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III. LYSERGIC ACID DIETHYLAMIDE AND RELATED COMPOUNDS

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RELATIONSHIP BETWEEN SPATIAL ARRANGEMENT AND MENTAL EFFECTS

Since the discovery in 1943 – at first in a personal study and then in a subsequent systematic investigation – of the extraordinarily pronounced and specific effects of *d*-lysergic acid diethylamide on the human mind (5), the problem of the relationship between the chemical structure of this compound and its pharmacological and mental effects has continuously occupied our interest.

After the elucidation of the structure of lysergic acid, the component common to all natural ergot alkaloids (3), the stereochemistry of this compound has been determined in recent years (6). As a result, we now know not only the structural linkage but also the spatial arrangement of the individual atoms in the molecule of lysergic acid and in the molecule of lysergic acid diethylamide (LSD).

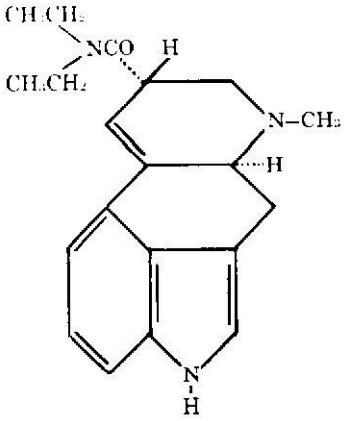
The structure of LSD and the spatial arrangement of its substituents are shown in Formula I (Fig. 1).

In order to obtain some idea of the relationship between the chemical structure and the pharmacological or mental effects, we have modified the molecule of LSD in the following three ways: *(a)* variations in the amide grouping, *(b)* substitutions in the ring system and *(c)* variations in the spatial arrangement of the atoms.

Variations in the amide grouping: Systematic variation of the substituents in the amide group has resulted in the synthesis of a great number of substances. These are listed in Table I. Pharmacological and clinical investigations of this group of compounds, which includes some derivatives with interesting effects, have not yet been concluded.

Substitutions in the ring system: The hydrogen in position 1 or 2 of

the lysergic acid system has been replaced by an acetyl, alkyl or halogen group, (Fig. 2.)



I **Fig. 1**

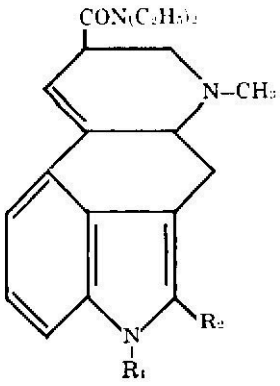


Fig. 2

Some of these compounds have already been studied in clinical trials, others are still the subject of extensive investigations in human beings and animals.

Variations in the spatial arrangement of the atoms: It is well known that almost all organic compounds from which plant and animal organisms are built up, such as amino acids, carbohydrates and steroids, are optically active, i.e., they possess one or several asymmetric carbon atoms to which four different substituents are attached.

Lysergic acid, a metabolic product of the fungus *Claviceps purpurea*, has an asymmetric structure. The molecule has two asymmetric centers, at C 5 and at C 8. Theoretically, four stereoisomers are possible. These have been synthesized by us and are shown in Formulae I – IV.

The dotted line from the asymmetric carbon atoms signifies that the substituent involved is situated *behind* the plane of the paper,[1] the continuous line indicates that the substituent is situated *in front* of the plane of the paper. Formula I is that of *d*-lysergic acid diethylamide. (LSD should, strictly speaking, be designated *d*-LSD). If the spatial arrangement of the substituent groups at both asymmetric carbon

[1] The ring structure of lysergic acid is flat and is assumed to lie in the plane of the paper, so that the spatial arrangement of the substituent groups as depicted in the formulae approximates reality.

atoms is changed, *l*-lysergic acid diethylamide (*l*-LSD) is obtained. This (Formula II) is a mirror image of LSD. If the spatial arrangement of the substituent groups in *d*-LSD is modified only at C 8, a compound is obtained which is designated as *d*-iso-LSD (Formula III). If only the substituent groups at C 5 in *d*-LSD are changed, a compound is obtained which is designated as *l*-iso-LSD (Formula IV). This is a mirror image of *d*-iso-LSD (Formula III).

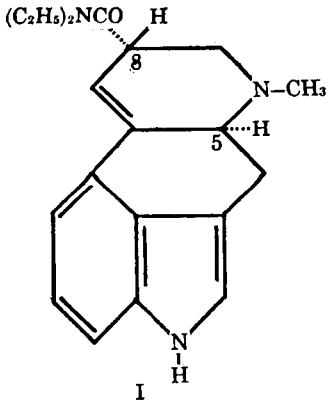
TABLE I

Variations in the acid amide group of the LSD molecule.

