THE BIOCHEMISTRY OF
B VITAMINS

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GENERAL INTRODUCTION

American Chemical Society's Series of Chemical Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in cooperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical progress. The American Chemical Society named as Trustees, to make the necessary arrangements for the publication of the Monographs, Charles L. Parsons, secretary of the Society, Washington, D. C.; the late John E. Teeple, then treasurer of the Society, New York; and the late Professor Gellert Alleman of Swarthmore College. The Trustees arranged for the publication of the ACS Series of (a) Scientific and (b) Technological Monographs by the Chemical Catalog Company, Inc. (Reinhold Publishing Corporation, successor) of New York.

The Council of the American Chemical Society, acting through its Committee on National Policy, appointed editors (the present list of whom appears at the close of this sketch) to select authors of competent authority in their respective fields and to consider critically the manuscripts submitted.

The first Monograph of the Series appeared in 1921. After twenty-three years of experience certain modifications of general policy were indicated. In the beginning there still remained from the preceding five decades a distinct though arbitrary differentiation between so-called "pure science" publications and technologic or applied science literature. By 1944 this differentiation was fast becoming nebulous. Research in private enterprise had grown apace and not a little of it was pursued on the frontiers of knowledge. Furthermore, most workers in the sciences were coming to see the artificiality of the separation. The methods of both groups of workers are the same. They employ the same instrumentalities, and frankly recognize that their objectives are common, namely, the search for new knowledge for the service of man. The officers of the Society therefore combined the two editorial Boards in a single Board of twelve representative members.

Also in the beginning of the Series, it seemed expedient to construe rather broadly the definition of a Monograph. Needs of workers had to be

recognized. Consequently among the first hundred Monographs appeared works in the form of treatises covering in some instances rather broad areas. Because such necessary works do not now want for publishers, it is considered advisable to hew more strictly to the line of the Monograph character, which means more complete and critical treatment of relatively restricted areas, and, where a broader field needs coverage, to subdivide it into logical sub-areas. The prodigious expansion of new knowledge makes such a change desirable.

These Monographs are intended to serve two principal purposes: first, to make available to chemists a thorough treatment of a selected area in form usable by persons working in more or less unrelated fields to the end that they may correlate their own work with a larger area of physical science discipline; second, to stimulate further research in the specific field treated. To implement this purpose the authors of Monographs are expected to give extended references to the literature. Where the literature is of such volume that a complete bibliography is impracticable, the authors are expected to append a list of references critically selected on the basis of their relative importance and significance.

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This volume is dedicated to

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Permission to use the following material is acknowledged with thanks: Table 2, pp. 250-251, Table 3, p. 253 and Table 4, p. 253, from Williams and Spies: *Vitamin B_1 and Its Use In Medicine*, copyright 1938, by the Macmillan Company. Table 6, p. 257, *Journal of Nutrition*, L. J. Roberts, Figure 3, p. 313, *Indian Journal of Medical Research*, P. S. Sarma. Table 20, pp. 324-325, Food and Nutrition Board, National Research Council. Tables 29 and 30, pp. 366-367, Academic Press, C. W. Denko. Table 34, p. 389. *Proceedings of the Society for Experimental Biology and Medicine*, F. G. Brazda. Figure 17, p. 405, *Journal of Nutrition*, J. Salcedo, Jr. and L. E. Holt, Jr. Figures 18-20, pp. 416-418, *Lancet*, T. D. Spies.

PREFACE

We have sought in this volume to fulfill, with respect to the chosen field, the two fundamental purposes set forth at the time the American Chemical Society Monograph Series was instituted.

First, we have attempted to present the material "in readable form, intelligible to those whose activities may be along a wholly different line" to the end that they may gain perspective and interest and appreciation of the fundamental unity existing in the broad area involving physical as well as biological science.

Second, we have sought to promote research in the field of the B vitamins "by furnishing a well digested survey of the progress already made in that field and by pointing out directions in which investigation needs to be extended." In connection with this latter purpose we have had in mind two groups: the oncoming advanced students who from year to year must have a means of becoming acquainted with the field, and the ever increasing number of chemists whose fundamental training has been in some other branch but who are turning to biochemistry as an attractive field of investigation.

