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U.D.C. 547.86:547.867

CHEMISTRY OF ALLOXAZINES AND ISOALLOXAZINES

V. M. Berezovskii and T. V. Eremenko

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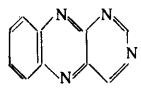
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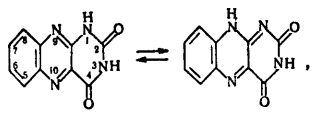
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I. INTRODUCTION

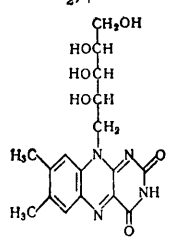
1,2,3,4-Tetrahydro-2,4-dioxo-derivatives of benzopteridine — the condensed pyrimido[4,5-*b*]quinoxaline cyclic system



are called "alloxazines". They exist in two tautomeric forms

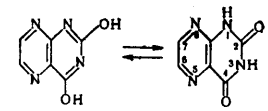


one of which, when "frozen" by substitution of the hydrogen atom at $N_{(9)}$, is the source of the isoalloxazine series. The most important naturally occurring member of this series, riboflavin (vitamin B_2)†



belongs to the yellow pigments of the "flavin" group. Riboflavin is one of the few isoalloxazines possessing biological activity; it is present in the animal organism.

Alloxazines and isoalloxazines are close in structure to the pteridines, compounds containing a condensed pyrimidopyrazine ring system. The product of condensing 2,4-dihydroxypteridine in the lactam form (called lumazine)



with benzene is alloxazine (benzolumazine).

Pteridines are widely distributed in the animal and vegetable world, as innumerable natural pterins — derivatives of 2-amino-4-hydroxypteridine such as leucopterin, xanthopterin, erythropterin, rhizopterin, folic acid (vitamin B_c).

The alloxazines were discovered in 1891 by Kühling[5], unsubstituted alloxazine being obtained for the first time by condensation of *o*-phenylenediamine hydrochloride with alloxan. In the next few years a number of compounds of this type were obtained[6,7] but then for a long time this field of chemistry failed to attract attention. The intensive examination of the alloxazine and isoalloxazine series developed only after the discovery by Osborne and Mendel[8] in 1913 that a water-soluble factor contained in milk is necessary for the growth of young rats which are on a diet of proteins and other purified components, the isolation of this factor from milk[8,9], egg yolk[10], liver[11,13], dandelions[14], malt[15], and other sources[16], and the observation (in 1932)[17-21] that 6,7,9-trimethylisoalloxazine is formed in the photolysis of the water-soluble factor (vitamin B_2) in alkaline medium. In 1935 the exact empirical formulae ($C_{17}H_{20}O_6N_4$) of a strongly fluorescing orange crystalline substance (m.p. 280°-282°), which was isolated from milk[22], was established. Simultaneously Karrer and coworkers[23,24] and Kuhn *et al.*[25] synthesised vitamin B_2 (riboflavin) and hence demonstrated its structure unequivocally.

Riboflavin is widely distributed in nature both as itself and in the form of coenzymes and flavin enzymes; it is found in almost all cells of animal and vegetable organisms and in the cells of many microorganisms. Some of them, for example *Eremothecium ashbyii*, are capable of producing riboflavin[26,27] and the coenzyme flavin-adenine dinucleotide[28,29] in quantities considerably exceeding that that required for exchange of substances in their cells.

An enzyme containing vitamin B_2, the so-called "yellow oxidising enzyme"‡, was first isolated from yeast by Warburg and Christian[17,18] in 1932, even before the structure of vitamin B_2 was established.

II. SYNTHESIS OF ALLOXAZINES FROM *o*-PHENYLENEDIAMINES AND ALLOXAN

One of the most important and most general methods for the synthesis of alloxazines is the condensation of aromatic *o*-diamines with α-dicarbonyl compounds of the pyrimidine series.

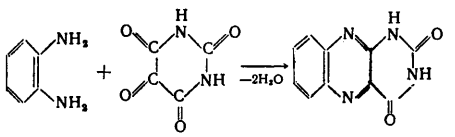
Aromatic *o*-diamines react fairly easily with aliphatic and aromatic α-dicarbonyl compounds (α-dialdehydes and

† The determination of the structure and method of synthesis of riboflavin, its physical and chemical properties, and the relation between structure and biological activity, established through the synthesis of intermediate substances and flavin coenzymes, have previously been given in review articles[1,2,3] and in "Khimiya Vitaminov" (Chemistry of the Vitamins)[4].

‡ This is normally called the "old yellow enzyme" (Ed. of Translation).

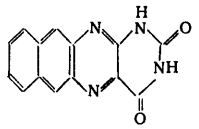
α-diketones or ketals) to form phenazines or quinoxalines. The reaction was first used by Claus[30] in 1873 to synthesise phenazine and then extended to its derivatives[31]. Quinoxaline was first obtained, by the condensation of *o*-phenylenediamine with glyoxal at 60°-70°, by Hinsberg[32] and Körner[33], and its derivatives were prepared from substituted *o*-phenylenediamines and α-dicarbonyl compounds[34,35].

This method was proposed[5] for the preparation of alloxazine from *o*-phenylenediamine hydrochloride and alloxan:



Alloxan, 5-oxobarbituric acid, is a ketone, as is confirmed by addition reactions with amines[36], substitution reactions[37], etc.; it also possesses acidic properties.

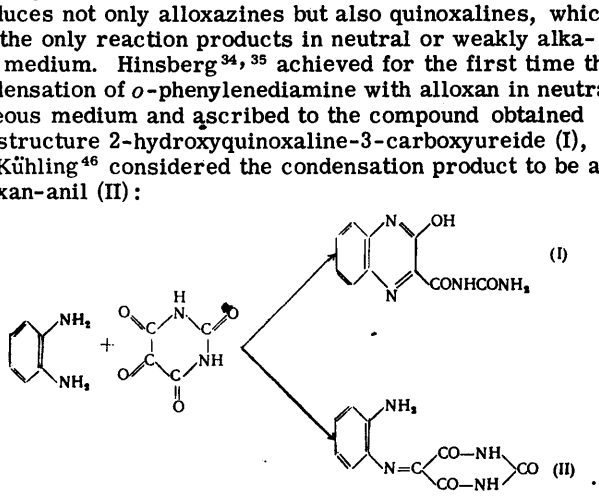
Condensation of aromatic *o*-diamines with alloxan in an acid medium has been used to obtain alloxazines with the following substituents: 6- or 7-methyl[5], 6,7-dimethyl[38,39], 6,8- or 5,7-dimethyl, 7,8- or 5,6-dimethyl[39], 5,7,8- or 5,6,8-trimethyl, 6,7,8- or 5,6,7-trimethyl, 5,6,7,8-tetramethyl[40], 6- or 7-ethyl[41], and 6- or 7-phenyl[42]. Alloxazine-6- or alloxazine-7-sulphonic acid[43], alloxazine-6- or alloxazine-7-β-acrylic acid[43], the lactone of 5(or 8)-hydroxymethylalloxazine-6(or 7)-carboxylic acid, and the lactone of 8(or 5)-amino-7(or 6)-hydroxymethylalloxazine-6(or 7)-carboxylic acid[44] have been prepared; benzoalloxazine



has been synthesised[42].

