126. B.P. 711380 (1954); Chem.Abs., 49, 1243 (1955).
127. J.S.Sconce, A.N.Johnson, and Y.T.Pucker, U.S.P. 2502392 (1950); Chem.Abs., 44, 6552 (1950).
128. G.H.Denison, N.W.Furby, and R.O.Bolt, U.S.P. 2528347 (1950); Chem.Abs., 288 (1951).
129. F.J.Watson and R.C.Morris, U.S.P. 2509620 (1950); Chem.Abs., 45, 792 (1951).
130. Dutch P. 71899 (1953); Chem.Abs., 47, 9527 (1953).
131. G.H.Denison, N.W.Furby, and R.O.Bolt, U.S.P. 2528348 (1950); Chem.Abs., 45, 289 (1951).
132. J.S.Ard, Analyt.Chem., 23, 680 (1951).
133. J.S.Ard, Analyt.Chem., 25, 1743 (1953).
134. A.D.Cross, "Introduction to Practical Infra-Red Spectroscopy" (Translated into Russian), Inostr.Lit., Moscow, 1961.
135. B.M.Gatehouse, S.E.Livingstone, and R.S.Nyholm, J.Chem.Soc., 4222 (1957).
136. R.H.Hughes, J.Martin, and N.D.Coggeshall, J.Chem. Phys., 24, 489 (1956).
137. T.C.Waddington, J.Chem.Soc., 4341 (1958).
138. J.R.Ferraro, J.Inorg.Nuclear Chem., 10, 319 (1959).
139. R.H.Nuttal, D.W.A.Sharp, and T.C.Waddington, J.Chem. Soc., 4965 (1960).
140. R.D.W.Kemmit, R.H.Nuttal, and D.W.A.Sharp, J.Chem. Soc., 46 (1960).
141. R.Mecke and W.Kutzelnigg, Spectrochim.Acta, 16, 1216 (1960).
142. J.P.Mathieu and H.Poulet, Spectrochim.Acta, 16, 696 (1960).
143. T.Hooker, E.J.Geerring, and A.H.Maude, U.S.P. 2841243 (1958).
144. Chem.Eng.News, 36, 37, 66 (1958).
145. Chem.Eng., 65, 20, 60 (1958).
146. Chem.Eng., 67, 9, 108 (1960).
147. H.Müller, E.Müller, and A.Müller, Austrian P. 182707 (1955).
148. E.McBee, C.Roberts, J.Idol, and R.Earle, J.Amer.Chem. Soc., 78, 1511 (1956).
149. A.N.Johnson, U.S.P. 2996553 (1961); Chem.Abs., 56, 1363 (1962).
150. S.Levin and R.M.Noyes, J.Amer.Chem.Soc., 80, 2401 (1958).
151. M.Gazith, Columbia University Microfilm No.21787, Dissertation; Chem.Abs., 51, 17363 (1957).
152. Chem.-Ztg., 20, 678 (1960).
153. A.R.Jones, U.S.P. 2501678 (1950).
154. B.M.Sturgis, A.A.Baum, and J.H.Trepagnier, Ind.Eng. Chem., 39, 64 (1947).
155. L.M.Kogan, Zhur.Prikl.Khim., 36, 824 (1963).
156. L.M.Kogan, Vinogradarstvo i Vinodelie SSSR, No.8, 38 (1961).
157. L.M.Kogan, "Materialy Vsesoyuznogo Nauchno-Metodicheskogo Soveshchaniya po Zashchite Vinograda ot Vreditelei i Boleznei" (Reports of the All-Union Scientific and Methodical Congress on the Protection of Grapes against Pests and Disease), Sel'khozizdat Ministerstva Proizvodstva i Zagotovok Sel'khozproduktov Moldav.SSR, Kishinev, 1962, p.101.
158. S.I.Vol'fkovich, L.M.Kogan, N.S.Stroganov, and L.V.Sledneva, Zhur.Khim.Prom., 498 (1963).
159. L.M.Kogan, Ya.I.Prints, V.I.Orlov, V.M.Kozlov, N.M.Burmakin, N.P.Ignatova, and P.F.Slonovskii, USSR P. 120384 (1959); Byulleten' Izobretenii, No.11, 49 (1959).
160. G.A.Kiryukhin, in "Tezisy Dokladov na Konferentsii Ukrainskoi Akademii Sel'skokhozyaistvennykh Nauk" (Abstracts of Papers Presented at the Conference of the Ukrainian Academy of Agricultural Sciences), Izd.UASKhN, Kiev, 1960.
161. G.A.Kiryukhin, Zashchita ot Vreditelei i Boleznei, No.7, 48 (1961).
162. "Postanovlenie Vsesoyuznogo Soveshchaniya po Voprosu Zashchity Vinogradnikov ot Vreditelei i Boleznei", Sadovodstvo, Vinogradarstvo i Vinodelie Moldavii, No.10, 47 (1961).
163. Ya.I.Prints, Priroda, No.12, 48 (1961).
164. Ya.I.Prints, V.M.Kozlov, and P.F.Slonovskii, in Sbornik, "Filloksera i Mera Bor'by s Nei" (Collected Papers on Phylloxera and Means of Combating It), No.1 (Edited by Ya.I.Prints), Izd. "Shtiintsa", Akad.Nauk Moldav.SSR, Kishinev, 1961.
165. I.Kazas, A.Gorkavenko, and V.Poichenko, "Filloksera i Mera Bor'by s Nei" (Phylloxera and Means of Combating It), Krymizdat, Simferopol', 1960.
166. Ya.I.Prints, "Kul'tura Evropeiskogo Kornesobstvennogo Vinograda v Moldavii" (Culturing the European Rooting Vine in Moldavia), Izd.Kartya Moldovenesko, Kishinev, 1960.
167. P.V.Sazonov, Zashchita Rastenii ot Vreditelei i Boleznei, No.6, 34 (1962).
168. I.A.Kazas, in "Materialy Vsesoyuznogo Nauchno-Metodicheskogo Soveshchaniya po Zashchite Vinograda ot Vreditelei i Boleznei" (Papers Presented at the All-Union Scientific and Methodical Congress on the Protection of Grapes against Pests and Disease), Sel'khozizdat Ministerstva Proizvodstva i Zagotovok Sel'khozproduktov Mold.SSR, Kishinev, 1962, p.8.
169. Ya.I.Prints, *ibid.*, p.20.
170. F.P.Polivtsev and A.F.Vorotynina, *ibid.*, p.24.
171. G.A.Kiryukhin, *ibid.*, p.48.

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ADVANCES IN THE CHEMISTRY OF THIAMINE

A. M. Yurkevich

CONTENTS

I. Introduction 189

II. Reactions not involving cleavage of the thiazolium ring 189

1. Sulphite cleavage of thiamine 189
2. Reactions of thiamine with carbonyl compounds 190
3. Hydrogenation of thiamine 190

III. Reactions resulting in cleavage of the thiazolium ring 190

1. Inactive thiamine; formation of thiamine anhydride 190
2. Unsymmetrical disulphides of thiamine 191
3. Cyanothiamine and its reactions 191

IV. Acylation of thiamine and its derivatives 192

V. Thiamine–protein complexes 192

VI. Derivatives of thiamine 193

1. Salts and esters of thiamine 193

2. Derivatives of the thiol form of thiamine 193

3. New natural compounds closely related to thiamine 193

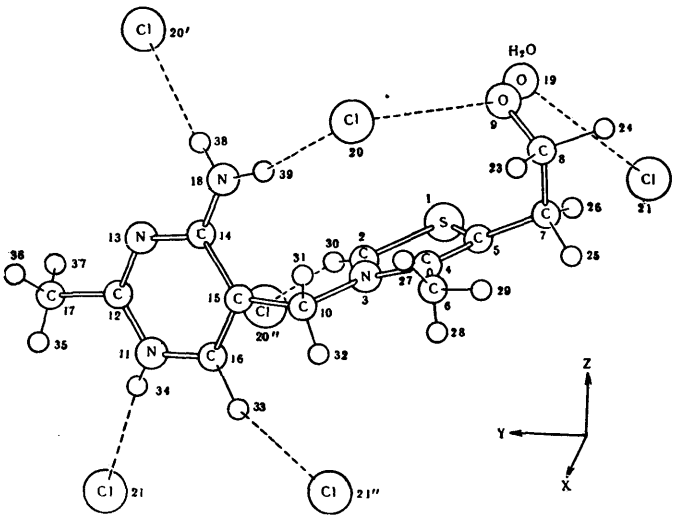
4. Analogues of thiamine 194

VII. Development of industrial methods for synthesising vitamin B_1 194

1. Synthesis from 5-2′-hydroxyethyl-4-methylthiazole 195

2. Synthesis of vitamin B_1 *via* "thiothiamine" 195

VIII. Mechanism of the action of vitamin B_1 196



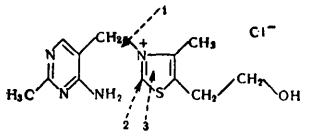
Three-dimensional model of vitamin B_1.

I. INTRODUCTION

The main lines of research and the results obtained during recent years on one of the most important vitamins of the B group, thiamine, have consisted in the development and improvement of manufacturing processes, a more thorough investigation of chemical properties, and finally elucidation of the mechanism of its action in biochemical processes.