In keeping with the title of the volume and the purposes set forth, we have not included full discussions of the organic chemistry or technology of the substances involved, nor have we given a historical treatment of their discovery and identification. To trace all the misconceptions and inevitable blunderings which have entered into the development of our present knowledge and at the same time to do justice to the numerous investigators would be an impossible task, and from the standpoint of our purposes an attempt would not be worthwhile.

We agree with the late G. N. Lewis' statement, "a monograph of this sort belongs to the ephemeral literature of science. The studied care which is warranted in the treatment of the more slowly moving branches of science would be out of place here. Rather with the pen of a journalist we must attempt to record a momentary phase of current thought, which may at any instant change with kaleidoscopic abruptness."

Although the four authors have found themselves to be in substantial agreement on most points, in the presentation of the material in the four sections they have used their respective judgments, expressed their own

individual opinions and organized the material in accordance with their own thinking on the subject. One of our primary aims has been to present constructive and suggestive viewpoints, and in so doing we have had to run the risk of being in error. This risk could have been avoided by compiling an uncritical review with none of the reviewers' opinions expressed, but to have done this would have effectively defeated the purpose of the book.

We wish to beg the indulgence of our readers for mistakes and imperfections that may be found, and if they are such as can be remedied in later printings or editions we will appreciate having them called to our attention. There has been some unavoidable duplication in different areas of the discussion, but this has been retained whenever doing so would contribute materially to the unity and understandability of the particular section. In view of the magnitude of the task, which turned out to be even greater than we had anticipated, and because the preparation of the manuscripts had to be superimposed upon active research and/or teaching programs, we hope that our readers will be charitable in judging the product of our labors.

It has not been feasible to synchronize our efforts completely and in the respective sections the literature has not been completely reviewed up to exactly the same date. Even within sections the up-to-dateness may vary slightly from topic to topic. For example, the citation of individual crucial papers up through April or May, 1950, does not mean that all of the literature has been covered up to that point. We cannot hope that the material which we have presented will remain up-to-date for long. Indeed, a sincere desire to promote research is equivalent to hoping that this volume will rapidly become out-of-date. But, like Professor Lewis, we can hope that necessary changes will involve "matters of detail rather than of essence."

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Austin, Texas
June 15, 1950

CONTENTS

Section A

CHARACTERIZATION, DISTRIBUTION, ASSAY AND BIOGENESIS OF B VITAMINS

Roger J. Williams

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Chapter 1A

B VITAMINS: WHAT THEY ARE

Historically the term "vitamin B" was applied to the water-soluble organic material present in yeast, wheat germ, protein-free milk, etc., which was found to be necessary in small amounts for the nutrition of young animals. At the time this designation came into general use the dietary importance of minerals, proteins (amino acids), carbohydrates, fats, "vitamin A," and vitamin C was recognized, and "vitamin B" meant something distinct from these other recognized food materials.

When it became evident that vitamin B was not a single substance but several, the designations B_1, B_2, B_3, etc., were introduced. These have more recently given way in most cases to names for the specific chemical substances involved: thiamine, riboflavin, etc. We shall discuss later specific cases of substances which according to one's point of view may or may not be included among the "B vitamins."

The time may well arrive when the term "B vitamin" will be abandoned, and each specific chemical substance will be considered entirely as a separate entity. At the present time, however, there is good reason for retaining the term, because B vitamins appear to have common attributes which set them apart from all other vitamins.

Microbiological assay methods have made it possible to learn that the specific compounds commonly considered as members of the B family are universally distributed *in all living cells*, whether of plant, animal or bacterial origin. Since this appears not to be true of any of the other vitamins, it was suggested elsewhere that B vitamins may be tentatively defined as *those which occur as indispensable constituents of all living matter*.[1] If this suggestion is valid, their fundamental importance is self-evident.

Studies relating to the functioning of individual members of the B family of vitamins have demonstrated that they are integral parts of biological catalytic systems and that they constitute essential factors in the metabolic machinery of widely diverse forms. It seems probable that this is true of all of the B vitamins, and an amended definition may include this idea. In this case, we may say that B vitamins are those which enter into the catalytic systems of all living cells.