It follows from these examples that the synthesis of substituted alloxazines from alloxan and unsymmetrically substituted *o*-diamines does not always lead to a single compound. In many cases a mixture of two or more isomers of alloxazine is formed, the separation of which is very difficult.

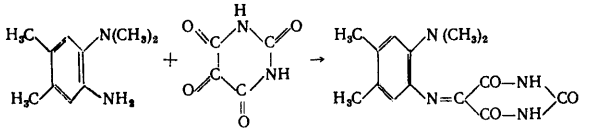
When insufficient acid is present the reaction of *o*-phenylenediamines with alloxan is not well defined and produces not only alloxazines but also quinoxalines, which are the only reaction products in neutral or weakly alkaline medium. Hinsberg[34,35] achieved for the first time the condensation of *o*-phenylenediamine with alloxan in neutral aqueous medium and ascribed to the compound obtained the structure 2-hydroxyquinoxaline-3-carboxyureide (I), but Kühling[46] considered the condensation product to be an alloxan-anil (II):



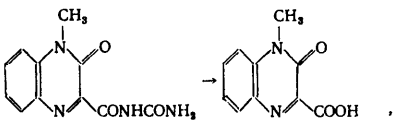
Many authors have ascribed an alloxan-anil structure to analogous substances obtained by condensation of alloxan with aromatic *o*-diamines in various solvents in the absence of mineral acids; in these syntheses the following *o*-diamines were used: *N*-methyl-*o*-phenylenediamine in methanol[36], *N* 4,5-trimethyl-*o*-phenylenediamine[47], *N*-(2-amino-4,5-dimethylphenyl)-*L*-arabitylamine in aqueous alcohol and acetic acid[48], *N*-(2-amino-4,5-dimethylphenyl)-*D*-ribitylamine in pyridine[49], etc.

However, such a structure for the condensation products is doubtful. They do not undergo cyclisation in acidic media and are easily hydrolysed by alkali to derivatives of 2-hydroxyquinoxaline-3-carboxylic acid or of the corresponding 1,2-dihydro-2-oxoquinoxaline compounds, *i.e.* the same compounds which are formed in the cleavage of alloxazines and isoalloxazines by alkali[50]. They are not cleaved by acids as is characteristic for Schiff bases and is observed, for example, with 5-(*p*-dimethylaminoanil)-alloxan.

Nevertheless, from *o*-diamines with one tertiary nitrogen atom, which excludes the possibility of condensation to quinoxalines, substances with an alloxan-anil structure are obtained[51]:



Hinsberg's quinoxaline-ureide structural formula (I) for the substances obtained from alloxan and *o*-diamines is proved, for example, by the fact that 1,2-dihydro-1-methyl-2-oxoquinoxaline-3-carboxylic acid can be obtained from its ureide:



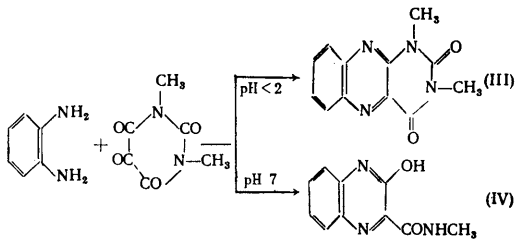
not only by alkali cleavage but by hydrolysis with 2 *N* hydrochloric acid[50], *i.e.* under conditions which would preclude cleavage of the pyrimidine ring if this were present in the molecule. Ultraviolet adsorption spectra[52] also confirm the ureide structure for the compound in question.

Alloxan is not stable towards alkaline reagents. In the presence of baryta water it is converted into alloxanic acid. According to Hinsberg[34] alloxan is converted even under milder conditions to the acyclic alloxanic acid, which then condenses with *o*-diamines to a quinoxaline derivative.

It is possible that the initial unstable product of the reaction of alloxan with aromatic *o*-diamines is the alloxan-anil which in acidic medium undergoes cyclisation without cleavage of the pyrimidine ring to give alloxazines and isoalloxazines, but under acid-free condensation conditions in the presence of free *o*-diamine cyclises to the quinoxaline-ureide.

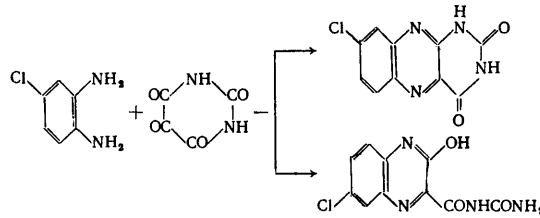
The condensation of *o*-phenylenediamine hydrochloride with dimethylalloxan produces 1,3-dimethylalloxazine (III)[5,53] while condensation in a neutral medium gives the

methylamide of 2-hydroxyquinoxaline-3-carboxylic acid (IV)[53]:



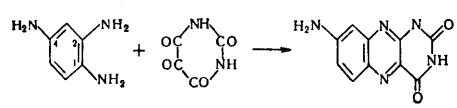
The formation of the second condensation product evidently occurs because even in a neutral medium dimethylalloxan is broken down to the monomethylamide of mesoxalic acid, which then condenses with the *o*-diamine[53]. This is proved by previously treating dimethylalloxan with an equivalent amount of alkali, the dimethylalloxan easily decomposing to methylamine, carbon dioxide, and the monomethylamide of mesoxalic acid; the last condenses with *o*-diamine to give (IV)[54].

Depending on the medium the 5-CO group of alloxan reacts preferentially with one of the amino-groups of 4-chloro-*o*-phenylenediamine with subsequent closing of the pyrazine ring. 7-Chloroalloxazine is obtained on heating in 1-5 *N* hydrochloric acid or in glacial acetic acid in the presence of 0.1 mole boric acid at 18°-20°; in 10% aqueous acetic acid or alcohol the ureide of 6-chloro-2--hydroxyquinoxaline-3-carboxylic acid is formed in 96% yield[55]:



Condensation in glacial acetic acid without boric acid produces an equal mixture of both substances[55]. In this reaction the catalytic effect of boric acid, which was established earlier in the formation of isoalloxazines[56], is shown clearly.