Thiamine, whose structure was established in 1936, is now produced annually in tens and hundreds of tons in many countries of the world. The methods for its production are continually being improved. Tens of derivatives of thiamine are known which possess varying biological activity and have varied clinical applications. The synthesis of analogues of thiamine and the investigation of their properties have acquired great significance, their study having promoted an understanding of the role of individual structural groupings in the vitamin molecule. Finally, the detailed investigation of the chemical properties of thiamine has enabled new products to be synthesised (propyl thiamine disulphide, *S*-benzoylthiamine *O*-monophosphate, etc.) and the mechanism of the biochemical action of vitamin B_1 to be elucidated.

The chemical properties of thiamine and its derivatives are determined to a large extent by the extremely reactive thiazolium ring.



The known reactions of thiamine can be divided into two groups: (i) reactions (1) and (2) which do not involve cleavage of the thiazolium ring; and (ii) reactions (3) which result in cleavage of the thiazole ring with formation of various derivatives of the unsaturated thiol. The arrows with attached numerals in the above formula show the direction of attack of reagents in the various processes.

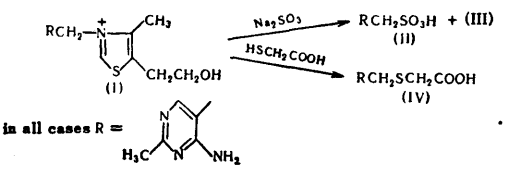
A recent X-ray analysis of thiamine chloride has established interesting peculiarities in the spatial structure of the vitamin. The accompanying diagram shows a projection of a three-dimensional model. The planes of the pyrimidine and thiazolium rings are at an angle of 76° to one another. As a result of this relative arrangement of the rings, position 2 in the thiazole ring is not shielded by the amino-group.

II. REACTIONS NOT INVOLVING CLEAVAGE OF THE THIAZOLIUM RING

1. Sulphite Cleavage of Thiamine

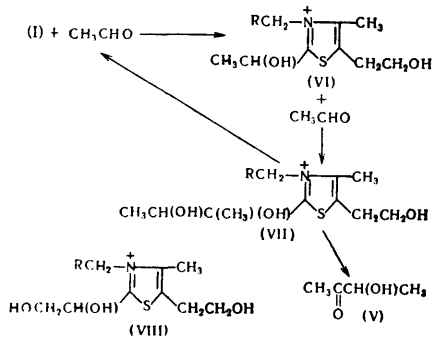
Sulphite cleavage of thiamine (I) leads to the formation of 4-amino-2-methylpyrimidin-5-ylmethanesulphonic acid (II) and 2-(4-methylthiazol-5-yl)ethanol (III). A recent reinvestigation of this reaction[2] has shown it to be specific to thiamine derivatives containing a quaternary nitrogen atom. Thus cleavage of the vitamin is not observed in strongly alkaline solutions, in which thiamine exists in the thiol form. In concentrated solution hydrogenated derivatives of thiamine (containing a tertiary nitrogen atom in the thiazoline ring) also are not cleaved. In dilute solutions they are oxidised to thiamine, after which the usual cleavage of the vitamin takes place.

Reaction with thioglycollic acid also results in the degradation of thiamine, with the formation of a pyrimidinylmethyl sulphide (IV) and the substituted thiazole (III):[3]



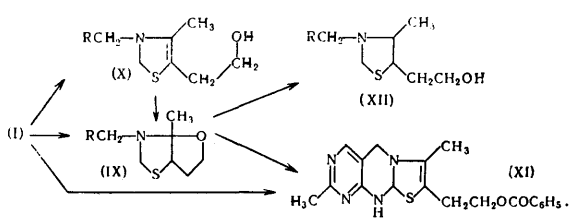
2. Reactions of Thiamine with Carbonyl Compounds

The interaction of thiamine with carbonyl compounds represents a typical electrophilic substitution. Investigation of this reaction has established the role of thiazolium derivatives as natural catalysts for aldol condensations. Mizuhara[4] was the first to observe that acetoin (V) is formed when thiamine is treated with pyruvic acid in weakly alkaline medium (pH 8.5). Condensation of thiamine with acetaldehyde under these conditions results in "α-hydroxyethylthiamine" (VI), in which the hydroxyethyl group has been added at position 2 of the thiazole ring. Another compound is also formed, and is found to have the structure of an "acetointhiamine" (VII).[5] Thus the formation of acetoin from acetaldehyde in non-enzymatic processes involves the following reactions:



The reaction is general in character[5], formaldehyde under these conditions giving a dihydroxyethyl derivative of thiamine (VIII). The analogous reactions with hydroxyacetaldehyde and hydroxypyruvic acid result in the formation of mixtures of sugars.

3. Hydrogenation of Thiamine

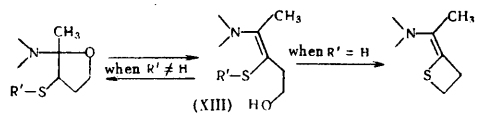


Investigation of the properties of dihydrothiamine, which is formed by the hydrogenation of thiamine[10], has shown that in fact it has the structure of a perhydrofurothiazole[6] (IX), as has been confirmed by comparing the infrared spectra of dihydrothiamine with those of substances possessing an analogous structure. Only very cautious reduction of thiamine with sodium hydrotrimethoxyborate gave the isomeric dihydrothiamine (X), in which closure of the hydrogenated furan ring could be effected simply by heating in water[7]. In addition to these substances, hydrogenation also yields a pseudodihydrothiamine, which has been found to be a pyrimido[4,5-*d*]thiazolo[3,4-*a*]pyrimidine[8]. Benzoylation of dihydrothiamine in pyridine yields the benzoate of the pseudo-form (XI).[11] Reduction of thiamine and of dihydrothiamine with sodium tetrahydroborate gives tetrahydrothiamine (XII).[9]

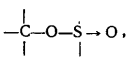
III. REACTIONS RESULTING IN CLEAVAGE OF THE THIAZOLIUM RING

1. Inactive Thiamine; Formation of Thiamine Anhydride

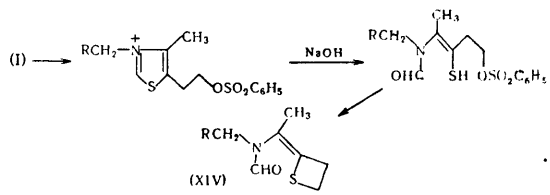
Thiamine is hydrolysed in alkaline media to thiol forms of the vitamin, which are derivatives of an unsaturated thiol. The properties of these derivatives are determined by the specific atomic grouping (XIII) present in all these compounds:



This grouping is liable to undergo various rearrangements, which occur under mild conditions. When the second valency of the sulphur forms part of a thiazole ring, ready closure of a perhydrofurothiazole ring is observed (as occurs with dihydrothiamine); if, however, a thiol group is adjacent to the double bond, dehydration to a thietan occurs. Formation of the four-membered ring is facilitated in arenesulphonic esters of thiamine, in which the atomic grouping

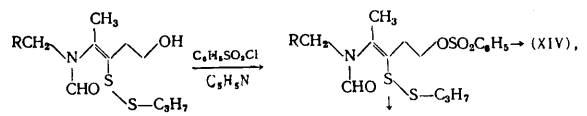


is readily broken between carbon and oxygen atoms. Therefore, in contrast to the monophosphoric ester of thiamine, the substituted sulphonates are extremely unstable, and in alkaline media undergo fundamental and irreversible changes. In alkaline solution thiamine is inactivated after the addition of only 1–3 drops of benzenesulphonyl chloride.[12] It has now been found that such treatment of the vitamin involves formation of a substance having the empirical formula $C_{12}H_{16}ON_4S$. This compound is not converted back into thiamine by cysteine, and hence does not contain a disulphide bond. It has the structure of an anhydride of the thiol form of the vitamin (XIV),[13] and has been called thiamine anhydride:



Thiamine anhydride, and also the corresponding sulphone formed by its oxidation with hydrogen peroxide, have practically no biological activity[14].

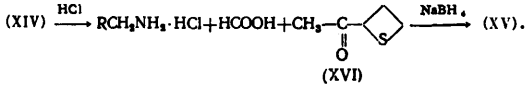
Careful treatment of thiamine chloride, or of alkyl thiamine disulphides in pyridine in the cold, with alkanesulphonyl or arenesulphonyl chlorides yields the corresponding sulphonates of the thiamine disulphides[15]:



which in alkaline alcoholic media are converted into thiamine anhydride (XIV).

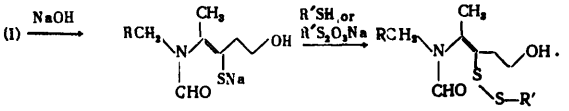
In order to elucidate the mechanism of this reaction, a study has been made of the behaviour of the benzenesulphonates of thiamine and thiamine disulphide in alkaline media. The former ester was found to be converted into thiamine anhydride even at pH 8, whereas more concentrated alkali is required for decomposition of the latter[16]. Treatment of β-deoxy-β-chloroethylthiamine with aqueous alkali gives the same result[17].

