for the formation of those encountered individually in the case of the alkaloids. If possibility (*b*), *i.e.* different positions (4), (5) and (5), (10) (or (10), (9)) for the double bond in each series of alkaloids, is assumed, a more involved situation would arise. Although possible, the chance for different substances preponderating as products of hydrogenation in each series of alkaloids would appear less likely than in the alternative scheme (*a*), and it is not clear that the divergent behavior of lysergic acid could be so well explained.

A final point has been the experience with the reduction of the isomeric dihydrolysergic methyl esters to the dihydrolysergols. In our previous work on the reductive cleavage of ergotinine and ergotamine with sodium and butyl alcohol,[7] two isomeric alcohols, α- and β-dihydrolysergol, were obtained. Likewise, on similar treatment of lysergic methyl ester the same substances resulted. It was therefore of interest to attempt to correlate these dihydro alcohols with the two dihydrolysergic acids resulting from the hydrogenation and hydrolysis of the two series of alkaloids.

The above α-dihydrolysergic acid (from ergotoxine) has been found to be identical with the previously described dihydrolysergic acid obtained by reduction of lysergic acid with sodium in amyl alcohol.[8] This was confirmed by the comparison of the methyl esters from both sources. If α-dihydrolysergic methyl ester is reduced with sodium in butyl alcohol, the resulting substance proved to be the alcohol, α-dihydrolysergol. On the other hand, when the methyl ester of γ-dihydrolysergic acid (from the dextrorotatory alkaloids) was similarly reduced, an alcohol was also obtained which proved, however, to be different from the previously described β-dihydrolysergol obtained as a product of the reductive cleavage of ergotinine. This substance has therefore been called *γ-dihydrolysergol* and its precursor, *γ-dihydrolysergic acid*. The

[7] Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, **108**, 595 (1935); *Science*, **81**, 256 (1935).

[8] Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, **106**, 393 (1934).

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previously mentioned β-dihydrolysergol obtained from the alkaloids was not, however, encountered in the reduction of the above α or γ esters. It is possible that this alcohol has its origin in epimerization on carbon atom (7), while the lysergic acid is still conjugated in the alkaloid. However, the exact relationship of these isomeric alcohols will require further investigation.

In the foregoing, the attempt has been made to reconcile the observed facts with the structural formula for lysergic acid, which has been deduced. This has been found to be possible, but at the same time such a formula is advanced with proper reservation because of the general nature of the evidence which is available. Attempts to synthesize a substance of the assumed structure for lysergic acid are now in progress.

EXPERIMENTAL

Catalytic Reduction of Ergotinine—0.2 gm. of ergotinine, $[\alpha]_D^{25} = +394°$ ($c = 0.5$ in chloroform), was treated with 0.05 gm. of Adams and Shriner's catalyst and 2 cc. of glacial acetic acid. After shaking for 1 hour in hydrogen under about $2\frac{1}{3}$ atmospheres pressure, the rate of absorption of hydrogen had become much slower. A brilliant fluorescent purple-blue color developed immediately when the reduction started. The reduction was interrupted at the end of 3 hours when 1.8 moles of hydrogen had been absorbed.

The catalyst was filtered off and the black-colored filtrate was evaporated to dryness on the steam bath under reduced pressure. It was found to contain colloidal platinum which was removed by treating the ethyl alcoholic solution with bone-black. The still dark colored filtrate was evaporated to dryness again. All attempts to obtain the hydrogenated alkaloid in a crystalline form failed.

Hydrolysis of Hydrogenated Ergotinine. γ-Dihydrolysergic Acid—The crude amorphous product from above was dissolved in a solution containing 2 cc. of methyl alcohol, 2 cc. of water, and 0.56 gm. of potassium hydroxide. The mixture was refluxed in an atmosphere of hydrogen for 2 hours, and then diluted with an equal volume of water. After filtering from a slight amount of tarry material and removal of methyl alcohol by evaporation under reduced pressure, the solution was made slightly acid to Congo

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red with sulfuric acid. The solution was then made alkaline with sodium carbonate and evaporated to dryness under reduced pressure. The solid residue was extracted with hot ethyl alcohol and the extract was evaporated to dryness. The residue was dissolved in 5 cc. of water and the solution was made slightly acid to Congo red with sulfuric acid. Ammonia was then added and the solution was concentrated over a free flame until crystalline material began to separate. The volume of solution at this point was approximately 2 cc. After cooling in ice for several hours, the crystals were collected with a little water. The yield was 35 mg. The material was further purified by recrystallization with bone-black from water. It is dextrorotatory. $[\alpha]_D^{25} = +32°$ (c = 0.22 in pyridine). It does not show a sharp melting point, but darkens rapidly at 300° and decomposes at 330° when the temperature is raised rather rapidly.

$C_{16}H_{18}O_2N_2$. Calculated, C 71.06, H 6.72; found, C 71.40, H 6.79

γ-Dihydrolysergic Acid Methyl Ester—70 mg. of γ-dihydrolysergic acid were treated with 5 cc. of absolute methyl alcohol and saturated with dry hydrogen chloride. After standing at room temperature for 1 hour, the solvent was evaporated under reduced pressure. The residue was treated with 10 cc. of ether and cooled in ice. Excess cold ammonia was added with good chilling and the mixture was shaken until all was in solution. The ether layer was dried over anhydrous potassium carbonate and then evaporated to dryness. The viscous residue could not be made to crystallize from any solvent. This residue was finally used for reduction to the alcohol as follows.