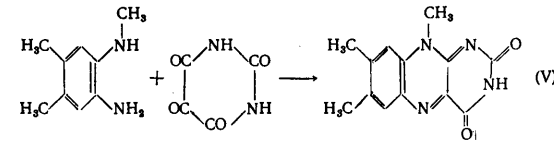
The reaction of 1,2,4-triaminobenzene with alloxan, which gives 7-aminoalloxazine in the presence of boric acid[57] is of particular interest



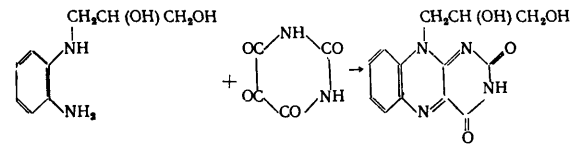
Evidently the opposed inductive effects of the amino-groups in the *para*-positions and, to some extent, in the *ortho*--positions diminish the conjugation of the *p* electrons of the nitrogen atom with the π electrons of the benzene ring to a different degree for the various amino-groups, and the amino-groups must occur in the following order as regards their nucleophilic character: 1-NH_2 > 4-NH_2 > 2-NH_2. Hence the electrophilic centre of the carbonyl group is preferentially attacked by the most nucleophilic nitrogen atom, that in position 1, which also determines the further course of the reaction with the second amino-group and the structure of the substance formed.

III. SYNTHESIS OF ISOALLOXAZINES FROM PRIMARY--SECONDARY AROMATIC *o*-DIAMINES AND ALLOXAN

Isoalloxazines were first obtained in 1934. Kuhn and his coworkers[47,58,59] prepared 9-methylisoalloxazine by the condensation of *N*-methyl-*o*-phenylenediamine hydrochloride with alloxan in water at 50°-60°, and 6,7,9-trimethylisoalloxazine (lumiflavin, 9-methylflavin§) in 75% yield by the condensation of *N* 4,5-trimethyl-*o*-phenylenediamine hydrochloride with alloxan under the same conditions



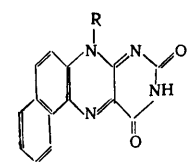
At the same time Karrer *et al.*[60] obtained 9-(2,3-dihydroxypropyl)isoalloxazine by heater *N*-(2,3-dihydroxypropyl)-*o*-phenylenediamine dihydrochloride with alloxan in alcohol



In contrast to alloxazines, isoalloxazines with a strictly definite structure are formed from primary-secondary aromatic *o*-diamines, as a consequence of the predominating reaction of the primary amino-group with the 5-oxo--group of alloxan.

Isoalloxazines have been synthesised with the following substituents in the 9-position: ethyl, benzyl[61], cyclohexyl[62], 2-hydroxyethyl[41], 2-hydroxypropyl[63], 3-hydroxypropyl[64], and carboxyethyl[65]. Derivatives which have been prepared with substituents in other positions are as follows: 9-(2--hydroxyethyl)-8-methyl[40,66], 6,8,9-trimethyl[61,62,67], 9--(1-*D*-dulcityl)-7-methyl[24,68], 7-methyl-9-(1-*D*-ribityl)[69-71], 9-(1-*D*-mannityl)-7-methyl[68], 7-ethyl-9-(1-*D*-ribityl)[72], 9-(1-*L*-arabityl)-6,7-tetramethylene[73], 9-(1-*D*-arabityl)-6,7--trimethylene[73], 5,7-and 6,8-dimethyl-9-(1-*D*-ribityl), 9-(1-*D*-arabityl)-6,8-dimethyl, 5,6-and 5,7-dimethyl-9-(1--*L*-arabityl)[74,75], 5,6,7-trimethyl-9-(1-*D*-ribityl), 9-(1-*D*--arabityl)-5,6,7-trimethyl, 5,6,7-trimethyl-9-(1-*D*-xylityl), and 9-(1-*D*-lyxityl)-5,6,7-trimethyl[76].

Other derivatives obtained are *D*- and *L*-arabo-[22,68,77], *D*- and *L*-ribo-[23-25,77,78], *D*-lyxo-[77], *D*-2′-deoxyribo-[69], and *D*-gluco-[68], flavins, 2′,3′-dihydroxypropylflavin[41,62], flavin acetic acid[62,79], and also benzoisoalloxazines such as 9-(1-*D*-ribityl)- and 9-(1-*L*-arabityl)-benzo[*h*] isoalloxazines[72]



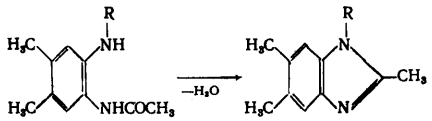
where R = *D*-ribityl or *L*-arabityl.

§ In accordance with a terminology frequently used but not very systematic, we use the term flavins for derivatives of 6,7-dimethylisoalloxazine.

In trivial names pentose and hexose substituents are designated by the name of the corresponding sugar, *e.g.* 6,7-dimethyl--9-(1-*D*-sorbityl)isoalloxazine is called *D*-glucoflavin.

Some isoalloxazines can be synthesised in good yields using hydrochloric acid as a catalyst. By this means compounds have been obtained with simple alkyl, aryl, or alkylaryl substituents in position 9, such as 9-methyl[58,80], 6,9-dimethyl (80%)[81], 9-(1-naphthyl)[42], 9-(1,3-dihydroxy--2-propyl)[82], 9-(2-phthalimidoethyl)[83], 9-methyl-6-sulphonic acid[80], and also 9-benzylbenzo[*h*]isoalloxazine[42].