The thietan ring with the substituted *endo*-ethylene group is fairly stable: hydrolysis of thiamine anhydride with hydrochloric acid yields methyl 2-thietanyl ketone (XVI) which is reduced with sodium tetrahydroborate to 1-2′-thietanylethanol (XV):[18]

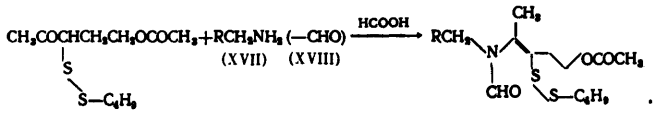


2. Unsymmetrical Disulphides of Thiamine

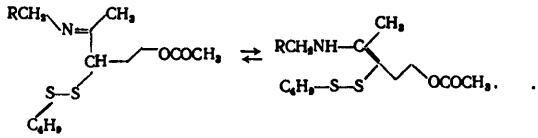
One of the most important reactions of the thiol form of vitamin B_1 is the formation of disulphide derivatives of thiamine. Treatment of thiamine with alkane-, arene-, and aralkane-thiols and with organic thiosulphates yields the corresponding alkyl, aryl, and aralkyl thiamine disulphides, which show vitamin activity[19]:



Another method of synthesising unsymmetrical thiamine disulphides consists in the condensation of 3-acetyl-3-butyldithiopropyl acetate with 4-amino-5-aminomethyl-2-methylpyrimidine (XVII) or its formyl derivative (XVIII), and treatment of the product with formic acid[20]:



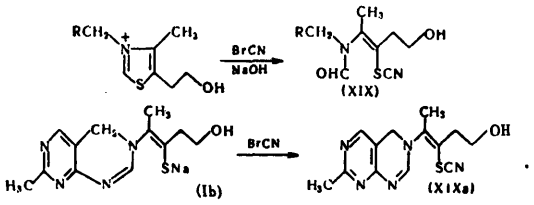
The above synthesis implies as a probable intermediate stage the tautomeric change:



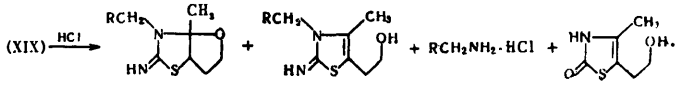
Alkylation of thiamine mononitrate with triphenylmethyl chloride and with derivatives of benzyl chloride yields benzyl thiamine sulphides[21].

3. Cyanothiamine and Its Reactions

The action on thiamine of cyanogen bromide in alkaline solution produces fundamental changes in the vitamin, the thiazole ring undergoing cleavage with formation of the so-called "cyanothiamine" (XIX),[22,26] which represents a new fat-soluble form of thiamine.[23] Also, the cyclic thiol of vitamin B_1 (Ib) is converted[24] by cyanogen bromide into the corresponding thiocyanate, which is termed "neocyanothiamine" (XIXa). This reaction has been investigated in detail, the influence of various substituents being studied, and has been shown to be fairly general for thiazolium salts containing various substituents in positions 3, 4, and 5:

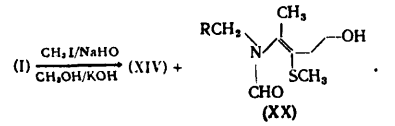


Hydrolysis of the unsaturated thiocyanate formed from 3-benzyl-5-2′-hydroxyethyl-4-methylthiazolium yields 3-benzyl-5,6,7,8-tetrahydro-2-imino-8-methylfuro[2,3-*d*]-thiazole, which has been isolated as the picrate. Similar treatment of "cyanothiamine" (XIX) produces a mixture of various compounds[25]:

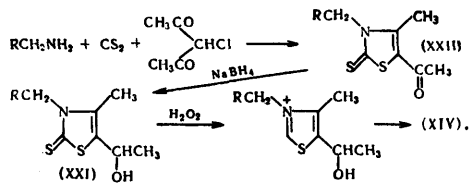


Heating "cyanothiamine" (XIX) with organic acids also results in cleavage with formation of a mixture of various acylated products[25]. Boiling (XIX) in butanol gives thiamine anhydride (XIV).[22]

A subsequent detailed investigation[27] of the inactivation of "cyanothiamine" (XIX) and its conversion into thiamine anhydride (XIV) has shown that methanolic alkali also effects this change, an *S*-methyl derivative of the B_1 thiol (XX) separating at the same time. This latter compound has been obtained also by the action of methyl iodide on the vitamin in alkaline solution, as well as by treatment with methanolic caustic potash:



It is interesting that the position of the hydroxyl in the hydroxyethyl group is of no significance for the formation of thiamine anhydride. The latter (XIV) is formed also from the 5-1′-hydroxyethylthiamine (XXI), which has been obtained from the corresponding 5-acetylthiazoline-2--thione (XXII):[27]



The presence of sulphur adjacent to the double bond is a necessary condition for the formation of a thietan ring.

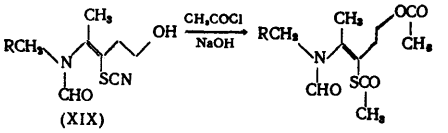
Thus, like other alkyl thiocyanates, 2-thiocyanatopentan-3-ol in methanolic alkali[27] merely yields disulphides[28]:

$$CH_3CH(SCN)CH_2CH(OH)CH_3 \rightarrow [CH_3CH(OH)CH_2CH(CH_3)-S-]_2.$$

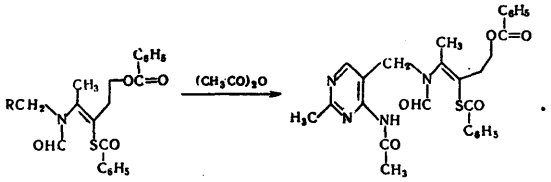
IV. ACYLATION OF THIAMINE AND ITS DERIVATIVES

Many *S*-acyl derivatives — *p*-nitrobenzoyl, *p*-chlorobenzoyl, *p*-toluoyl, phenylacetyl, cinnamoyl, furoyl, furylacryloyl, thenoyl, and butyryl — have been obtained by the acylation of thiamine *O*-monophosphate[29]. Dihydropyran acts on *S*-aroylthiamines to give ethers of the vitamin, *S*-aroyl-*O*-tetrahydropyranylthiamines[21].

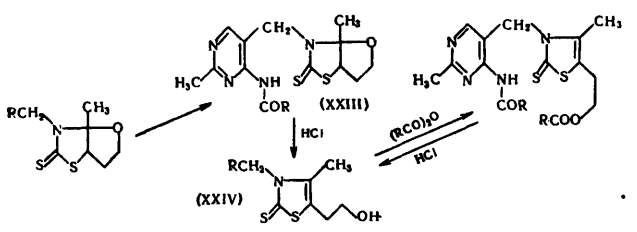
Acylation of "cyanothiamine" (XIX) with acid chlorides yields *OS*-diacylthiamines[30]:



The stability of the *S*-acyl derivatives of thiamine depends on the acidity of the medium and the nature of the acyl group. When *S*-benzoylthiamine is heated in an acid medium, migration of the benzoyl group is observed with formation of *O*-benzoylthiamine. This reaction goes better at pH 5. Aliphatic *S*-acylthiamines are less stable than the aromatic and heterocyclic derivatives, which may be explained by the inductive and steric effects of acylthiamines[31]. Acylation of *OS*-dibenzoylthiamine and *OS*-diacetylthiamine with acetic anhydride yields *N*-acetyl-*OS*-dibenzoylthiamine and *NOS*-triacetylthiamine respectively[32]. Other *N*-acyl derivatives have been obtained in a similar manner[33]. On the other hand, treatment of *S*-benzoylthiamine with succinyl anhydride has given *S*-benzoyl-*O*-succinylthiamine[34].

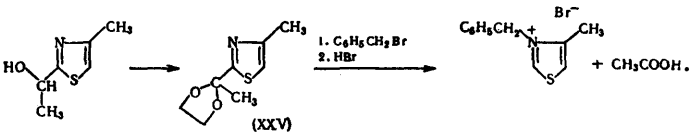


A study has been made of the acylation of one of the most important intermediates in the synthesis of thiamine, the 3-pyrimidinylmethylthiazoline-2-thione or so-called "thiothiamine" (XXIV).[35] However, such reactions cannot be used for the synthesis of biologically important *N*-acylthiamines, since *N*-acylthiazolinethiones are readily hydrolysed by dilute acid. Acyl derivatives of perhydrofurothiazolethione (XXIII) are equally readily hydrolysed by acids, the tetrahydrofuran ring being at the same time cleaved with the formation of "thiothiamine" (XXIV):



Nevertheless, the diethyl and diphenyl phosphates formed by the phosphorylation of "thiothiamine" (XXIV) are resistant to the action of hydrogen peroxide, and are readily converted into the corresponding substituted phosphates of thiamine[36]. It has also proved possible to phosphorylate *S*-benzoylthiamine, with the resulting synthesis of *S*-benzoylthiamine *O*-phosphoromorpholidates[37].

C_2-Acyl derivatives of thiamine have not yet been obtained owing to their instability[38]. Oxidation of 2-1′-hydroxyethyl-4-methylthiazole has given 2-acetyl-4-methylthiazole in the form of a dioxolan derivative (XXV), which is converted by benzylation and hydrolysis into 3-benzyl-4-methylthiazolium bromide:



In another case the extraordinarily unstable 2-acetyl-3,4-dimethylthiazolium system was obtained. 2-Benzoyl-3,4-dimethylthiazolium iodide, prepared from 2-benzoyl-4-methylthiazole and methyl iodide in dimethylformamide, decomposed into methyl benzoate and 3,4-dimethylthiazolium iodide on dissolution in methanol.