Since the water solubility or fat solubility of a compound is not absolute

but rather a matter of degree, we have not included the loose term "water solubility" as an essential characteristic of a B vitamin. Indeed, if the idea of the existence of a distinctive group of vitamins which function catalytically in all living cells is a valid one, it is conceivable that we may eventually come to include some of the "fat-soluble" compounds among the B vitamins. Of such compounds already recognized, possibly the most likely candidates for inclusion are the vitamins E, which appear to be widely distributed in diverse organisms and tissues.[2] If these vitamins should be found to be part of the catalytic machinery of all cells, there would seem to be no very valid reason for excluding them from the B vitamins. The fact that a separate letter designation has been used for them would not preclude this possibility. Biotin, which was early called "vitamin H," is now recognized as a member of the B family. The question of the universal occurrence of B vitamins in relation to other vitamins is discussed further in Chapter IIA.

One of the interesting observations which in a measure appears to differentiate the B vitamins from the members of the so-called fat-soluble group is the fact that in the case of the fat-soluble vitamins there are in every instance several naturally occurring and distinct chemical structures which possess the specific vitamin activity, whereas among the B vitamins the physiological activity is more specifically associated with a single chemical structure. It is true that in several instances among the B vitamins, modified structures possess specific vitamin activity, but in general each B vitamin is represented by a single substance or at least by a few very closely related structures. As an instance of the latter, in case a specific vitamin (*e.g.*, nicotinamide, riboflavin) is involved as a catalytic hydrogen carrier, it is reasonable that both the oxidized and reduced forms should have physiological activity; likewise, if a vitamin is a catalyst for ammonia transfer (*e.g.*, pyridoxal), it is not surprising that an aminated form (pyridoxamine) should possess physiological activity.

We may now profitably consider in a critical manner the meaning and significance of the word "vitamin"—a term the meaning of which we have so far in this discussion taken for granted. It involves historically a nutritional concept and has come to be applied almost exclusively to certain organic substances which function in the nutrition of higher animals. While a considerable number of the B vitamins were discovered and isolated using yeasts and bacteria as test organisms, they have not been admitted to the family of vitamins unless they have been found to be nutritionally effective for higher animals.

A substance which counteracts a vitamin deficiency is not, however, necessarily designated a vitamin. If this were so, thiamine pyrophosphate,

coenzymes I and II, riboflavin nucleotides, and even flavoproteins, etc., would be considered as vitamins because they are capable of counteracting respectively thiamine, niacin and riboflavin deficiencies. Actually, they are not designated as vitamins. The easiest way out of the difficulty in a specific case is to consider as a vitamin only the *simplest* compound capable of performing the specific nutritional function. In cases where two or more compounds of about the same complexity function alike nutritionally, each may conveniently be called a vitamin. Nicotinic acid and nicotinamide on the one hand, and pyridoxal, pyridoxamine and pyridoxine on the other, are examples.

The importance of some of the compounds commonly designated as vitamins does not rest, moreover, solely upon their functioning in nutrition. Nicotinamide from the nutritional standpoint may not be essential for animals if tryptophan is abundantly supplied, yet it is a nutritional substance and is important in that it constitutes a part of the metabolic machinery in every cell. Even though mammals generally, including human beings, are probably capable of synthesizing nicotinamide in their bodies from tryptophan, it is nonetheless a compound of great biochemical interest and importance. Likewise, the importance of thiamine, riboflavin, pantothenic acid and other members of the B family of vitamins does not depend only upon the fact that they cannot be synthesized by higher animals. As essential parts of the metabolic machinery, they are most fundamental, regardless of their nutritional importance. Their nutritional functioning may even be considered of secondary significance.

Looking at the matter with these facts in mind we may suspect that the B vitamins actually belong to a larger group of organic catalytic units which are indispensable to all cells, but which may or may not be vitamins in the nutritional sense. Some of these indispensable units may be uniformly synthesized by higher animals. We have no name for this inclusive group of catalytic substances,* if such exists, and it appears premature to discuss them at present. Until the time arrives when we fully recognize the existence of such a group, it will be well to retain the term "vitamin" and the nutritional concept which underlies it. A substance therefore cannot be classed as a vitamin unless it functions nutritionally for higher animals.