Monoacyl derivatives of *o*-phenylenediamine can also be used for the condensation with alloxan in a medium of hydrochloric acid; they are deacylated as the reaction occurs but the yield of flavins is then not high because the predominant reaction is an intramolecular removal of water, the original diamine undergoing cyclisation to a substituted benzimidazole[22,68]

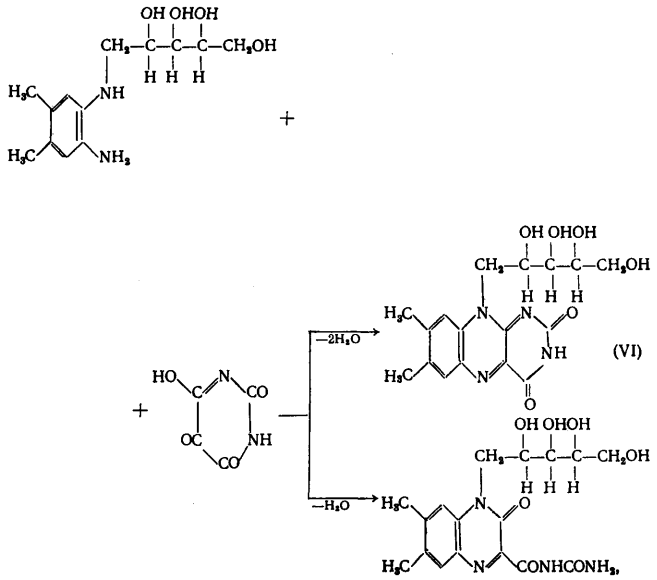


Dilute hydrochloric acid or methanol saturated with hydrogen chloride are successfully used as catalysts for synthesis of isoalloxazines, mainly when the original *o*-diamines contain aminoalkyl or alkyl derivatives of nitrogen heterocycles as *N*-substituents, the isoalloxazines formed being isolated as the hydrochlorides. The reactions are usually carried out by heating to 100° or by boiling the reaction mixture; the isoalloxazines are obtained in good yield. Under these conditions isoalloxazines with the following substituents in position 9 have been obtained: 2-aminoethyl[83], 2-diethylaminoethyl[84], 3-aminopropyl (65% yield), 4-diethylaminobutyl (33.8%), 3-diethylamino-2--hydroxypropyl (65%), 2-(2-hydroxyethylamino)ethyl (68.2%), 3-piperidinopropyl (59.5%), and 3-morpholinopropyl (70%)[85].

Isoalloxazines with substituents in other positions have also been obtained: 9-(2-diethylaminoethyl)-6-methyl (62%), 9-(3-diethylaminopropyl)-6-methyl (48.8%), 9-(2-diethylaminoethyl)-6-methoxy, 9-(3-diethylaminopropyl)-6--methoxy[84], 9-(3-diethylaminopropyl)-6,7-dimethoxy, 9--(3-diethylaminopropyl)-6,7-dimethyl[86], 6-chloro-9-(2--diethylaminoethyl), and 6-chloro-9-(3-diethylaminopropyl)[84].

However, many isoalloxazines are synthesised in the presence of hydrochloric acid in very poor yields. It was found that, if 9-alkylisoalloxazines are obtained in good yields on condensing *o*-diamine hydrochlorides with alloxan in aqueous or alcoholic medium, the condensation of many *N*-hydroxyalkyl-*o*-diamines occurs with low yields of 9-hydroxyalkylisoalloxazines, and with pentose substituents the yield of isoalloxazines falls to as low as 5-10%.[55] Increasing the acidity of the medium for the reaction in dilute hydrochloric acid, for example, in the preparation of isoalloxazines with the substituents: 9-(1-*L*-arabityl), 9-(1-*L*--arabityl)-7-methyl, 7-methyl-9-(1-*D*-xylityl), 7-methyl--9-(1-*D*-sorbityl), 6,7-dimethyl-9-(1-*L*-rhamnityl)[22,68], 6,7-dimethyl-9-(1-*L*-xylityl)[77], and 9-(2-hydroxyethyl)--6,8-dimethyl[66], only increases the yields a little and they all remain below 20%.

If acetic acid is used in place of the mineral acid, for example, in the condensation of *N*-(2-amino-3,4-dimethylphenyl)-*D*-ribitylamine with alloxan, apart from the reaction in which two molecules of water are removed to produce riboflavin (VI) in 5-10% yield, there is a second reaction in which only one molecule of water is lost[48,87] and a substance with a quinoxaline structure is formed[49,50];



the latter is 1,2-dihydro-6,7-dimethyl-2-oxo-1-(*D*-ribityl)-quinoxaline-3-carboxylic acid ureide.

It was found, in a systematic study of the effect of substituents in the aromatic ring, that in some cases addition of boric acid gives a higher yield of flavins. However the catalytic activity of boric acid does not depend on complex formation with the hydroxyl groups because its presence in the reaction medium also increases the yield of isoalloxazines which do not contain hydroxyl groups in the side chain[56]. Crystalline pyroboroacetate $[(CH_3COO)_2B]_2O$, which is obtained from acetic anhydride and boric acid, can be used as a catalyst[56].

The following substances were synthesised with high yields using a boric acid catalyst in a medium of acetic acid: *D*-, *DL*-, and *L*-araboflavins[56,88,89], *D*-riboflavin (over 70% yield); methyl-, pentyl-, and allyl-flavins[88], and 9-phenyl-[56,88], 6,9-diphenyl-[42], 6,9-dimethyl- (80% yield)[81], 9-(1-*D*-dulcityl)-6-methyl-(65%), 9-(1-*D*-dulcityl)-6--methoxy-(51%)[90], 6-methyl-9-(1-*D*-ribityl)-[91], 6-ethyl-7--methyl-9-(1-*D*-ribityl)-, and 9-(1-*L*-arabityl)-6-ethyl-7--methyl-[72] isoalloxazines were also synthesised. 5,6-Dimethyl-9-(tetraacetyl-*D*-ribit-1-yl)isoalloxazine has also been obtained[72]; this is hydrolysed by sodium methoxide to 5,6-dimethyl-9-(1-*D*-ribityl)isoalloxazine, or isoriboflavin, antivitamin B_2.[92,93] 9-Phenylbenzo[*j*]- and 9-benzylbenzo[*h*]-isoalloxazines have been prepared[42].

The increase in the yields of some isoalloxazines was nevertheless small: thus, 6-ethyl- and 6,7-diethyl-9-(1--*D*-ribityl)isoalloxazines were obtained with only 29% and 30% yields respectively[90,95].

Extensive searches were made for bacterial inhibitors and therapeutically active agents among halogen-substituted isoalloxazines. The condensation of alloxan with halogen--substituted aromatic *o*-diamines was accomplished in the presence of boric acid. The following compounds were obtained:

A. 6-Chloroisoalloxazines with the following substituents in position 9: 1-*D*-arabityl (66% yield)[90,96], 1-*L*-arabityl (67%),

1-*D*-xylityl (52%)[91], 1-*D*-dulcityl (70%), 1-*D*-mannityl (64%), 1-*D*-sorbityl[91,97], 1-*D*-ribityl[98], and 3-diethylaminopropyl[99].