2-Benzoyl-3,4-dimethylthiazolium iodide was found to have a very high free energy of hydrolysis[39]. The value calculated for 2-acetylthiamine phosphate places this compound among other classic phosphates (ATP, etc.), while the presence of a labile bond in position 2 of 2-acylthiazolium allows us to speak of a new type of "high-energy bond".

V. THIAMINE–PROTEIN COMPLEXES

Thiamine forms stable complexes with several proteins, for example by precipitation on casein[40]. Ovalbumin and denatured milk protein with thiamine disulphide form thiamine itself and undialysable protein–thiamine complexes[41] having 90% of the activity of the vitamin.

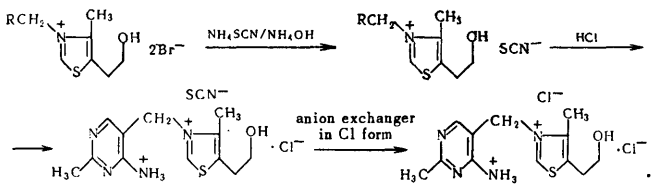
Further work has shown[42] that this complex has a disulphide structure, since the vitamin is liberated on treatment with cysteine or sodium thiosulphate.

The protein of soya-bean oil firmly retains thiamine after being frozen and then allowed to melt again[43]. The adsorption of various derivatives of thiamine — the hydrochloride, nitrate, thiocyanate, dihexadecyl sulphate, and dibenzoate — has been investigated. They are all found to combine firmly with the protein, and have been isolated after treatment with proteinase and Taka-Diastase and after acid hydrolysis of the adsorbate. After denaturation of a protein, its capacity for adsorption is affected by hydroxylamine solution; mercury *p*-chlorobenzoate does not affect this property. Hence it is concluded that the active centre in a protein which is responsible for combination with thiamine contains a carbonyl group. It is noteworthy that thiamine diphosphate also forms a quite stable complex with an apoenzyme. Although the affinity of thiamine diphosphate for carboxylase is 3.3×10^{-6}, the enzyme dissociates very slowly[4]. No other quantitative data have been published to characterise the bond between thiamine and a protein.

VI. DERIVATIVES OF THIAMINE

1. Salts and Esters of Thiamine

Much work has been done during recent years on the synthesis of various salts and derivatives of thiamine[44-60], and tens of derivatives of vitamin B_1 have been described, including various halides. Monosalts, including thiamine mononitrate, which has been extensively used in clinical practice[44], have been obtained by partial neutralisation to pH 6 of the chloride of thiamine hydrochloride, the so-called thiamine chloride, followed by salting out with appropriate salts. The mononitrate, together with other salts, can also be obtained by an ion-exchange method[61]. Thiamine bromide hydrobromide is first converted into thiamine thiocyanate by treatment with ammonium thiocyanate in ammonium hydroxide, and the product is dissolved in hydrochloric acid and passed through an anion-exchanger:



Chlorides and other salts of thiamine are obtained in this way.

A method has been described for converting vitamin B_1 bromide hydrobromide into the hydrochloride of the chloride which is based on the greater volatility of the alkyl bromides produced on treatment of the former with anhydrous hydrogen chloride in the lower aliphatic alcohols[62].

The hydrochlorides of thiamine bromide and iodide have been prepared by the action of concentrated hydrochloric acid on the thiamine halides followed by precipitation with acetone[52]. The sulphate[47] and also various alkane- and arene-sulphonates of thiamine[48-51] have been synthesised and studied. Thiamine sulphate has been obtained by treatment of the hydrochloride with chlorosulphuric acid[47].

Most of the substituted sulphonates are sparingly soluble in water. The following salts of thiamine have been prepared: the cyclohexylmethanesulphonate, mesitylenesulphonate, diphenylmethane-*pp'*-disulphonate, 2,2-diphenylpropane-*pp'*-disulphonate, 2,2-dibenzylpropane-*pp'*-disulphonate, 2,2',4,4',6,6'-hexamethylbiphenyl-3,3'-disulphonate, and naphthalene-1,5- and -2,6-disulphonates[54].

The salts formed by thiamine and dibenzylthiamine with cyclohexylsulphamic acid are fairly stable[51].

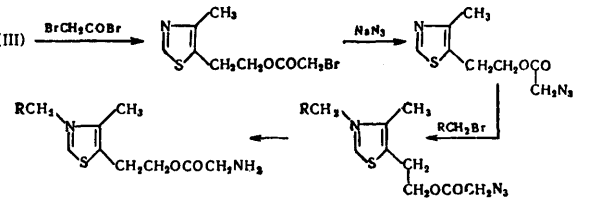
Thiamine di(hexadecylsulphonate), which is sparingly soluble in water, is more stable than thiamine chloride on heating, and can be successfully used for addition of the vitamin to bread and other foodstuffs.

Salts — the sulphate, fumarate, nitrate, chloride, bromide, iodide, oxalate, saccharinate, and di(hexadecylsulphonate) — have also been obtained by double decomposition of the Eosin–vitamin B_1 complex with the corresponding acids[53].

Various salts of thiamine with organic acids have been prepared — the monosaccharinate[57], disaccharinate[63], tannate[58], salicylate and various of its derivatives[59], and glycyrrhizate (the acid has been isolated from *Glycyrrhiza uralensis*[56]) — as well as thiamine derivatives of gibberellin[64], the dodecyl phosphate[45], and other salts such as the tetraphenylborate[46]. A coloured salt of thiamine with an acid sulphopyrazoline azo dye has been prepared[60].

Various esters of the hydrobromide and the hydrochloride of thiamine have been prepared — the octanoic, lauric, myristic, palmitic, stearic, succinic, and phthalic esters[65]. Animals readily assimilate them, especially the palmitic ester[17].

Attempts to prepare amino-acid and carbohydrate derivatives of thiamine are also of great interest. From 2-(4-methylthiazol-5-yl)ethyl azidoacetate and 4-amino-5-bromomethyl-2-methylpyrimidine has been obtained thiamine azidoacetate, reduction of which gives thiamine glycinate. Its phenylacetates have been synthesised in a similar manner[66].



Thiamine *S*-β-D-glucoside has been synthesised from *O*-benzoylthiamine hydrochloride and bromoacetyl-α-glucose[67].

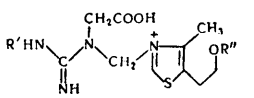
2. Derivatives of the Thiol Form of Thiamine

During recent years reports have appeared on the production of new types of vitamin B_1 preparations which are derivatives of the thiol form of thiamine. Several tens of unsymmetrical disulphides have been synthesised[68-76]. Among these, Japanese investigators have suggested as new vitamin preparations — propyl thiamine disulphide (a structural analogue of allylthiamine), tetrahydrofurfuryl thiamine disulphide, and also 8-(methyl 6-acetyldihydrothiooctanoate)thiamine disulphide[68]. These compounds have been synthesised by the methods described above.

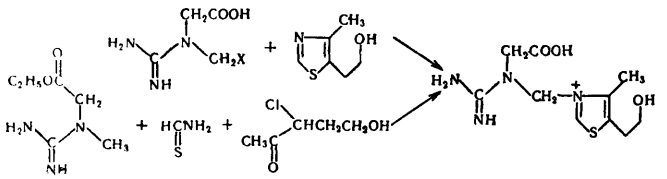
An effective new preparation, *S*-benzoylthiamine-*O*-monophosphoric ester of "cyanothiamine" (XIX).[30] Treatment of (XIX) and its *O*-benzoyl derivative with thiols yields the corresponding thiamine disulphides[75]. It has been established that allyl and propyl thiamine disulphides, *OS*-diacetylthiamine, and *OS*-dibenzoylthiamine are absorbed in the intestine more readily than is thiamine chloride, while propyl thiamine disulphide is able to maintain the highest vitamin B_1 level in the blood[77].

3. New Natural Compounds Closely Related to Thiamine

Two natural products have recently been isolated from Japanese garlic[78]. They resemble thiamine in their action, and have been termed scordinines A and B. They both contain what has been termed a thiamidine grouping



Like vitamin B_1, the scordinines contain thiazole rings, but the pyrimidine moiety has been replaced by a creatine grouping. The basic structure of the scordinines has been synthesised in two ways:

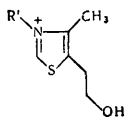


The two compounds differ only in the substituents R′ and R″, the structure of which has not been precisely established. It is known only that scordinine A, which is formed in garlic after several months of storage, contains a phosphatide.

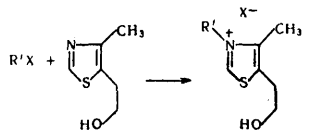
A new group of unsymmetrical pyrophosphates has been discovered, among them a thiamine diphosphate–3-acetamido-3,6-dideoxyhexose, which like the nucleoside sugar diphosphates, acts as a donor of glycosidic residues in the biosynthesis of the exopolysaccharide of *Xanthomons campestris* [79].