Reduction of γ-Dihydrolysergic Acid Methyl Ester. γ-Dihydrolysergol—65 mg. of the above amorphous ester were dissolved in 4 cc. of anhydrous butyl alcohol. The solution was boiled and 0.2 gm. of sodium was added. The mixture was at once vigorously shaken to emulsify the sodium and was maintained at the boiling temperature until all had dissolved. The solution was diluted with water and evaporated under reduced pressure until all butyl alcohol had been removed. The solid material which separated could not be extracted with ether. The mixture was acidified with a slight excess of sulfuric acid, and then neutralized with a slight

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excess of sodium carbonate. After concentration of the solution to dryness under reduced pressure, the residue was extracted with hot ethyl alcohol. The alcoholic extract on evaporation left a residue. On digestion with 2 cc. of hot water, apparently crystalline material remained, which was collected with water. It weighed 30 mg. On recrystallization from methyl alcohol imperfectly formed tables or rhombs resulted. The material darkened at 234° and melted with decomposition at 255° depending somewhat on the rate of heating. It was dextrorotatory, $[\alpha]_D^{25} = +33°$ ($c = 0.24$ in pyridine).

$C_{16}H_{20}ON_2$. Calculated, C 74.96, H 7.87; found, C 74.95, H 7.59

Catalytic Reduction of Ergotoxine—0.1 gm. of ergotoxine ethanesulfonate (from Burroughs Wellcome and Company) in 2 cc. of glacial acetic acid was shaken with 50 mg. of Adams and Shriner's catalyst and hydrogen under an excess pressure of $1\frac{1}{3}$ atmospheres. After 2.5 hours, approximately 3 moles of hydrogen had been absorbed and the reduction had become rather slow. The catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was treated with ethyl alcohol and again evaporated to dryness. The residue was treated with 5 cc. of water and a slight excess of ammonia. The amorphous alkaloidal precipitate which remained was filtered off. It weighed 70 mg. and could not be made to crystallize from any solvent.

Hydrolysis of Hydrogenated Ergotoxine. α-Dihydrolysergic Acid—The above amorphous residue was treated with a solution containing 1 cc. of water, 1 cc. of methyl alcohol, and 0.28 gm. of potassium hydroxide. After the material was refluxed for 1.5 hours in an atmosphere of hydrogen, the methyl alcohol was partially removed by evaporation under reduced pressure. The remaining solution was diluted with water and made barely acid to Congo red with sulfuric acid. This was followed by addition of ammonia in slight excess and upon concentration over a free flame to about 2 cc. when crystallization occurred. After cooling, 20 mg. of leaflets were collected with water. After recrystallization with bone-black from water, it darkened rapidly at 300° and finally decomposed at 330°, depending somewhat on the rate of

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heating. It was levorotatory, $[\alpha]_D^{25} = -89°$ ($c = 0.09$ in pyridine).

$C_{16}H_{18}O_2N_2$. Calculated, C 71.06, H 6.72; found, C 71.17, H 6.72

This acid, which we shall call α-dihydrolysergic acid, was indistinguishable in properties from the dihydrolysergic acid previously described as a reduction product of lysergic acid.[8] This was confirmed by the preparation of the following methyl ester which was prepared as in the case of the γ ester. After recrystallization from benzene, it melted at 182° after preliminary softening at 180°. A mixed melting point with the dihydrolysergic methyl ester previously reported showed no depression. It is levorotatory. $[\alpha]_D^{25} = -52°$ ($c = 0.23$ in methyl alcohol).

Reduction of α-Dihydrolysergic Methyl Ester. α-Dihydrolysergol—50 mg. of the ester were reduced in 4 cc. of butyl alcohol with 0.2 gm. of sodium, as in the case of the γ isomer. The reaction mixture was worked up in identical manner. 20 mg. of crystalline material, which was sparingly soluble in water, were finally obtained. After recrystallization from methyl alcohol the material melted at 279–280°, depending somewhat on the rate of heating. A mixed melting point with α-dihydrolysergol[7] showed no depression. Its identity was confirmed by its general properties and rotation, $[\alpha]_D^{25} = -86°$ ($c = 0.27$ in pyridine).

$C_{16}H_{20}ON_2$. Calculated, C 74.96, H 7.87; found, C 74.90, H 8.16

Catalytic Reduction of Ergotamine and Hydrolysis—Ergotamine tartrate (Sandoz Chemical Works) was treated with sodium carbonate solution and the base was extracted with hot chloroform. The chloroform residue was recrystallized from dilute acetone. $[\alpha]_D^{25} = -140°$ ($c = 0.43$ in chloroform). This material was used for the reduction. 0.1 gm. was dissolved in 2 cc. of glacial acetic acid and shaken with hydrogen and 25 mg. of Adams and Shriner's catalyst. When reduction began, a characteristic brilliant bluish purple fluorescence developed. After 2 hours, 1.6 moles of hydrogen had been absorbed and the absorption had become slow. The reduction products were hydrolyzed exactly as described in the case of ergotoxine. Upon recrystallization of the resulting dihydrolysergic acid, 18 mg. of the characteristic leaflets

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of the α form were obtained. $[\alpha]_D^{25} = -115°$ ($c = 0.235$ in pyridine).