B. 6,7-Dichloroisoalloxazines with the following substituents in position 9: 1-*D*-ribityl (80%)[97,99,100], 1-*D*--arabityl[90,96,97], 1-*L*-arabityl[96], 1-*D*-xylityl[90,96], 1-*D*--sorbityl[96,100], 1-*D*-dulcityl[96,97,101], 1-*D*-rhamnityl[97], 1-*D*-mannityl[90,96], 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl[102], diethylaminoethyl, 4-diethylamino-1-methylbutyl[98], diethylaminodecyl, diethylaminoundecyl[102].

C. Chloroisoalloxazines with substituents in various positions: 7-chloro-8-diethylaminoethyl (41%), 7-chloro-9--diethylaminopropyl (70%)[103,104], 7-chloro-9-(4-diethylamino-1-methylbutyl) (82%)[104], 6-chloro-7-methyl-9-(1-*D*--ribityl), 7-chloro-6-methyl-9-(1-*D*-ribityl) (64%)[105], and 6-methyl-7-chloro-9-(1-*D*-sorbityl) (48%)[90].

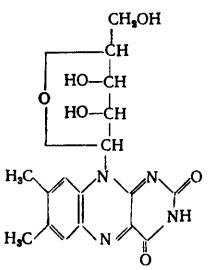
D. 6,7-Dibromoisoalloxazines with the following substituents in position 9: 1-*D*-ribityl, 1-*L*-arabityl, and 1-*D*--galactyl.[97] 6-Fluoroisoalloxazines with the following substituents in position 9: 1-*D*-ribityl, 1-*D*-arabityl, and 1-*D*-galactyl.[97]

Boric acid in an acetic acid medium catalyses the condensation of alloxan with primary-secondary aromatic *o*-diamines which contain aminoalkyl derivatives as *N*-substituents, but the isoalloxazines are not always obtained with good yields.

The yields of isoalloxazines fall as the aminoalkyl substituent in position 9 becomes more complex and as the number of substituents in the benzene ring increases: 9--(3-diethylaminopropyl) (77%), 9-(3-diethylaminopropyl)--8-methyl (62%), 9-(3-diethylaminopropyl)-6,8-dimethyl (50%), 9-(4-diethylamino-1-methylbutyl)-6,7-dimethyl (68%)[105], 9-(4-diethylamino-1-methylbutyl)-7-methoxy (40%), 9-(4-diethylamino-1-methylbutyl)-6,8-dimethyl (20%), 9-(4-diethylamino-1-methylbutyl)[106].

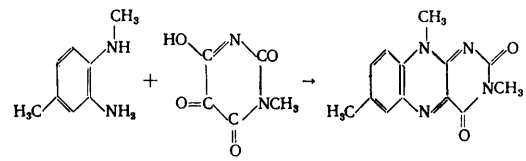
The method discussed gives good results in the condensation of initial diamines containing also negative substituents such as the nitro-group; 9-(2-hydroxyethyl)-6--nitro-[107] and -6,7,9-trimethyl-8-nitro-isoalloxazines[108] have been obtained.

Condensation of *O*-acetylated *N*-glycosyl-*o*-diamines and alloxan under mild conditions in a mixture of acetic and boric acids at 20° gave the corresponding *O*-acetylated *N*-glycosylisoalloxazines (65%) from which *D*-, *DL*-, and *L*--arabofuranosylflavins and *D*-ribofuranosylflavin were obtained by mild deacetylation in an alcoholic solution of ammonia[109]



There is no information as to which configuration (α- or β-) the substances obtained have. They are easily decomposed in cold dilute acid to form lumichrome[109].

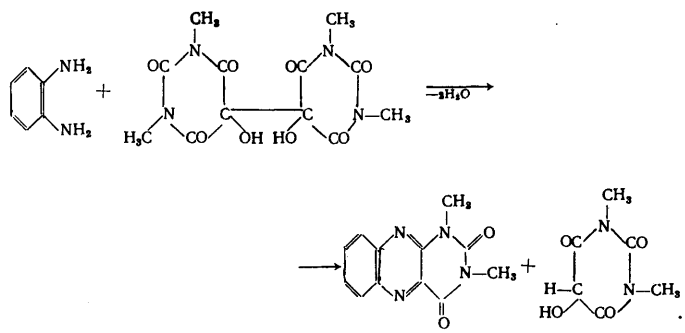
Since monomethylated alloxan is capable of lactam-lactim tautomerism only through the group with the unsubstituted hydrogen atom, -NH-CO-, the condensation of methylalloxan with *N*-phenyl(alkyl)-*o*-phenylenediamines gives, in contrast to the alloxazines, *N*-methylated isoalloxazines with unequivocal structure. 3-Methyl-9-phenyl- and 3,9-dimethyl-isoalloxazine were obtained by this means from, respectively, *N*-phenyl- and *N*-methyl-*o*--phenylenediamine in water or in acetic acid in the presence of boric acid[56,67,110,111]. 3,6,9-Trimethylisoalloxazine was obtained, in hydrochloric acid solution, from 3-amino-4-methylaminotoluene and methylalloxan[81]



The following have also been obtained from methylalloxan: 3-methylriboflavin[101] and 6,7-dichloro-9-(1-*D*--dulcityl)-3-methylisoalloxazine[101].

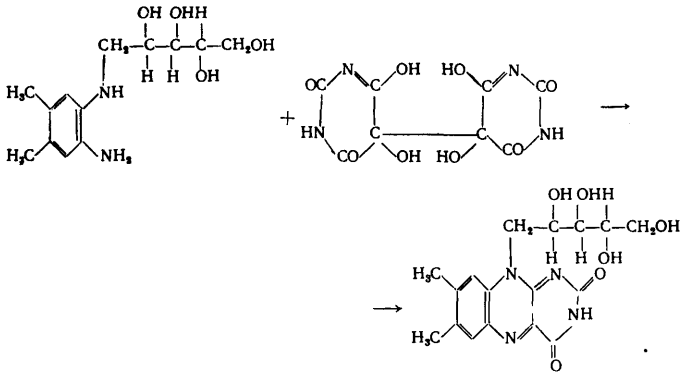
IV. SYNTHESIS OF ALLOXAZINES AND ISOALLOXAZINES FROM AROMATIC *o*-DIAMINES AND ALLOXANTIN OR DIALURIC ACID

Besides alloxan, the products of its reduction — alloxantin and its methylated derivatives — enter into the condensation reaction with *o*-phenylenediamine. However, the reaction takes place somewhat differently than with alloxan; one of the hetero-rings of alloxantin is split off in the form of dialuric acid. Thus, in the condensation of 3,4-diaminotoluene with symmetrical dimethylalloxantin 1,6-, 1,7-, 3,6-, or 3,7-dimethylalloxazine is formed[5,112] while 1-(or 3-(methylalloxazine is obtained from *o*-phenylenediamine[5,113]; condensation of 3,4-diaminotoluene with tetramethylalloxantin produces 1,3,6- or 1,3,7-trimethylalloxazine while *o*-phenylenediamine gives 1,3-dimethylalloxazine[5,112].