4. Analogues of Thiamine

Investigation of the relation between structure and biological activity in thiamine derivatives long ago led to the synthesis of pyrithiamine and other substances possessing the properties of antivitamins. The systematic synthesis of various analogues of thiamine allowed several links to be noted between structure and biological activity. In all cases the analogues were built up according to the principle of so-called "isosteric inhibition", the synthesised analogue of general formula

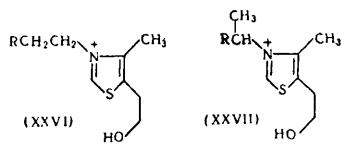


being similar in volume and configuration to the natural vitamin. In this way changes were introduced into the pyrimidine portion of the molecule. All these analogues were usually synthesised by the reaction



where R′ is a heterocyclic radical.

2-Trifluoromethylthiamine proved to be a vitamin inhibitor and possessed interesting biological properties [80]. For example, it suppressed the development of leukaemia and the growth of a transplanted carcinoma in mice on a diet deficient in vitamin B_1.

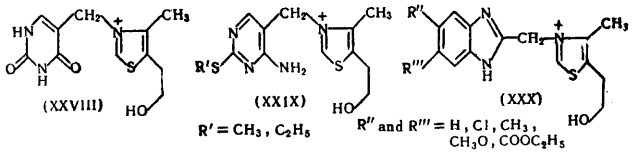


Investigation of the catalytic properties of the synthetic thiamine homologues (XXVI) and (XXVII) on a model system reproducing the synthesis of acetoin (V) showed that the former has 67%, and the latter (XXVII) 5%, of the activity of thiamine [81]. None of the homologues possessed vitamin activity in microbiological tests with *Kloeckera brevis*.

6-Methylthiamine had about one-third of the activity of thiamine [82], while other results gave its activity as 18% of the latter [83].

A study of derivatives of vitamin B_1 in which the 2-methyl group had been replaced by ethyl, methoxymethyl, 2′-ethoxyethyl, phenoxymethyl, and 1′-bromoethyl groups showed most of them to be inactive in reactions involving decarboxylation. The only exceptions were 2′-ethoxyethylthiamine, whose activity in the decarboxylase reaction was low, and methoxymethylthiamine, which behaved as an antivitamin [84].

Heterocyclic analogues of thiamine have been synthesised — 3-(1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-ylmethyl)thiazolium [85] (XXVIII) derivatives, alkylthiopyrimidine analogues such as Methioprim (XXIX), [86] and also benzimidazole [87] analogues (XXX):



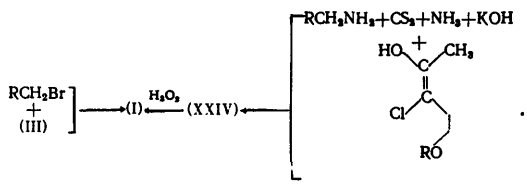
It must be noted that the synthesis of analogues on the principle of isosteric inhibition, which in many cases has proved so effective in the search for drugs, has not yet given any practical result in the thiamine field. This is primarily an indication of the highly specific chemical structure of the vitamin.

Nevertheless, the discovery of the natural antibiotic bacimethrin (from *Bacillus megaterium*), which is active against yeasts and bacteria, and the establishment of its structure as identical with 4-amino-5-hydroxymethyl-2-methoxypyrimidine [88], give grounds for hoping that practical advances may be expected in this field too.

VII. DEVELOPMENT OF INDUSTRIAL METHODS FOR SYNTHESISING VITAMIN B_1

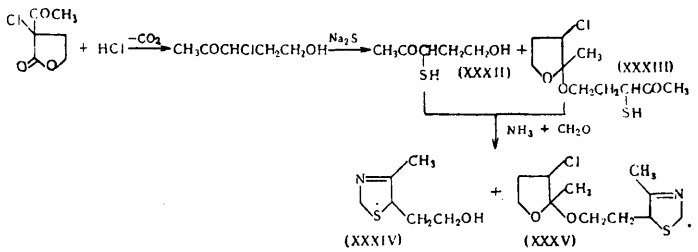
Various syntheses of thiamine have already been described in detail [89]. Two main processes are used in various countries for the production of vitamin B_1 — (i) from 5-bromomethylpyrimidine and 5-2′-hydroxyethyl-4-methylthiazole and (ii) *via* 3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-2′-hydroxyethyl-4-methylthiazole-2-thione (XXIV) (the so-called "thiothiamine"). The history of the appearance of the second industrial method for synthesising vitamin B_1 in Japan is linked with the struggle between Japanese and American pharmaceutical firms for the market. Although the large-scale production of vitamin B_1 has been organised in the USSR too, no final choice has yet been made of a particular method of synthesis. New

research on the synthesis of this vitamin is developing these two traditional processes.

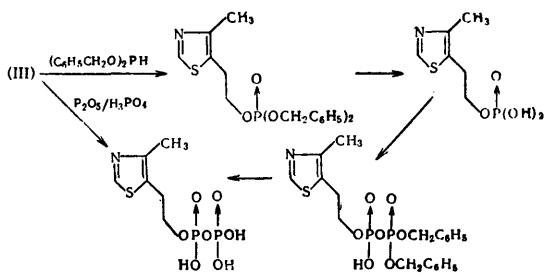


1. Synthesis from 5-2′-Hydroxyethyl-4-methylthiazole

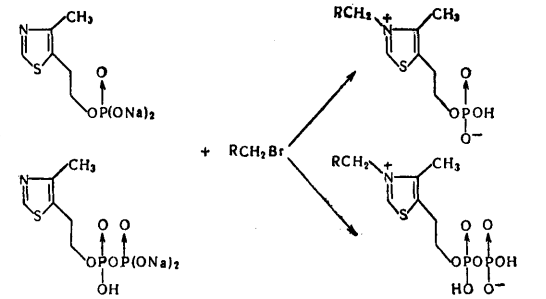
In a new method of synthesising the thiazole component of thiamine[90], α-acetyl-α-chloro-γ-butyrolactone is treated with concentrated hydrochloric acid to give 3-chloro-5-hydroxypentan-2-one, which with alcoholic sodium sulphide solution yields a mixture of 5-hydroxy-3-mercaptopentan--2-one (XXXII) and 5-(3-chlorotetrahydro-2-methylfur--2-yloxy)-3-mercaptopentan-2-one (XXXIII). Treatment of this mixture with paraformaldehyde and ammonia together with hexamethylenetetramine gives a mixture of 2-(4-methyl-Δ^3-thiazolin-5-yl)ethanol (XXXIV) and the corresponding tetrahydrofuryl ether (XXXV):



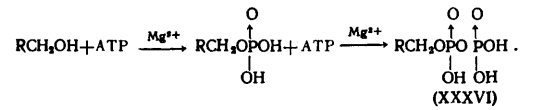
A new method has recently been described for obtaining thiamine phosphates[92], which supplements the well-known processes consisting essentially in treating thiamine with pyrophosphoric acid and then separating the phosphorylation products on chromatographic columns[91] to obtain the monophosphate and the diphosphate (TMP and TDP). 2-(4-Methylthiazol-5-yl)ethanol (III) is first phosphorylated in various ways:



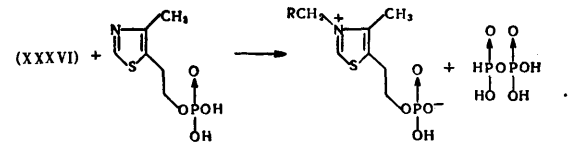
and the resulting monophosphoric and diphosphoric esters of thiazolylethanol are condensed with 4-amino-5-bromomethyl-2-methylpyrimidine to give high yields of TMP and TDP:



This method of synthesising thiamine phosphates resembles the biosynthesis of thiamine in many microorganisms. An enzyme present in cell-free extracts of yeasts has been found to catalyse condensation of the pyrimidine and thiazole moieties of thiamine[93]. This enzyme is activated by ATP. It is accepted[94] that the principal intermediate in the biosynthesis of thiamine is 5-(4-amino--2-methylpyrimidin-5-yl)methyl diphosphate (XXXVI). The main mechanism in the biosynthesis of thiamine involving this compound is represented by the following sequence of reactions: 4-amino-5-hydroxymethyl-2-methylpyrimidine is phosphorylated twice by means of ATP:



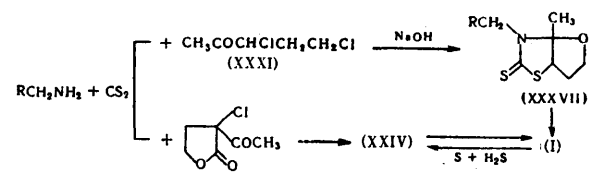
The resulting diphosphate reacts with the thiazolylethyl monophosphate, which itself has been formed by the phosphorylation of 2-(4-methylthiazol-5-yl)ethanol. This reaction yields TMP, and hydrolysis of the phosphoric ester bond yields thiamine:



Several methods of synthesising ^{35}S-labelled thiamine have been described which represent repetitions of various previously known processes[95,96].

