In connection with the section on scientific autographs, 'Agents and Actions' will occasionally publish personal accounts and documents of important contributions to pharmacology. We have asked Dr. A. Hofmann, who discovered LSD and the 'remarkable, but not unpleasant state of intoxication' it may cause, to initiate this series.
(Ed. Agents and Actions)

Notes and Documents Concerning the Discovery of LSD

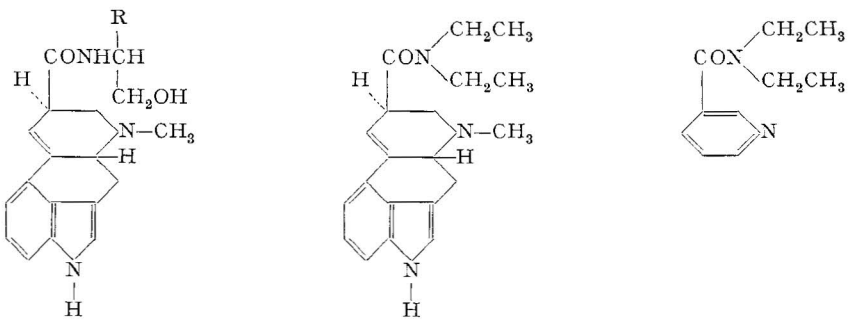
by A. HOFMANN
Sandoz Ltd., Basle, Switzerland

It is frequently stated in the literature that LSD was discovered by chance. This brief account will show that LSD was not merely the fruit of a chance discovery, but the outcome of a more complex process in which chance merely served to trigger off a more intensive investigation.

d-Lysergic acid diethylamide (laboratory designation: LSD 25) was prepared as part of a systematic chemical and pharmacological investigation of partially synthetic amides of lysergic acid. Using a newly developed procedure it had proved possible to combine lysergic acid, the basic structural element of the ergot alkaloids, with amines in peptide linkage. The specific oxytocic principle of ergot, ergometrine (ergobasine, ergonovine), had been produced in this way – this was the first partial synthesis of a natural ergot alkaloid – and by modifying the alkanolamine side chain of ergometrine a new synthetic derivative, Methergin®, was obtained. In its pharmacological properties this new substance was superior to the natural alkaloid, and today it finds employment throughout the world in obstetrics for the arrest of haemorrhage. Although interest centred mainly on oxytocic and haemostatic activity in these investigations, the new method of synthesis was also employed to prepare amides of lysergic acid which, on the basis of their chemical structure, might be expected to possess different pharmacological properties. Thus, among other compounds the author synthesised lysergic acid diethylamide with the intention of obtaining an analeptic. This plan was adopted because of the structural relationship between LSD and the well-known circulatory stimulant nikethamide (Coramine®); (cf. the structural formulae [Fig. 1]).

Fig. 2 shows the entry in the author's laboratory notebook concerning the last stage in

Figure 1



Ergometrine (R = CH_3) LSD Coramine®
Methergin® (R = CH_2CH_3)