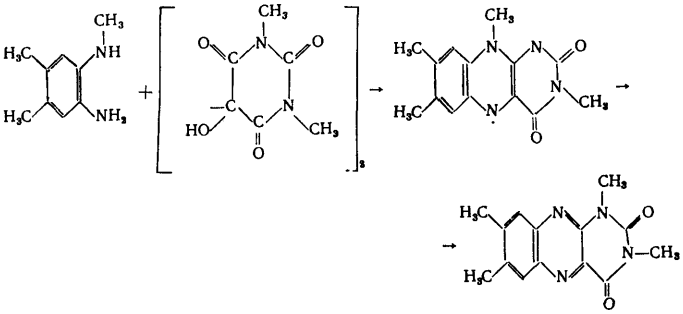
The reaction takes place in acetic acid in the presence of boric acid. The dialuric acid formed is slowly oxidised by atmospheric oxygen to alloxantin.

Unsubstituted alloxantin condenses with *N*-(2-amino-4,5-dimethylphenyl)-*L*-lyxitylamine hydrochloride on heating in alcohol to form *L*-lyxoflavin [114]:



Riboflavin is obtained from *N*-(2-amino-4,5-dimethylphenyl)-*D*-ribitylamine and a mixture of alloxantin with alloxan [115,116] or alloxantin alone, or dialuric acid in the presence of atmospheric oxygen in alcoholic hydrochloric acid [117,118].

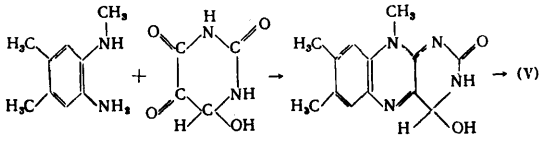
2′,3′,4′-Triacetyl-*D*-araboflavin was obtained from alloxantin and *N*-(2-nitro-4,5-dimethylphenyl)-2,3,4-triacetyl-5-trityl-*D*-arabitylamine [119]. The reaction of tetramethylalloxantin with *N*,4,5-trimethyl-*o*-phenylenediamine proceeds in the absence of air in glacial acetic acid with formation of a semiquinonoid radical of a substituted isoalloxazine, which is oxidised slowly with demethylation and formation of a colourless alloxazine — 1,3-dimethyl lumichrome [80]:



It is not clear at what intermediate stage the demethylation at position 9 takes place. The semiquinonoid intermediate separates from dilute hydrochloric acid in the form of violet rhodoflavin with the grouping:



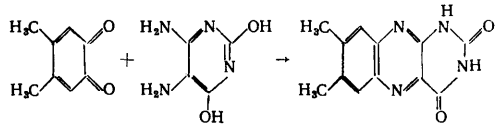
The possibility of using isodialuric acid is of interest. For example, the condensation of *N*,4,5-trimethyl-*o*-phenylenediamine with isodialuric acid in glacial acetic acid takes place with difficulty through the intermediate 4,4-dihydro isoalloxazine, which is unstable and is oxidised in an acidic medium in the presence of air to lumiflavin [120,121]:



6-Methylisodialuric acid can be used in place of isodialuric acid in the reaction with *o*-diamine; under the influence of atmospheric oxygen the C–C bond of the methyl group at position 4 in the isoalloxazine ring of the intermediate compound is broken and lumiflavin is again formed [121]. It should be noted that in alkali solutions isodialuric acid isomerises to dialuric acid.

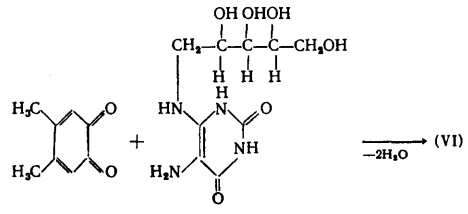
V. SYNTHESIS OF ALLOXAZINES AND ISOALLOXAZINES FROM AROMATIC *o*-QUINONES AND DIAMINODIHYDROXYPYRIMIDINES

The synthesis of an alloxazine molecule from *o*-diamines and α-dicarbonyl compounds can be achieved starting not from aromatic *o*-diamines but from *o*-diaminopyrimidines, condensing them with α-dicarbonyl aromatic compounds. Thus, lumichrome is formed (68% yield) on boiling 4,5-dimethyl-1,2-benzoquinone with 4,5-diamino-2,6-dihydroxypyrimidine in acetic acid [122]



(VII)

Isoalloxazines are obtained in a similar way. For example, riboflavin (VI) is formed (29% yield) in the reaction of 5-amino-4-(*D*-ribitylamino)uracil with 3,4-dimethyl-1,2-benzoquinone:



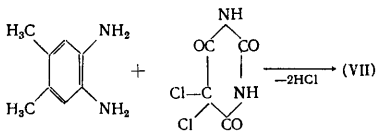
and from the corresponding diaminopyrimidines lumiflavin (40% yield) and 9-hydroxyethyl-, 9-(1-*D*-mannityl)-, and 9-(1-*D*-sorbityl)-flavins are obtained [123].

VI. SYNTHESIS OF ALLOXAZINES AND ISOALLOXAZINES FROM AROMATIC *o*-DIAMINES AND HALOGENOBARBITURIC ACIDS

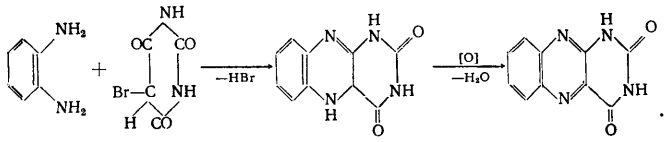
To build up the pyrazine ring in alloxazines and isoalloxazines, Matsukawa and coworkers [124,125] and Tishler and coworkers [49,126,127] proposed the condensation of α-halogenoketones of the pyrimidine series, in particular 5,5-dibromo- and 5,5-dichloro-barbituric acid, with *o*-phenylenediamines. The 4-oxo-group of the halogen-substituted barbituric acid takes part in the ring formation.

