in itself suggested that the function of the adrenals is to increase the resistance of the organism to alarming stimuli; furthermore, we observed that a marked enlargement of the adrenals is a constant result of exposure to damaging stimuli, an observation which corroborates the assumption that these glands play an important rôle in the defence of the organism against alarming agents.

It has been claimed that the adrenal is particularly important for the maintenance of normal body temperature, for the prevention of fatigue following exhausting muscular exercise, for the detoxification of various harmful substances and for the maintenance of a constant blood sugar level. Exposure to variable surrounding temperature, excessive muscular exercise, toxic doses of various drugs or agents apt to cause hypoglycemia, act as alarming stimuli. Consequently a decreased resistance to such agents is to be expected if we assume that the function of the adrenals is to prevent the damaging effects of the alarm reaction. But this evidence was not sufficiently conclusive to justify such a theory. We therefore proceeded to experiment with a large number of rats which we adapted to cold, muscular exercise or various drugs. Since damaging agents cease to elicit an alarm reaction after adaptation has occurred, we could expect this experiment to show whether the damage caused by a certain stimulus in an adrenalectomized animal is the result of the stimulus as such or of the alarm reaction which it produces. We found that animals previously adapted to such stimuli as muscular exercise, cold or toxic doses of drugs will tolerate exposure to these same stimuli very well, even after the adrenals have been removed, while exposure to the same stimuli invariably kills not-adapted, adrenalectomized controls, with symptoms characteristic of adrenal insufficiency and of the alarm reaction.

We concluded from these observations that one of the most important functions of the adrenals is to increase the resistance to alarming stimuli. Since most stimuli are "alarming" when the organism is first confronted with them, the adrenals play a very important rôle in the first stage of adaptation to the conditions of the environment. After this first stage, however, the changes necessary for the acquisition of further adaptation take place in the peripheral tissues. In this stage, the stimulus ceases to be "alarming" and therefore the adrenal hormones are no longer required for the process of adaptation.

We assumed that the symptoms of the alarm reaction are mainly due to the liberation from the tissues of some toxic metabolite (possibly histamine or some physiologically similar compound). If this assumption should prove to be correct, one would have to conclude that the function of the adrenals is to detoxify this metabolite. In this event, there would be no contradiction between our interpretation of adrenal deficiency and the intoxication theory as such or possibly even its more modern modification, the histamine intoxication theory (Lucas). The circulatory theory (Swingle and co-workers) and the carbohydrate theory (Britton and Silvette) consider one symptom of the alarm reaction—the circulatory disturbance in the first case, and the hypoglycemia in the second case—to be the basic cause of all the deficiency symptoms. In the light of our findings, these seem to be the result rather than the cause of the deprivation syndrome. The cause of it is the decreased resistance to alarming stimuli. That is why all these deficiency symptoms will appear in adrenalectomized animals at a time when they would otherwise not be evident—that is, immediately following exposure to an alarming stimulus. It seems quite likely that the loss of sodium which is the basic change according to those who believe in the sodium deficiency theory (Loeb, *et al.*) or the increase in potassium (Zwemer) or the deficiency in phosphorylation (Verzar) or the increase in non-protein nitrogen—all of which have been considered to be the primary change—are also symptoms rather than the cause of adrenal insufficiency.

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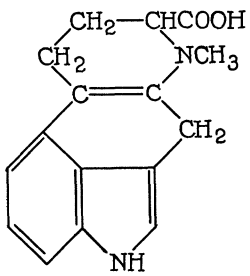
THE SYNTHESIS OF SUBSTANCES RELATED TO LYSERGIC ACID

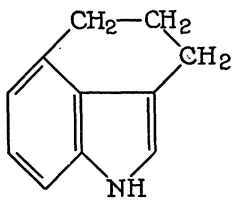
A VERY probable structure for lysergic acid (formula I), the characteristic constituent of the ergot alkaloids, has been derived from the interpretation of, among other things, its characteristic groupings and degradation products.[1] Recently attempts have been made to substantiate this formulation by synthesis. As a first step we have checked the possibility of the production of that portion of this structure composed of the 3-ring system, 3,4-trimethylene indole (formula II). A method to accomplish this was found in the reduction of naphthostyril (the lactam of 8-amino-1-naphthoic acid) with sodium in butyl alcohol. As a by-product a substance normally to be expected was simultaneously formed, *viz.*, 1-hydroxymethyl-8-amino-1,2,3,4-tetrahydronaphthalene. The identities of these substances were shown by their production by a different procedure, namely, reduction of the methyl ester of 8-amino-1,2,3,4-tetrahydro-1-naphthoic acid.