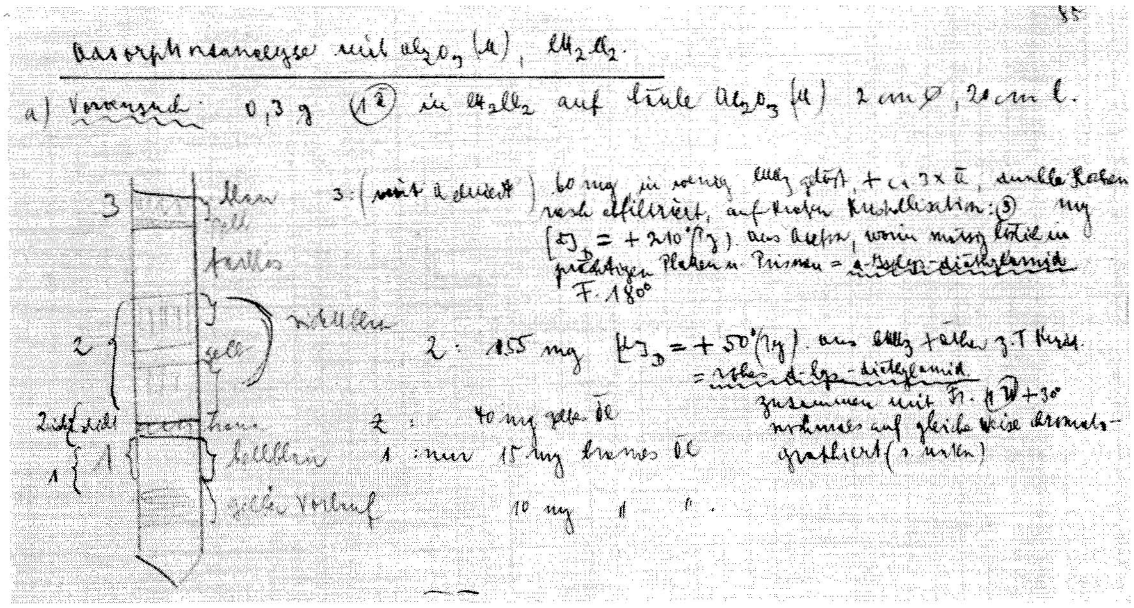


Figure 2

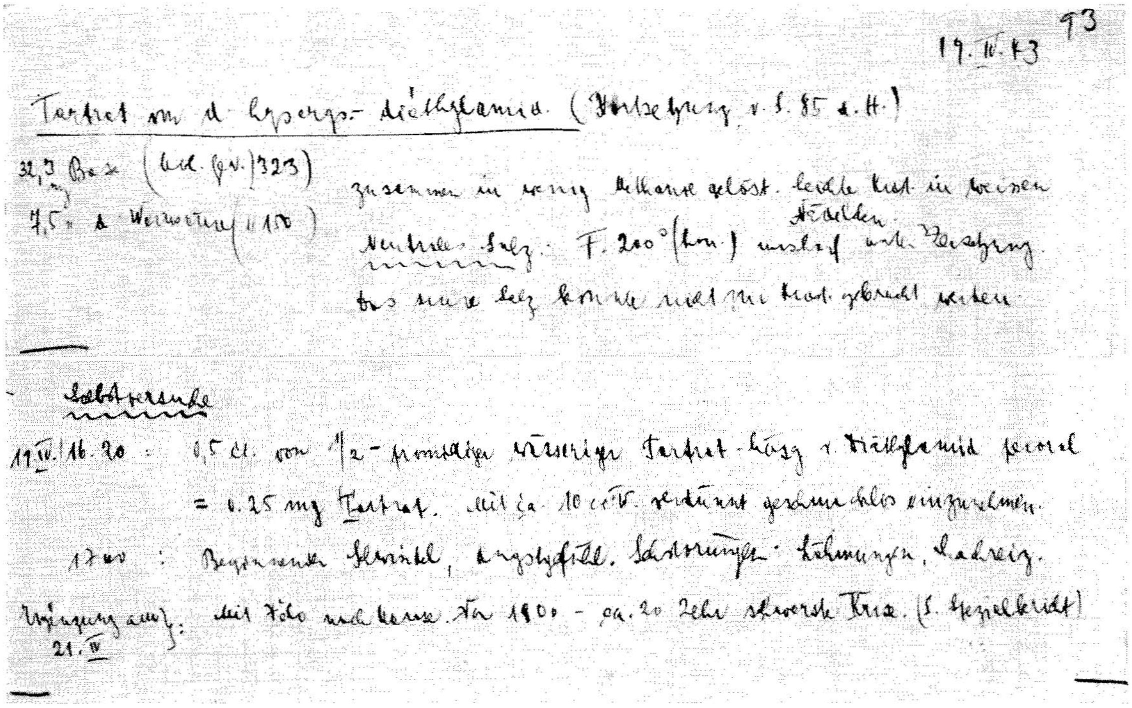


Figure 3

the synthesis of *d*-lysergic acid diethylamide, namely the purification and the removal of the inactive isomer, *d*-isolysergic acid diethylamide, by columnar chromatography.

In the course of this work the author experienced a remarkable but not unpleasant state of intoxication which lasted for 2–3 hours and was characterised by extraordinarily intense stimulation of the imagination and an altered awareness of the world around him. On closing his eyes he saw a succession of fantastic, rapidly changing images of a striking reality and depth, alternating with a vivid, kaleidoscopic play of colours.

The nature and course of this condition gave reason to suspect that it might have been due to a trace of the substance with which the author had been working on that particular day. With this in mind he ingested a quantity of the suspected compound, *d*-lysergic acid diethylamide, three days later on 19 April 1943, by way of a personal experiment. Since the free base was very poorly soluble in water, the readily soluble, easily crystallised tartrate was prepared for this purpose. This preparation, *d*-lysergic acid diethylamide tartrate subsequently became widely known as LSD-25.

Fig. 3 shows a further entry in the laboratory notebook, concerning the preparation of the tartrate and of the solution for the personal experiments.

The plural, experiments, was used advisedly since the test described was envisaged as the first of a series: the dose of 0.25 mg was regarded as the smallest which might be expected to elicit any effect. At that time no substance was known which exhibited clearly marked activity in such a minute dose. The plan was to increase the dose systematically, thereby cautiously exploring the suspected psychotropic activity of the compound. However, it so happened that 0.25 mg, though a minute quantity, was still a gross overdosage. This may be gathered from the entry, made only with great difficulty in the laboratory notebook 40 minutes after ingestion: 'Onset of dizziness, feeling of anxiety, visual disturbances, paralysis, urge to laugh!' The supplementary note entered two days later: 'Went home by bicycle. From 18^{00}–20^{00} h very severe crisis (see special report)' refers to a report to the Head of the Pharmaceutical Department at that time, Professor A. Stoll, in which the symptoms and subjective experiences in the first planned personal experiment with LSD are described at length. Extracts from this original report have appeared in various scientific publications on LSD.

Received 23 June 1969.