2. Synthesis of Vitamin B_1 *via* "Thiothiamine"

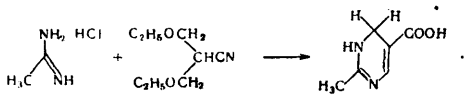
Various methods have been described for obtaining the thiazolinethione "thiothiamine" (XXIV).[97] Condensation of 4-amino-5-aminomethyl-2-methylpyrimidine (XVII) and carbon disulphide with 3,5-dichloropentan-2-one (XXXI) leads to the formation of 3-(4-amino-2-methylpyrimidin--5-yl)methyl-2,3,7,8-tetrahydro-4-methylfuro[2,3-*d*]thiazolidine-2-thione (XXXVII), oxidation of which gives thiamine[98,99]:



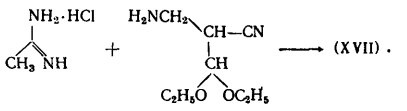
Treatment of "thiothiamine" (XXIV) with hydrogen peroxide in the presence of carbonates of the alkaline earth metals[100] leads to the formation of monosalts of thiamine — the monochloride, monoiodide, mononitrate, and monothiocyanate.

The conversion of "thiothiamine" into thiamine is reversible: if thiamine is heated with sulphur or with hydrogen sulphide, "thiothiamine" is formed[101].

In the subsequent improvement of the method of synthesis *via* "thiothiamine", great attention has been paid to various alternative syntheses of 4-amino-5-aminomethyl--2-methylpyrimidine (XVII) from derivatives of β-alkoxy- or β-amino-propionitriles. Bisethoxymethylacetonitrile reacts with acetamidine to form 3,4-dihydro-2-methylpyrimidine-5-carboxylic acid[102]:



The pyrimidine (XVII) has been obtained in about 60% yield from α-aminomethyl-ββ-diethoxypropionitrile and acetamidine[103]:



A similar result has been obtained by heating β-acetoxy--α-ethoxymethylenepropionitrile with acetamidine in an autoclave at 140–150°, and hydrolysing the product with a 10% solution of alkali[104].

VIII. MECHANISM OF THE ACTION OF VITAMIN B_1

Study of the reactions of thiamine with aldehydes and keto-acids has revealed very important new properties of the vitamin. Thiamine and its phosphoric esters can effectively catalyse reactions of the aldol condensation type. These observations have finally enabled the mechanism of the biological action of vitamin B_1 to be understood.

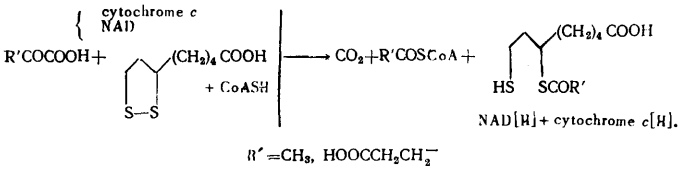
In the organism thiamine undergoes phosphorylation, and in the form of the diphosphoric ester takes part in many biocatalytic processes. Thiamine pyrophosphate — or more correctly thiamine diphosphate (TDP) — forms part of many enzymes, in which it acts as prosthetic group or coenzyme, being quite firmly combined with the apoenzyme, a protein[105].

More than ten different enzymes are now known in which TDP has been shown to act as coenzyme[106], among them being enzymes or enzyme systems which effect the decarboxylation of pyruvic acid or other keto-acids, as well as enzymes which catalyse metabolic reactions of carbohydrates of the aldol synthesis or reverse aldol type. They include:

(1) α-Carboxylase, which effects the decarboxylation of α-keto-acids to the corresponding aldehydes and carbon dioxide:



(2) Various pyruvic acid and α-ketoglutaric acid dehydrogenases (oxidases), whose effect is to decarboxylate and oxidise these substrates. The role of acceptors of hydrogen and acyl groups (the role of cosubstrates and oxidation coenzymes) in these reactions is filled by lipoic acid, nicotinamide-adenine dinucleotide (NAD), cytochrome *c*, and coenzyme A:



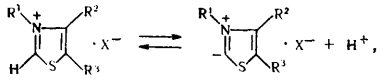
(3) A group of enzymes which effect reactions that are the reverse of the aldol condensation, for example phosphoketolase.

(4) Enzymes which catalyse aldol synthesis, among them being a transketolase from yeasts, which effects the formation of sedoheptulose 7-phosphate and glyceraldehyde 3-phosphate from xylulose 5-phosphate and ribose 5-phosphate. This group of enzymes includes an acetoin-forming complex from *Aerobacter aerogens* and a glyoxylic acid carboligase.

Although the participation of TDP in decarboxylation and other reactions of α-keto-acids has now been known for more than a quarter of a century[107,108], its mechanism remained obscure until recently. Many different hypotheses were put forward, supported to varying extents by chemical models, but none of them received experimental confirmation in the study of biological systems.

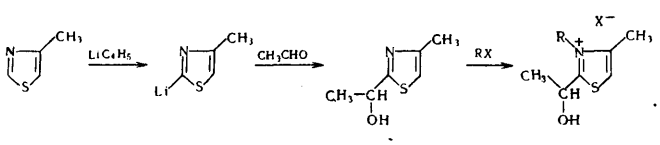
Breslow[109] has suggested a model general mechanism for the action of thiamine which combines two processes, decarboxylation of the keto-acid and an acyloin condensation. The role of cyanide, which catalyses the acyloin condensation, is to form a reactive intermediate carbanion with the aldehyde, which in turn reacts with a second molecule of the aldehyde to give the acyloin.

Thiazolium derivatives also are capable[110] of giving reactive intermediate carbanions, to which pyruvic acid adds on readily. Study of the isotopic exchange of deuterium with thiazolium has shown the existence of the tautomeric equilibrium[111]

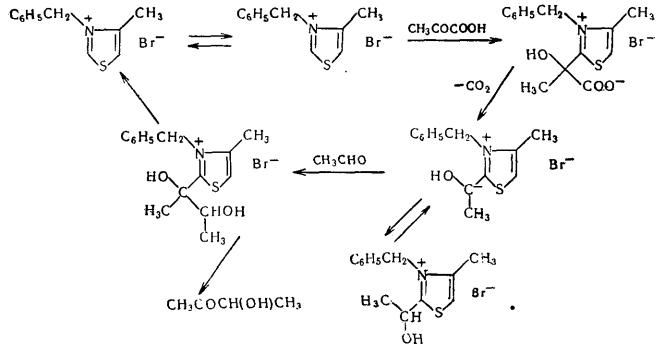


since 3,4-dimethylthiazolium and 3-benzyl-4-methylthiazolium bromides readily exchange hydrogen in position 2 of the thiazolium ring for deuterium in heavy water. The carbanion readily adds on pyruvic acid, the mechanism of this reaction being analogous to the first stage in the acyloin condensation. Decarboxylation yields the intermediate 1-thiazol-2′-ylethanol.

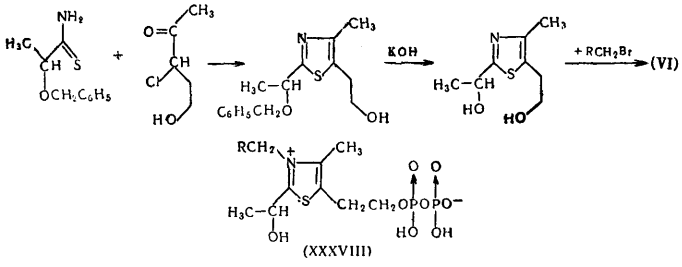
Such derivatives have been prepared by an independent method[112] involving organolithium compounds:



3-Benzyl-2-1′-hydroxyethyl-4-methylthiazolium bromide has been prepared in this way and proves to be an active catalyst for the synthesis of acetoin from pyruvic acid. The mechanism of this reaction has been represented by the scheme



The benzyl group has been found to play an important part, since 2-1′-hydroxyethyl-3,4-dimethylthiazolium bromide possesses far weaker catalytic properties. This view is supported by the observation that, at 25° and pH 5.37, deuterium exchange is three times as rapid with the 3-benzyl derivative than with the 3-methylthiazolium salt. This observation throws light on the role of the pyrimidine moiety of thiamine: it is obviously necessary to produce the electronic interaction which will facilitate formation of the carbanion. The great effectiveness of thiamine is thus explained by the greater electrophilic effect of the pyrimidinyl than of the phenyl group. "2-Hydroxyethylthiamine", *i.e.* the hydrochloride of DL-3-(4-amino-2-methylpyrimidin-5-yl)-methyl-2-1′-hydroxyethyl-5-2″-hydroxyethyl-4-methylthiazolium chloride[112], possesses similar properties, and replaces thiamine in the growth of microorganisms on nutrient media. Its synthesis leaves no doubt that the hydroxyethyl group is located at position 2 in the thiazole ring:

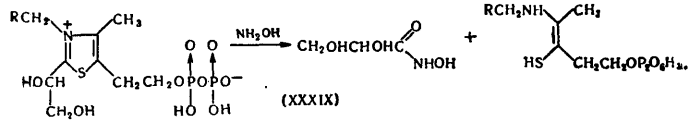


From a mixture of TDP and acetaldehyde was then isolated "2-1′-hydroxyethylthiamine diphosphate" (XXXVIII).[5] Labelled (XXXVIII) was prepared from acetaldehyde labelled at both carbon atoms, and was used subsequently in biochemical investigations. This compound was found to fill the role of "active acetaldehyde", the existence of which had been suggested previously.

