1. Sunlight and ultraviolet radiations from a quartz lamp produce either no effect or a stimulating effect on normal rats.

2. The pharmacological activity of quinine and quinidine sulphates was greater in animals exposed to light than those kept in darkness.

3. The absolute lethal doses of quinine and quinidine were smaller for animals kept in light than those kept in darkness.

4. As between the two optic isomers quinine and quinidine, the laevo-gyrous variety (quinine) was more toxic than the dextro-gyrous variety (quinidine).

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SUPRARENIN (SYNTHETIC EPINEPHRIN).*

BY CASIMIR FUNK, HARRY E. DUBIN AND LOUIS FREEDMAN.

One of the most notable achievements of modern chemistry and science is the synthesis of the naturally occurring alkaloid, epinephrin. This drug, which is probably the most powerful physiologic substance known, is found in the medulla of the suprarenal gland in all animals and was first obtained in an impure condition in 1897 by Abel and Crawford. It was finally purified by Takamine in 1901, and its chemical structure was definitely established in 1903. From then on, efforts were directed toward its synthesis in the laboratory, this being accomplished independently by several workers a year later.

The synthesis of this highly important pharmaceutical was not considered complete, however, until the racemic form, in which it is obtained when synthesized, was resolved into its two optically active components. This was accomplished several years later by Stolz and his co-workers by means of fractional crystallization of the bitartrates, and also by the action of a fungus—*penicillium glaucum.*

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The development of the synthetic process on an economic basis was necessarily slow and tedious. The process is a complicated one as it consists of about nine different chemical reactions, involving the isolation and purification of each intermediate. It took several years of painstaking research before we were able to finally develop in our laboratories an economic process which would give us a pure and uniform substance, absolutely identical with the natural product.

The starting material used in this process is pyrocatechol, which is monohydroxyphenol. By the action of chloracetyl chloride this compound is converted into chloraceto-pyrocatechol. This is then treated with methylamine to form methylamino aceto pyrocatechol, a product having distinct pressor action and known as "adrenalone." This product, on subjection to reduction, yields racemic suprarenin (synthetic epinephrin). Racemic suprarenin consists of a uniform, optically inactive mixture, being 50% laevo suprarenin and 50% dextro suprarenin. The highly physiologically active laevo component is then separated from its optical isomer by converting the racemic compound into the bitartrate, and removing the *l*-suprarenin bitartrate by fractional crystallization and purifying it by subsequent recrystallization. In this way the laevo compound is obtained absolutely free of the dextro component.

Ever since racemic suprarenin was resolved into its optically active components there has been considerable controversy over the relative physiologic activity of these two stereo-isomeric compounds. Although investigators in this field are in accord with the fact that the laevo variety is many times more active physiologically than the dextro variety, there seems to be marked disagreement as regards their relative activity.

Cushing, and Abderhalden and Mueller have determined that the optically active laevo component of racemic suprarenin is the main carrier of the physiologic effect, while the dextro component possesses only one-fifteenth the effect of the natural *l*-epinephrin. Recent articles of French authors, however, tend to obscure the results of the previous investigators. Richaud, particularly, concludes from his tests on blood pressure that *l*-suprarenin is but a few per cent. more effective than the racemic form so that therapeutically the latter is practically equivalent to the natural product.

Fromherz, however, disagrees with Richaud in the interpretation of his results, although he states that Richaud's experimental data do not differ much from those of Abderhalden and Mueller.

Fromherz, in a very recent publication, gave the results of his observations on the increase in blood pressure in rabbits by injections of pure *d*-suprarenin. This antipode was obtained by splitting the racemic base with *d*-tartaric acid, removing the *l*-suprarenin *d*-bitartrate and then recovering the *d*-component from the mother liquor. The *d*-suprarenin was once again converted into its bitartrate, purified by recrystallization and the base finally obtained by precipitation with ammonia. From a series of curves which he made, Fromherz found that 0.3 mg. of *d*-suprarenin is a little less effective than 0.01 mg. *l*-suprarenin, and that 0.5 mg. *d*-suprarenin is approximately equal to 0.015 mg. *l*-suprarenin. From these observations he drew the conclusion that the *d*-component is only 1/30 to 1/40 as effective as *l*-suprarenin, and that therefore racemic suprarenin possesses only 51 to 52 per cent. of the effectiveness of the natural or the synthetic *l*-suprarenin.

The purity of the *l*-suprarenin can be tested according to three different methods, any one of which, when carefully controlled, gives an exact indication of the purity of suprarenin whether it be the natural or the synthetic product.

The three methods available for the standardization of the drug are the chemical, physical and physiologic.