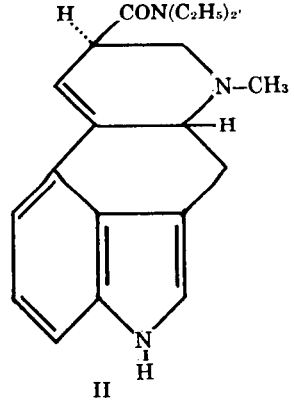
Amides of *d*-lysergic acid ($C_{15}H_{15}N_2.COR$) prepared for pharmacological investigation

R	d-lysergic acid	R	d-lysergic acid
$-N(H)(H)$	amide	$-N(CH_3)(CH(CH_3)(CH_3))$	methyl-isopropyl-amide
$-N(H)(CH_3)$	methylamide	$-N(CH_3)(CH(CH_3)(CH_2-C_6H_5))$	(+)-methyl-(β-phenyl)-isopropyl-amide
$-N(H)(CH_2CH_3)$	ethylamide	$-N(CH_2CH_3)(CH_2CH_3)$	*diethylamide (LSD 25)*
$-N(H)((CH_2)_2CH_3)$	propylamide	$-N(CH_2CH_3)((CH_2)_2CH_3)$	ethyl-propyl-amide
$-N(H)((CH_2)_3CH_3)$	butylamide	$-N((CH_2)_2CH_3)((CH_2)_2CH_3)$	di-n-propylamide
$-N(H)((CH_2)_4CH_3)$	amylamide	$-N(CH(CH_3)(CH_3))(CH(CH_3)(CH_3))$	di-iso-propylamide
$-N(H)((CH_2)_6CH_3)$	hexylamide	$-N((CH_2)_3CH_3)((CH_2)_3CH_3)$	di-n-butylamide
$-N(H)((CH_2)_6CH_3)$	heptylamide	$-N(CH_2-CH_2)(CH_2-CH_2)$	pyrrolidide
$-N(CH_3)(CH_3)$	dimethylamide	$-N(CH_2-CH=CH-CH_2)$	pyrrolinide
$-N(CH_3)(CH_2CH_3)$	methyl-ethylamide	$-N(CH_2-CH_2-CH_2-CH_2-CH_2)$	piperidide
$-N(CH_3)((CH_2)_2CH_3)$	methyl-propylamide	$-N(CH_2-CH_2-O-CH_2-CH_2)$	morpholide

LSD has the natural configuration of lysergic acid, i.e., the same spatial arrangement as the lysergic acid residue in the natural ergot alkaloids. *d*-iso-LSD is readily obtained from *d*-LSD by rearrangement, whereas *l*-lysergic acid, *l*-iso-lysergic acid and the corresponding diethylamides are synthetic products which can only be obtained by complicated chemical procedures.

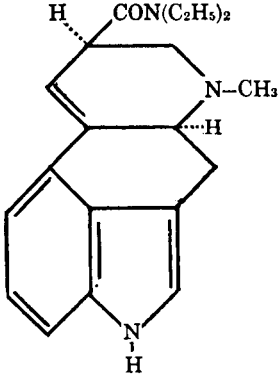


I
d–LSD

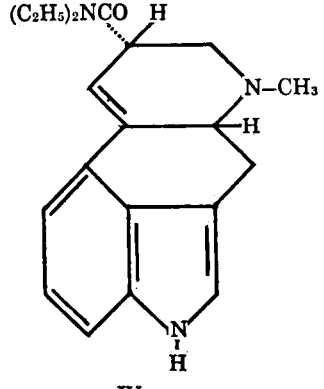


II
l–LSD

Fig. 3



III
d–iso–LSD



IV
l–iso–LSD

A trial on myself and on one coworker, under medical supervision, of the stereoisomers of LSD led to the following findings:

l-LSD, in doses up to 500 micrograms, produced no LSD-like symptoms. Above 500 micrograms, very slight drowsiness was noted.[2]

d-iso-LSD, in doses up to 250 micrograms, was completely without effect.

l-iso-LSD, in doses up to 500 micrograms, also proved to have no

[2] *l*-LSD was subsequently investigated elsewhere for its mental effects on human beings. In normal subjects who had made a marked response to 25 μg. LSD doses of 100 μg. *l*-LSD were without effect.

mental effects. After the ingestion of 500 micrograms, only mild nausea was noted.

As both persons participating in this study (the author and his assistant) had previously had a very marked response to 20 micrograms of LSD, it would appear that the three stereoisomers of LSD are at least fifteen to thirty times less active than *d*-lysergic acid diethylamide.

More extensive studies in human beings, using increasing doses would be necessary to determine whether there are qualitative and quantitative differences between the three relatively inactive isomers by comparison with *d*-lysergic acid diethylamide. However, these preliminary studies clearly show that the mental effects of LSD are highly stereospecific.

The dependence of pharmacological action on the configuration of asymmetric compounds has been repeatedly observed, not only with drugs having central actions but also with those causing peripheral actions. For example, *l*-hyoscine is sixteen to eighteen times more active than *d*-hyoscine in inhibiting the vagus and salivary glands (1); the action of levorotatory adrenaline on sympathetic nerve endings in blood vessels is twelve to fifteen times more powerful than that of (+)-adrenaline (1); the central effects of dextrorotatory desoxyephedrine and of levorotatory desoxyephedrine are in the ratio of 90 : 16 (4).

The observation of a stereospecific effect among the LSD isomers adds to the previous findings the demonstration of stereospecificity for a hallucinogenic substance.

It is perhaps no coincidence but of deeper biological significance that of the four possible isomers of LSD, only one, which corresponds to natural lysergic acid, causes pronounced mental effects. Evidently the mental functions of the human organism, like its bodily functions, are particularly sensitive to those substances which possess the same configuration as naturally occurring compounds of the vegetable kingdom.

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