Labelled 2-1′-hydroxyethyl-TDP has been shown[5] to be an intermediate in the formation of acetaldehyde by wheat-germ carboxylase, in the formation of acetoin by enzyme preparations obtained from *Aerobacter aerogens*, and in the formation of acetate by an artificial system simulating pyruvic acid oxidase.

The use of labelled bishydroxyethyl-TDP (XXXIX), prepared from labelled formaldehyde and TDP as well as from hydroxypyruvic acid and TDP in the presence of heart-muscle pyruvate oxidase[113], in reactions with ribose 5-phosphate catalysed by baker's yeast transketolase has provided a demonstration, based on the presence of the tracer in the resulting sedoheptulose 7-phosphate, of the role of (XXXIX) as an active intermediate in this reaction too[115].

The structure of 2-dihydroxyethyl TDP, "active glycollaldehyde" (XXXIX) has been proved by the hydroxamic reaction[114]:



Elucidation of the role of hydroxyethyl derivatives of thiamine enables discussion of enzyme reactions involving TDP to be based on a single mechanism.

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Knowledge of the mechanism underlying the action of thiamine yet again confirms the remarkable fact that all biochemical processes have their analogues in non-enzymatic reactions of organic compounds, the laws of which remain in force for enzyme reactions too.

1. J.Kraut and H.J.Reed, Acta Cryst., 15, 747 (1962).
2. C.Kawasaki, T.Suhara, and T.Horio, Yakugaku Zasshi, 78, 65 (1958); Chem.Abs., 52, 11859 (1958).
3. G.E.Bonvicino and D.J.Hennessy, J.Org.Chem., 24, 451 (1959).
4. S.Mizuhara and P.Handler, J.Amer.Chem.Soc., 76, 571 (1954).
5. L.O.Krampitz, I.Suzuki, and G.Greull, Proceedings of the Fifth International Congress of Biochemistry (Moscow 1961), Vol.4, 1963, p.321.
6. T.Matsukawa, H.Hirano, T.Iwatsu, and Sh.Yurugi, J.Vitaminol.(Osaka), 3, 213 (1957); Chem.Abs., 52, 5423 (1958).
7. G.E.Bonvicino and D.J.Hennessy, J.Amer.Chem.Soc., 79, 6325 (1957).
8. T.Matsukawa, H.Hirano, T.Iwatsu, and Sh.Yurugi, J.Vitaminol.(Osaka), 3, 218 (1957).
9. H.Hirano, Yakugaku Zasshi, 78, 1387 (1958); Chem.Abs., 53, 8145 (1959).
10. T.Iwatzu, J.Pharm.Soc.Japan, 75, 677 (1955); Chem. Abs., 50, 3459 (1956).
11. Sh.Ioshida and M.Kataoka, Pharm.Bull.(Japan), 5, 320 (1957); Chem.Abs., 52, 14588 (1958).
12. C.Kawasaki and I.Tomita, Vitamins (Kyoto), 16, 324 (1959).
13. C.Kawasaki, I.Tomita, and T.Motoyama, Vitamins (Kyoto), 13, 57 (1957); Chem.Abs., 54, 4595 (1960).
14. T.Motoyama, Yakugaku Zasshi, 79, 115 (1959); Chem. Abs., 53, 8225 (1959).
15. C.Kawasaki and I.Tomita, Yakugaku Zasshi, 78, 1160 (1958); Chem.Abs., 53, 5273 (1959).

16. C.Kawasaki and I.Tomito, Yakugaku Zasshi, 79, 295 (1959); Chem.Abs., 53, 15 090 (1959).
17. H.Takagi, T.Wada, and S.Inada, Takamine Kenkyusho Nempo, 11, 144 (1959).
18. H.Yonemoto, Yakugaku Zasshi, 77, 1128 (1957).
19. M.Fujiwara, H.Watanabe, T.Matzukawa, S.Yurugi, T.Iwatsu, and H.Kawasaki, U.S.P. 2 833 768 (1958).
20. Jap.P. 4970 (1959); Chem.Abs., 51, 14 282 (1960).
21. N.Yoshida and Y.Nakamura, Takemine Kenkyusho Nempo, 13, 37 (1961).
22. H.Yonemoto, Yakugaku Zasshi, 78, 1391 (1958); Chem. Abs., 53, 8146 (1959).
23. H.Yonemoto, Jap.P. 9268 (1959); Chem.Abs., 54, 16 472 (1960).
24. S.Kasahara, Chem.Pharm.Bull.(Tokyo), 8, 340 (1960).
25. H.Yonemoto, Yakugaku Zasshi, 78, 472 (1958).
26. S.Kasahara, Yakugaku Zasshi, 77, 1133 (1957).
27. H.Yonemoto, Yakugaku Zasshi, 79, 143 (1959); Chem. Abs., 53, 13 168 (1959).
28. H.Yonemoto, Yakugaku Zasshi, 79, 717 (1959).
29. M.Nagawa, M.Kataoka, and T.Yoshioka, Takamine Kenkyusho Nempo, 13, 20 (1961).
30. M.Asai and T.Konotsune, Takamine Kenkyusho Nempo, 13, 45 (1961).
31. A.Ito, K.Okamoto, W.Hamanaka, and K.Kawada, Takamine Kenkyusho Nempo, 13, 48 (1961); Chem.Abs., 56, 8697 (1962).
32. S.Yoshida, M.Kataoka, and R.Takasaki, Jap.P. 973 (1957); Chem.Abs., 52, 4300 (1958).
33. S.Yoshida and M.Kataoka, Chem.Pharm.Bull.(Tokyo), 6, 576 (1958).
34. T.Yoshioka and H.Ito, Takamine Kenkyusho Nempo, 13, 35 (1961).
35. S.Yoshida and R.Takasaki, Chem.Pharm.Bull.(Tokyo), 6, 527 (1958); Chem.Abs., 53, 12 291 (1959).
36. M.Kataoka and H.Ito, Takamine Kenkyusho Nempo, 13, 24 (1961).
37. T.Yoshioka and M.Kataoka, Takamine Kenkyusho Nempo, 13, 28 (1961).
38. R.Breslow and E.McNelis, J.Amer.Chem.Soc., 82, 2394 (1960).
39. C.P.Nash, C.W.Olsen, F.G.White, and L.R.Ingraham, J.Amer.Chem.Soc., 83, 4106 (1961).
40. S.Tada and O.Nakayama, Jap.P. 1899 (1958); Chem.Abs., 53, 3613 (1959).
41. G.E.Bonivicino and D.J.Hennessy, Internat.Z.Vitaminforsch., 30, 97 (1959).
42. J.Utsumi, K.Harada, K.Kohno, and H.Hirao, Vitamins, 27, 135 (1963).
43. C.Inagaki, H.Fukuba, T.Miyakawa, and S.Iwata, J.Vitaminol., 6, 43 (1960); Chem.Abs., 54, 21 217 (1960).
44. A.Takamizawa, S.Nakajima, and H.Sato, Yakugaku Zasshi, 79, 399 (1959); Chem.Abs., 53, 16 139 (1959).
45. I.Utsumi, C.Kowacki, K.Harada, T.Baba, and T.Takeuchi, Jap.P. 96 (1959); Chem.Abs., 54, 6770 (1960).
46. I.Uchimi, N.Tanaka, and K.Harada, Jap.P. 3995 (1959); Chem.Abs., 1568 (1960).
47. Jap.P. 6726 (1959); Chem.Abs., 15 405 (1960).
48. K.Okumura and Y.Sakurai, Shokuryo Kenkyusho Kenkyu Hokoku, No.11, 65 (1956); Chem.Abs., 53, 11 551 (1959).
49. Jap.P. 2295 (1959); Chem.Abs., 21 132 (1960).
50. Ko Ito and K.Inami, Jap.P. 6991 (1958); Chem.Abs., 54, 2380 (1960).
51. K.Kawahara, Y.Hochi, and K.Tani, Jap.P. 3347 (1959); Chem.Abs., 54, 13 152 (1960).
52. A.Takami, N.Toluyama, S.Nakajima, S.Hayashi, and H.Sato, Jap.P. 699 (1961); Chem.Abs., 56, 7446 (1962).
53. R.Yamamoto and T.Takahashi, Jap.P. 2775 (1957); Chem. Abs., 52, 4700 (1958).
54. A.Ito and K.Tokutake, Takamine Kenkyujo Nempo, 8, 47 (1956); Chem.Abs., 52, 297 (1958).
55. Hirano Hiroshi, Jap.P. 11 044 (1960); Ref.Zhur.Khim., 19L157 (1962).
56. Yoshizo Noji, Jap.P. 9196 (1961); Ref.Zhur.Khim., 19L158 (1962).
57. R.Yamamoto and T.Takahashi, Jap.P. 3879 (1957); Chem. Abs., 52, 5757 (1958).
58. M.Yamagishi, Jap.P. 6447 (1956); Chem.Abs., 52, 8214 (1958).
59. Jap.P. 786 143 (1957); Chem.Abs., 59, 8213 (1958).
60. R.Yamamoto, M.Harada, and T.Takahashi, U.S.P. 2 820 786 (1958); Chem.Abs., 52, 10 219 (1958).
61. G.Leichssenring, German P. 11 163 (1956); Chem.Abs., 53, 1389 (1959).
62. W.E.Stieg, U.S.P. 2 833 769 (1958); Chem.Abs., 53, 1388 (1959).
63. R.Yamamoto and T.Takagashi, Jap.P. 4328 (1957); Chem. Abs., 52, 5758 (1958).
64. H.Hirano and H.Yonemoto, Jap.P. 16 479 (1960); Chem. Abs., 56, 3573 (1962).
65. M.Kataoka, S.Ioshida, and M.Nagawa, Takamine Kenkyusho Nempo, 13, 31 (1960); Chem.Abs., 55, 6488 (1961).
66. M.Nagawa, Y.Baba, and T.Yoshioka, Takamine Kenkyusho Nempo, 13, 31 (1961).
67. K.Marayama and S.Morimura, Takamine Kenkyusho Nempo, 13, 42 (1961).
68. M.Ohara, K.Mizukani, Y.Deguchi, K.Fujisaki, S.Ueda, and T.Sekiguchi, Vitamins, 27, 393 (1963).
69. H.Kawasaki and S.Nogushi, Jap.P. 3878 (1957); Chem. Abs., 52, 5757 (1958).
70. H.Kawasaki, T.Iwatsu, and S.Yurugi, Jap.P. 3877 (1957); Chem.Abs., 52, 5757 (1958).
71. S.Yurugi and H.Kawasaki, Jap.P. 8030 (1956); Chem. Abs., 52, 11 970 (1958).
72. S.Yoshida and R.Takasaki, Jap.P. 6132 (1957); Chem. Abs., 52, 11 968 (1958).
73. S.Yurugi and T.Fushimi, Yakugaku Zasshi, 78, 602 (1958); Chem.Abs., 52, 18 423 (1958).
74. S.Yamada, T.Fujita, and T.Mizoquchi, Jap.P. 1832 (1957); Chem.Abs., 52, 5487 (1958).
75. C.Yonemoto, Jap.P. 13 023 (1960); Ref.Zhur.Khim., 17L234 (1962).
76. T.Wada, H.Takagi, H.Minakami, W.Hamanaka, K.Okamoto, A.Ito, and I.Sahashi, Science, 134, 195 (1961).
77. A.Ichibagase, Hukuoka Igaku Zasshi, 48, 1413 (1957); Chem.Abs., 52, 7545 (1958).
78. K.Kominato, German P. 1 063 334 (1959); Chem.Abs., 55, 18 025 (1961).
79. W.A.Volk and G.Ashwell, Biochem.Biophys.Res.Comm., 12, 116 (1963).
80. J.A.Barone, H.Tieckelmann, R.Guthrie, and J.F.Holland, J.Org.Chem., 25, 24 (1960).
81. J.Biggs and P.Sykes, J.Chem.Soc., 1849 (1959).
82. M.Horuishi, Yakugaku Zasshi, 78, 1224 (1958); Chem. Abs., 53, 5272 (1959).
83. J.Biggs and P.Sykes, J.Chem.Soc., 2595 (1961).
84. T.Kusch and J.Heinrich, Z.physiol.Chem., 315, 177 (1959).
85. S.Yamada and K.Achiwa, Chem.Pharm.Bull.(Tokyo), 9, 119 (1961).
86. T.Okuda and C.C.Price, J.Org.Chem., 24, 14 (1959).
87. A.M.Grimaldi and A.R.Day, J.Org.Chem., 27, 227 (1962).
88. H.C.Koppel, R.H.Springer, R.K.Robins, and C.C.Cheng, J.Org.Chem., 27, 3614 (1962).
89. V.M.Berezovskii, "Khimiya Vitaminov" (The Chemistry of Vitamins), Pishchepromizdat, Moscow, 1959, p.415.