Following this line of reasoning we may expand our definition of a B vitamin to include *those organic substances which act catalytically in all living cells and which function nutritionally for at least some of the higher animals.* We cannot guarantee, of course, that this delineation of B vitamins will remain valid indefinitely. If it should be found that some of the typical B vitamins lack a catalytic function or that some of them

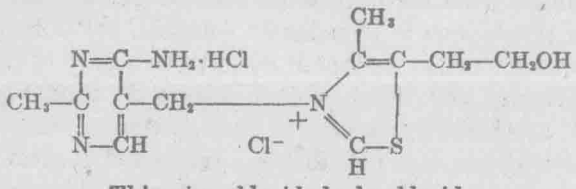
* The name "catalins" has, however, occurred to the author as an appropriate one.

are absent from certain types of cells, then our definition might have to be modified immediately. At present such modification does not appear likely.

Chemically Recognized B Vitamins

There are a number of specific chemical substances of known structure which are universally recognized as B vitamins. We may, therefore, gain a more specific idea of what is meant by the term "B vitamin" by discussing briefly these individual compounds.

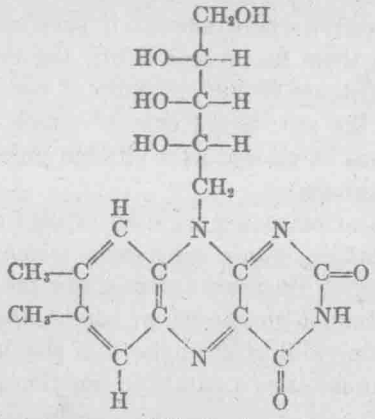
Thiamine (aneurin) earlier received the designation "B_1" in keeping with the fact that it was the first B vitamin to be discovered and isolated. There is substantially no confusion resulting from identifying vitamin



Thiamine chloride hydrochloride

B_1 as thiamine, because thiamine is the only naturally occurring structure which is capable of performing the vitamin functions (p. 684). More complex structures containing the thiamine unit as a part may function nutritionally, as may also products formed by reversible oxidation and reduction, if such exist. The chemistry of thiamine has been reviewed by R. R. Williams.[3]

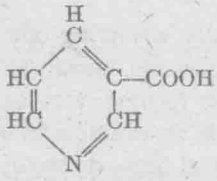
Riboflavin, earlier called vitamin B_2, has the structure indicated below and is the only naturally occurring structure possessing the characteristic vitamin activity. Several synthetic flavins have lesser biological activity;



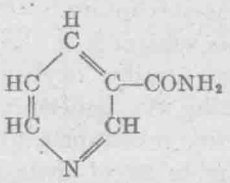
Riboflavin

esters and other simple derivatives of riboflavin may possess full activity, and conjugated forms such as the nucleotides or flavoproteins may be nutritionally effective in proportion to their content of combined riboflavin. The (reversibly) reduced form of riboflavin and its conjugates are also physiologically active. Since the establishment of its constitution and its synthesis in 1935 by Kuhn and Karrer and their co-workers, there have been few advances in the organic chemistry of riboflavin. A complete review of this topic may be found in the literature.[4]

Nicotinic Acid, Nicotinamide. These two compounds interchangeably possess vitamin activity and the only other naturally occurring compounds which can function nutritionally in the same manner are more complicated derivatives which may act because they contain the essen-



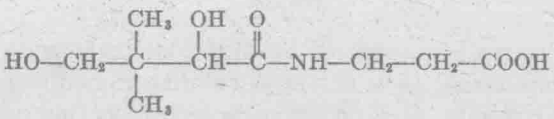
Nicotinic acid



Nicotinamide

tial structure in combined form. Combined forms, even naturally occurring ones, are not necessarily wholly effective. The chemistry of nicotinic acid is too old a topic in the field of organic chemistry to require comment here.

Pantothenic Acid. Probably this compound was mainly responsible for what was first designated "vitamin B_3"; it is the only naturally occurring one capable of performing the nutritional function. Conjugated forms



Pantothenic acid

may possess vitamin activity because they contain the fundamental structure in combination. The chemistry of pantothenic acid has been reviewed [5] and detailed material on the subject will be found in the literature cited in the review. Other material dealing with the chemistry of pantothenic acid will be found elsewhere in this volume (p. 464).

Pyridoxal, Pyridoxamine, Pyridoxine. For animals these three forms are nutritionally interchangeable and are often thought to be in equilibrium *in vivo*. Lactic acid bacteria often show incomparably greater response to pyridoxal or pyridoxamine or their phosphates [6] than to pyridoxine, so these forms of the vitamin which were discovered later

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