The chemical tests include, first, the various color reactions which are peculiar to the type of compounds of which epinephrin is a member. Second, the chemical analysis by means of which the carbon, hydrogen, and nitrogen content are determined. This latter method of identification, however, is unnecessary and is seldom used.

The physical constants include melting point and optical rotation. Any sample of *l*-epinephrin, synthetic or natural, which gives the theoretical melting point of 212° C., or in the form of its bitartrate melts at 149° C., and whose hydrochloride solution rotates the plane of polarized light to the left the theoretic number of degrees (−50°), must also exhibit 100% physiologic activity. A lowering of the respective melting points or an increase in the degree of polarization indicates at once that the particular sample under investigation contains some impurities or some racemic and less active epinephrin.

The physiologic test is based upon the ability of a given amount of epinephrin to produce a definite increase in blood pressure, as compared with the rise in blood pressure obtained with a known 100% standard. The purity of this 100% standard can, however, be determined only by physico-chemical means. The physiologic test is of necessity an arbitrary one as its results are dependent considerably on the animal and method used and the skill of the worker; and these tests have been known to vary, even on duplicate samples.

On the other hand, the only unarbitrary and constant method in assaying epinephrin, natural or synthetic, is by chemico-physical means. Chemical and physical tests not only show the absolute quantity of the laevo epinephrin but also the degree of purity of this substance, while the polarimetric readings show the optical activity which should check with the other tests. A minute quantity of the less active dextro-rotatory variety, admixed with the highly active laevo isomer, has a marked effect on both the melting point and optical rotation.

All optically active substances, when synthesized, occur in the optically neutral racemic form consisting of equal amounts of the active components which neutralize each other. These components are then separated by combining them with an optically active acid, if a base, and an optically active base, if an acid, In the case of suprarenin, to obtain the laevo form, a dextro acid such as dextro tartaric acid is used.

The compound obtained is then *l*-suprarenin-*d*-bitartrate from which the laevo active base can be obtained by precipitation with ammonia. This synthetic laevo compound is identical in every respect with the purified natural epinephrin obtained from the suprarenal glands.

Suprarenin or synthetic epinephrin is in many ways to be preferred to the natural product. The synthesis, being carefully controlled at each step and involving the use of chemicals of unvarying composition, yields a pure, stable, and uniform product exhibiting more than the required degree of physiologic activity. Natural epinephrin, on the other hand, being made from enormous quantities of

suprarenal glands of varied strength and origin, is likely to contain impurities that are inherent in the process of manufacture, and is also likely to undergo partial racemization with a consequent decrease in both optical and physiologic activity.

Aside from this, scientific progress has been along the lines of synthesis. No sooner has a natural product of therapeutic value been discovered, than attempts are made to isolate it to determine its chemical constitution and ultimately to synthesize it. We have such examples in suprarenin and thyroxin (the active principle of the thyroid gland). The isolation and synthesis of insulin would no doubt create a furore in the scientific world and would be a boon to humanity. Once the synthesis of a natural product is achieved, the medical and pharmaceutical professions are assured of a uniformly pure product which may be prepared at a price low enough to permit of its more general use.

In spite of the large amount of work which has been done on epinephrin, considerable progress can still be made in the field of research. Available data are still lacking regarding the exact relative physiologic activity of the two optically active components of racemic suprarenin. Also the field is still open for the synthesis of new derivatives which may be equal or superior to suprarenin and still be easy of manufacture.

We have recently described the preparation in our laboratory of three new derivatives of suprarenin which have unusual chemical interest and which may have valuable, physiologic properties. These new compounds which are at present under investigation are ethers of suprarenin in which the secondary alcoholic group is involved. Further research work is now being carried out in our laboratory on the chemistry of suprarenin and various compounds related to it.

BIOCHEMICAL DEPARTMENT
RESEARCH DIVISION
H. A. METZ LABORATORIES, INC.,
NEW YORK, N. Y.

THE ALKALINITY OF MAGMA MAGNESIÆ AS DETERMINED BY THE HYDROGEN ELECTRODE.*

BY R. B. SMITH AND P. M. GIESY.

Since the U. S. P. method for the determination of free caustic in Milk of Magnesia does not always appear to give reliable results, it was decided to investigate the p_H of Milk of Magnesia of various degrees of purity with a view to finding some more reliable method which would give reproducible results under all conditions.

Milk of Magnesia which had been thoroughly washed but which still contained an excess of water was found to have a p_H of 10.33. After slightly diluting the milk with water, the magnesium hydroxide was washed four times by decantation, centrifuging each time to effect settling. After the fourth washing it was diluted and boiled and allowed to cool in a stoppered flask. The p_H of this material was found to be 10.37.

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