90. M.Thiel, F.Asinger, and W.Stengler, Annalen, 619, 161 (1958).
91. G.Serchi, Chimica e Industria, 30, 39 (1954).
92. G.Leichssenring and I.Schmidt, Chem.Ber., 95, 767 (1962).
93. Y.Nose, K.Ueda, and T.Kawasaki, J.Vitaminol., 7, 92 (1961); Vitamin Abstracts, 15, N1, 12 (1961).
94. L.M.Lewin and G.M.Brown, J.Biol.Chem., 236, 2768 (1961).
95. M.J.Verrett and L.R.Cerecedo, J.Org.Chem., 22, 1695 (1957).
96. J.Würsch, Helv.Chim.Acta, 41, 46 (1958).
97. E.J.Maxion, U.S.P. 2799676 (1957); Chem.Abs., 52, 1284 (1958).
98. S.Yoshida, W.Ishizuka, and M.Kataoka, Jap.P. 10232 (1956); Chem.Abs., 52, 15599 (1958).
99. S.Yoshida and W.Isizuka, Jap.P. 8285 (1956); Chem.Abs., 11950 (1958).
100. O.Shimmura, Jap.P. 18770 (1961); Chem.Abs., 57, 13763 (1962).
101. H.Hirano, Yakugaku Zasshi, 77, 1004 (1957); Chem.Abs., 52, 3828 (1958).
102. A.Takamisawa, S.Hayashi, and K.Tori, Jap.P. 2622 (1959); Chem.Abs., 54, 13152 (1960).
103. A.Takamisawa and K.Tokuyama, Jap.P. 3325 (1959); Chem.Abs., 54, 13152 (1960).
104. A.Takamisawa and K.Tokuyama, Jap.P. 6122 (1959); Ref. Zhur.Khim., 6L289 (1962).
105. M.Dixon and E.Webb, "Enzymes" (Translated into Russian), Inostr.Lit., 1960.
106. R.Abderhalden, Z.Vitamin-, Hormon-, u.Fermentforsch., 12, No.2/3, 83 (1962).
107. W.Langenbeck, Ergebn.Enzymforsch., 2, 314 (1933).
108. F.Lipmann, Nature, 138, 1097 (1937).
109. R.Breslow, J.Amer.Chem.Soc., 80, 3719 (1958).
110. R.Breslow, Chem.and Ind., 893 (1957).
111. R.Breslow, J.Amer.Chem.Soc., 79, 1762 (1957).
112. L.O.Krampitz, G.Greull, C.S.Miller, J.B.Bicking, H.R.Skeggs, and J.M.Sprague, J.Amer.Chem.Soc., 80, 5893 (1958).
113. F.La Fonseca-Wollheim, K.W.Bock, and H.Holzer, Biochem.Biophys.Res.Comm., 9, 467 (1962).
114. K.W.Bock, L.Jaenicke, and H.Holzer, Biochem.Biophys. Res.Comm., 9, 472 (1962).
115. N.N.Prochoroff, R.Kattermann, and H.Holzer, Biochem. Biophys.Res.Comm., 9, 477 (1962).

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THE KINETICS OF ION EXCHANGE ON SULPHONATED CATION EXCHANGERS

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CONTENTS

I. Fundamental problems in the theory of ion-exchange kinetics 199
II. Experimental methods of investigation 203
1. The shallow-bed technique 203
2. The "exchange in a limited volume of solvent" method 203
III. Self-diffusion in cation exchangers 203
IV. Diffusion of microcomponent ions 206
V. Kinetics of complete exchange 207
VI. Kinetic features of the exchange of large organic ions 209
VII. The relationship between diffusion and electrical conductivity in ion exchangers 210

A solution to the problem of creating high-quality ion exchangers, as well as a rational approach to the selection of optimum operating conditions for ion-exchange units and the regeneration of ion exchangers, is only possible with a detailed knowledge of both equilibrium and kinetic data.

However, while many studies have been concerned with the statics of ion-exchange processes the kinetics of ion exchange and the kinetic properties of ion exchangers have been investigated to a considerably lesser extent. Of the reviews which have appeared recently, three [1,2,3] should be noted in which problems of ion-exchange kinetics have been partially discussed. In Helfferich's detailed monograph [3], where the theory of ion-exchange processes is set out fairly fully, little attention is paid to experimental data on ion-exchange kinetics and, in particular, on the coefficients of diffusion and self-diffusion in ion exchangers; in addition, the investigations by Soviet authors are not sufficiently reflected. In the present review we would like to remedy this omission and pay particular attention to reviewing the theoretical and experimental information on the kinetics of ion exchange in the processes of self-diffusion, the diffusion of microcomponent ions, complete exchange, and the exchange of large ions on strongly acid cation exchangers. In presenting the information we shall not refer back to the problems set out in Helfferich's book.

I. FUNDAMENTAL PROBLEMS IN THE THEORY OF ION-EXCHANGE KINETICS

If an ion A from a solution replaced an ion B in an ion exchanger then the exchange process takes place primarily in the following stages: the diffusion of the ion A through the layer of liquid adjacent to the ion-exchange particle, the transfer of the ion A from the solution phase to the ion-exchanger phase, the diffusion and exchange of the A and B ions within the ion exchanger, the transfer of the B ion from the ion-exchanger phase to the solution phase, and diffusion of the B ion through the layer of solution adjacent to the ion-exchange particle. It should be borne in mind that due to the necessity for preserving the electroneutrality of the solution, the transfer of the ions during diffusion is balanced by a counter flow.

In the first stages of investigating ion-exchange kinetics (up to approximately 1950) some authors attempted to use the concept of "the order of reaction" of the ion-exchange process to explain the experimental results, assuming the