Hinsberg [35] had already observed in 1886-1887 the formation of quinoxalines in the reaction of aliphatic α-halogenoketones with aromatic *o*-diamines. It has been noted that 5,5-dibromobarbituric acid reacts easily with aliphatic amines and aniline [128]. The halogen atoms in 5,5-dibromobarbituric acid are not equivalent and they differ in their reactivity [129,130]. On the basis of spectroscopic data 5,5-dihalogenobarbituric acids have been ascribed the structure of trioxohexahyropyrimidines [131].

The condensation of 1,2-diamino-4,5-dimethylbenzene with 5,5-dichlorobarbituric acid at 100° in acetic acid produces 6,7-dimethylalloxazine in 59% yield; in pyridine the yield of lumichrome is increased to 90%:[49]



The use of 5-bromo- or 5,5-dibromo-barbituric acid in the condensation leads to lower yields[49], particularly with the monosubstituted compound. Thus, in the condensation of 5-bromobarbituric acid with *o*-phenylenediamine at 100° in pyridine, alloxazine is obtained in only 20.7% yield[49]:



However, aromatic *o*-diamines substituted in the ring with alkyl groups give better yields than *o*-phenylenediamine; the yield of lumichrome from the corresponding substituted *o*-phenylenediamine is 30%.[49]

The reaction with monohalogenobarbituric acids takes place through the formation of intermediate dihydroalloxazines which undergo dehydrogenation to alloxazines in the presence of atmospheric oxygen. However, the low yield is apparently not connected with the dehydrogenation reaction but with the difficulty of condensing amines with monohalogenated, as compared with dihalogenated, barbituric acids. The analogous dehydrogenation of dihydro- and tetrahydro-derivatives of pyrimidopyrazine ring systems (*e.g.* pterins) by atmospheric oxygen occurs very easily[4].

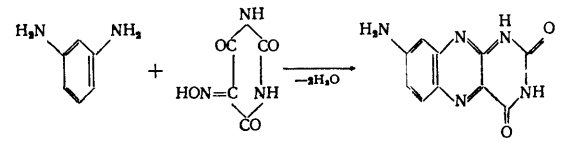
Besides acetic acid and pyridine, methanol and isopentanol are used as media for the condensation. Sodium acetate and borates can be used as catalysts but they are significantly inferior to pyridine[49].

Isoalloxazines are obtained in good yields from the condensation of 5,5-dichlorobarbituric acid with primary-secondary *o*-phenylenediamines in pyridine. Lumiflavin, benzylflavin (78% yield; 70% from 5-chlorobarbituric acid), *L*-araboflavin, and tetraacetylriboflavin have been synthesised from the corresponding starting materials[49,132]. Riboflavin was obtained in 85% yield from *N*-(2-amino-4,5-dimethylphenyl)-*D*-ribit-1-ylamine and 5,5-dichlorobarbituric acid in pyridine[49,126,127,132].

Riboflavin, *D*-araboflavin, and 9-hydroxyethyl-6-methylisoalloxazine were obtained previously from the corresponding primary-secondary *o*-phenylenediamines and 5-bromo- or 5,5-dibromo-barbituric acid in acetic acid in the presence of sodium acetate, sodium borate, or pyridine[124].

VII. SYNTHESIS OF ALLOXAZINES AND ISOALLOXAZINES FROM AROMATIC *m*-DIAMINES AND VIOLURIC ACID

In 1938 Ganapati[57] showed that *m*-phenylenediamine can be condensed with 5-isonitrosobarbituric acid (violuric acid) to obtain 7-aminoalloxazine. In this condensation the pyrazine ring in the alloxazines is obtained from the nitrogen atom of one amino-group of the *m*-phenylenediamine and the nitrogen of the isonitroso-group of violuric acid instead of from the two nitrogen atoms of *ortho*-substituted aromatic compounds:



The method has a limited value because it leads to formation only of 7-aminoalloxazines or 7-aminoisoalloxazines. An attempt to use *meta*-substituted anilines with nitro-, hydroxy-, and carboxy- or methyl groups for the condensation with violuric acid did not give positive results[133].

The condensation of *m*-phenylenediamine (or its derivatives) with violuric acid (or its *N*-substituted derivatives) is carried out in a neutral or weakly alkaline aqueous medium. 7-Methylamino- and 7-dimethylamino-alloxazine (66.5% yield)[103], 6-methyl-[133] and 1,3-dimethyl-7-aminoalloxazine[134] have been obtained. In the preparation of alloxazines, violuric acid reacts with the carbon atom in the position *para* to the most alkylated amino-group in the *m*-phenylenediamine derivatives.

In further study of the reactivity of *meta*-substituted anilines it was found that a methoxy-group provides sufficient electron density in the position *para* to itself for the condensation with violuric acid and furthermore this position is *ortho* to the amino-group. By this method, 6,7-dimethoxyalloxazine was obtained from 3,4-dimethoxyaniline[103].

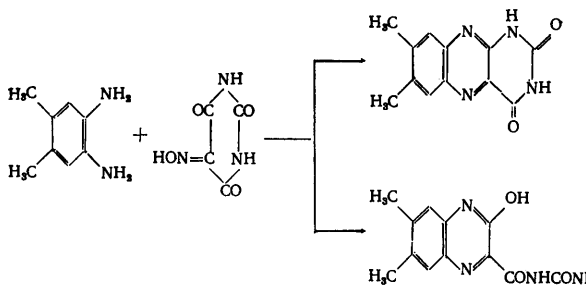
Condensation of *m*-diamines with violuric acid is also used to obtain 7-aminoisoalloxazines. 7-Amino-6,9-dimethylisoalloxazine[135,136], 7-amino-9-(1-*D*-arabityl)- or 7-amino-9-(1-*L*-arabityl)-6-methylisoalloxazine[137], 9-(2-diethylaminoethyl)-7-dimethylaminoisoalloxazine[103], 7-amino-9-methyl- and 7-dimethylamino-9-methyl-isoalloxazine (74% yield)[103] have been prepared.

The isomeric 7-amino-9-(2-diethylaminoethyl)isoalloxazine and amino-7-(2-diethylaminoethyl)alloxazine have been obtained from *N*-(2-diethylaminoethyl)-*o*-phenylenediamine and violuric acid[103].