$C_{16}H_{18}O_2N_2$. Calculated, C 71.06, H 6.72; found, C 71.10, H 6.77

Catalytic Reduction of Ergotaminine and Hydrolysis—0.23 gm. of crystalline ergotamine was dissolved in 10 cc. of methyl alcohol and refluxed in an atmosphere of hydrogen for 2 hours. The solution was cooled and the crystalline material collected. It weighed 0.07 gm. $[\alpha]_D^{25} = +382°$ ($c = 0.23$ in chloroform). When the mother liquor was further refluxed, another crop of ergotaminine could be obtained.

0.1 gm. of ergotaminine was reduced in 2 cc. of glacial acetic acid with 25 mg. of catalyst. In 1.5 hours, 1.67 moles of hydrogen had been absorbed. The resulting products were treated exactly as described under the reduction and hydrolysis of ergotinine. Upon recrystallization of the dihydrolysergic acid, 12 mg. of the characteristic polygonal crystals of γ-dihydrolysergic acid were obtained. $[\alpha]_D^{25} = +32°$ ($c = 0.22$ in pyridine).

$C_{16}H_{18}O_2N_2$. Calculated, C 71.06, H 6.72; found, C 71.17, H 6.63

Catalytic Reduction of Ergine and Hydrolysis—0.1 gm. of ergine, $[\alpha]_D^{25} = +332°$ ($c = 0.28$ in methyl alcohol), which was prepared from ergotinine according to the direction of Smith and Timmis,[9] was hydrogenated in 2 cc. of glacial acetic acid with 25 mg. of catalyst. 1.6 moles of hydrogen were absorbed in 40 minutes, and the reduction became slow. The reduction products were hydrolyzed as described under ergotinine. 20 mg. of dihydrolysergic acid were obtained, which showed the characteristic polygonal crystalline form of γ-dihydrolysergic acid. $[\alpha]_D^{25} = +29°$ ($c = 0.28$ in pyridine).

$C_{16}H_{18}O_2N_2$. Calculated, C 71.06, H 6.72; found, C 70.96, H 6.99

Catalytic Hydrogenation of Lysergic Acid—The reduction of this substance has been reported.[1] It is described again below, since this procedure has yielded two isomeric dihydrolysergic acids.

0.4 gm. of lysergic acid was hydrogenated in 3 cc. of glacial acetic acid with 25 mg. of catalyst. The hydrogenation was in-

[9] Smith, S., and Timmis, G. M., *J. Chem. Soc.*, 763 (1932).

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terrupted when 1.5 moles of hydrogen had been absorbed. The residue after removal of solvent was dissolved in 35 cc. of boiling water, bone-black was added, and then the mixture was quickly filtered while hot before crystallization began. The filtrate on cooling yielded 0.14 gm. of broad leaves which the rotation showed to be α-dihydrolysergic acid. $[\alpha]_D^{25} = -106°$ ($c = 0.255$ in pyridine). This was confirmed by its conversion into the ester, as previously reported.

The mother liquor was concentrated until crystals appeared. After cooling, the somewhat colored crystalline material was collected and weighed 90 mg. It was recrystallized with bone-black, and the characteristic crystalline form of γ-dihydrolysergic acid was obtained. The rotation was slightly low for this compound. $[\alpha]_D^{25} = +16°$ ($c = 0.235$ in pyridine). For further identification it was converted into the methyl ester which was in turn reduced to the corresponding γ-dihydrolysergol. The latter melted at 253°. $[\alpha]_D^{25} = +33°$ ($c = 0.27$ in pyridine).

Mutarotation of Lysergic Acid Methyl Ester—Lysergic acid, $[\alpha]_D^{25} = +30°$ ($c = 0.40$ in pyridine), was esterified, as previously reported, with diazomethane. It was found that upon recrystallization of this ester, the rotation varied somewhat. A solution of a sample which showed a rotation, $[\alpha]_D^{25} = +85°$ ($c = 0.305$ in methyl alcohol), was heated in a sealed tube at the temperature of boiling methyl alcohol for 0.5 hour. The solution became slightly colored and the rotation increased to $[\alpha]_D^{25} = +118°$ ($c = 0.305$ in methyl alcohol). The solution on heating an additional 2 hours became still darker in color, but the rotation remained constant at $[\alpha]_D^{25} = +118°$. An attempt to isolate the products after the mutarotation of the ester yielded crystalline material which, however, showed a rotation approximately that of the original ester, *viz.* $[\alpha]_D = +80°$ to $+90°$. A large fraction could not be made to crystallize.

A solution of α-dihydrolysergic methyl ester showed no change in rotation after heating in boiling methyl alcohol for 1 hour.

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