Trimethylene indole exhibits the usual indole reactions but not, however, the characteristic Keller reaction given by the ergot alkaloids (lysergic acid). A nearer approach to the synthesis of lysergic acid

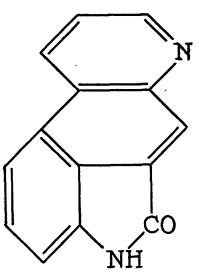
[1] W. A. Jacobs and L. C. Craig, *Jour. Biol. Chem.*, 115: 227, 1936.



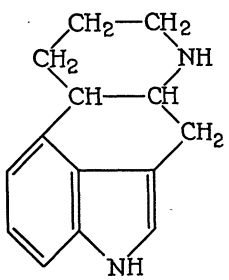
I



II



III



IV

itself has more recently been achieved as follows. 3-amino-1-naphthoic acid[2] by the Skraup reaction has given the corresponding β-naphthoquinoline carbonic acid which on nitration yielded a nitro-β-naphthoquinoline carbonic acid. The position occupied by the nitro group became evident after its reduction to the amino group, since lactamization then readily occurred with production of the substance given in formula III. In preliminary experiments, reduction of the latter with sodium and butyl alcohol yielded a mixture containing a substance apparently with the structure given in formula IV, since this mixture gave color reactions closely approaching those which are so characteristic of lysergic acid and its derivatives.

There is now in progress in this laboratory a logical extension of this work to include other substances related to lysergic acid and eventually to lysergic acid itself.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

AN AUTOMATIC DEHYDRATING DEVICE

A SIMPLE and satisfactory apparatus whereby histological and cytological tissues may be dehydrated gradually has been devised, thus preventing any shrinkage which may be due to improper upgrading in the alcohol series. By this method tissues for paraffin impregnation may be run up in twelve hours to three days, the length of time depending upon the rate of flow from the siphon.

Apparatus used: A 500 cc flask (A) filled with absolute alcohol is fitted with a one-holed rubber stopper to which is connected a piece of glass tubing about eight or nine inches long, the unattached end having a 15° bevel. The flask is placed upside down and held in place by a clamp on an iron stand (B).

Some distance below the flask, a stender (C) filled with water and containing the tissues is placed. The flask is lowered until the bottom of the bevel of the glass tube extends 1/16 inch below the water level in the stender. Leading from the stender, a piece of capillary tubing, bent at a 50° angle 1½ inches from one end and at the other end drawn to half the original bore, is held in place by a piece of plastic clay moulded over the edges of the stender (D). If the long arm of the siphon is placed in almost a vertical position, the liquid will drain off the tissues at a very rapid rate, but the greater the tendency toward a horizontal position, the more noticeable will be the decrease in the number of drops siphoned per minute. However, the siphon will not work unless the overflow end is placed on a lower level than the suction end, and the suction end must be placed near the bottom of the stender.

As the siphon drains the liquid off the tissues, the level of the mixture of alcohol and water falls below

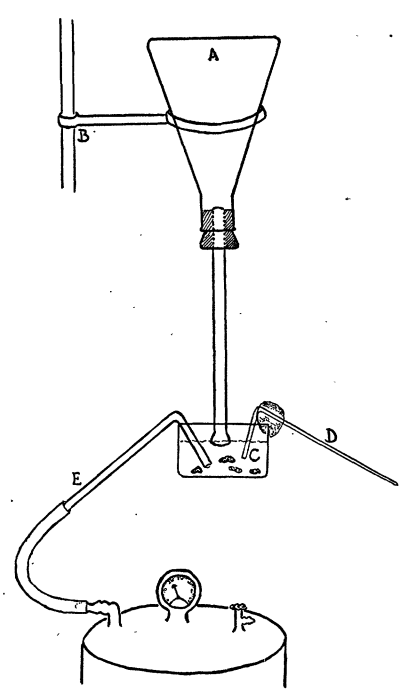

FIG. 1

[2] G. J. Leuck, R. P. Perkins and F. C. Whitmore, *Jour. Am. Chem. Soc.*, 51: 1834, 1929.