VIII. SYNTHESIS OF ALLOXAZINES FROM AROMATIC *o*-DIAMINES AND VIOLURIC ACID

In 1962 Berezovskii and Glebova proposed a new method for synthesising compounds of the alloxazine series: the condensation of *o*-phenylenediamines with violuric acid[138]. The reaction takes place in an alcoholic solution of acetic acid in the presence of boric acid. In the absence of boric

acid or in aqueous alcohol[139] the formation of ureides of quinoxalinecarboxylic acids is observed. Thus, under the appropriate conditions either lumichrome or 2-hydroxy--6,7-dimethylquinoxaline-3-carboxyureide are obtained from 4,5-dimethyl-*o*-phenylenediamine and violuric acid:



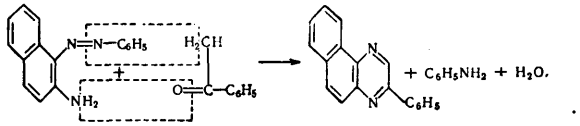
The pyrazine ring in these compounds is formed from the nitrogen atoms of the *o*-phenylenediamine; this is proved by the use of violuric acid labelled with ^{15}N in the isonitroso-group at position 5. The nitrogen atom of the isonitroso-group is split off as hydroxylamine[138]. Lumichrome is formed by reaction of 4,5-dimethyl-*o*-phenylenediamine with violuric acid and not with the product of its possible "deoximation" (alloxan); in control experiments, under the conditions of the condensation, alloxan is not detected even in the least traces[138].

In a mixture of aqueous acetic and boric acids the yield of alloxazines is raised. In dilute hydrochloric acid the yields of lumichrome and alloxazine reach 70.0% and 73.5% respectively[138].

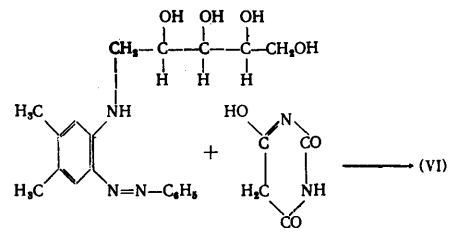
IX. SYNTHESIS OF ALLOXAZINES AND ISOALLOXAZINES FROM AROMATIC *o*-AMINOAZO-COMPOUNDS AND BARBITURIC ACID

In 1947 Tishler and coworkers obtained compounds of the isoalloxazine series by the condensation of secondary aromatic *o*-aminoazo-compounds with barbituric acid[92]. In many cases this method is simple to put into practice because barbituric acid is more readily available than alloxan or 5,5-dihalogenobarbituric acids, and secondary *o*-aminoazo-compounds more so than primary-secondary *o*-phenylenediamines.

Crippa earlier proposed the reaction of α, β-naphthylaminoazo-compounds with α-oxomethylene (or methyl) aliphatic compounds or their aromatic derivatives as a method of synthesising polycyclic quinoxaline derivatives. According to Crippa, under the influence of acid catalysts the amino-group first reacts with the carbonyl group forming an intermediate anil, after which ring formation takes place by reaction of the α-methylene (or methyl) group with the azo-group with elimination of an aromatic amine; this produces a 1,4-diazine ring[140,141,142]:



The condensation of secondary *o*-aminoazo-compounds with barbituric acid is carried out in dioxan in the presence of acetic acid. Riboflavin was obtained thus in 71% yield from *N*-(3,4-dimethyl-6-phenylazophenyl)-*D*-ribitylamine and barbituric acid[92]:

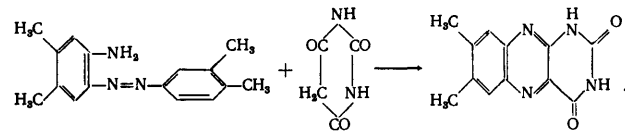


and from the corresponding *o*-aminoazo-compounds *L*-lyxoflavin (43% yield)[114,143-146], *D*-lyxoflavin[146], *D*-araboflavin, *D*-xyloflavin[147], 2′,3′,4′,5′-tetraacetylriboflavin[92], 5′-deoxyriboflavin[148], 2′-deoxyriboflavin (65.4%)[149], galactoflavin (25.6%)[150], and lumiflavin[151] were synthesised.

The substituents in the arylazo-group affect the yield of isoalloxazines in the condensation of barbituric acid with aromatic *o*-aminoazo-compounds[92].

The reaction has been shown to be catalysed by weak organic acids with dissocation constants K_a from 1.2×10^{-5} to 6.89×10^{-5}: for example, acids such as benzoic *p*-aminobenzoic, phenylacetic, nicotinic, or succinic[147]. The yield of riboflavin is raised from 21% to 62–70% when these catalysts are used.

Alloxazines have been obtained by condensation of barbituric acid with primary aromatic *o*-aminoazo-compounds[152]; for example, a naturally occurring alloxazine was synthesised from 1-amino-6-(3,4-dimethylphenylazo)--3,4-dimethylbenzene:



This reaction is catalysed by acetic and oxalic acids. 6-Methylalloxazine (88%) has been obtained by the same method[152].

The synthesis of the primary and some secondary *o*-aminoazo-compounds of the benzene series was achieved by rearrangement of triazines[149,150,153-155].

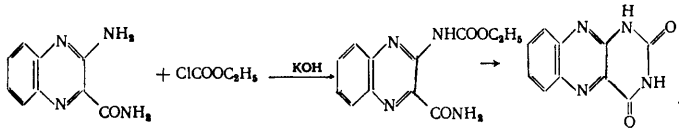
It is of interest that *o*-aminoazo-compounds of the benzene series with a methyl group in the position *ortho* to the azo-group do not condense with barbituric acid and alloxazines and isoalloxazines are not formed[152-156].

Derivatives of barbituric acid which cannot react in the α-oxomethylene form, *e.g.* 4-*O*-methylbarbituric acid and, apparently, *S*-methyl-2-thiobarbituric acid, do not condense with *o*-aminoazo-compounds and hence isoalloxazines of the corresponding types could not be obtained from these substances[121].

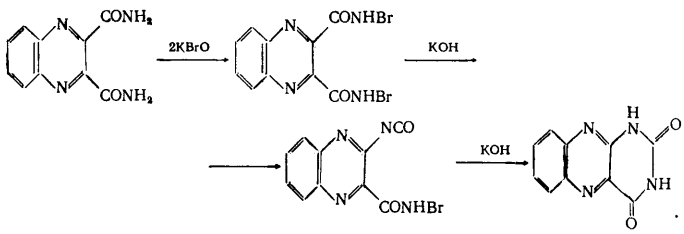
X. OTHER SYNTHESES OF ALLOXAZINES AND ISOALLOXAZINES

Quinoxalines can be converted into alloxazines by building up a pyrimidine ring on to the molecule. The action of a chloroformate ester on 2-aminoquinoxaline-3-carbonamide gives the corresponding quinoxaline urethane which

undergoes ring closure to alloxazine in good yield in the presence of sodium ethoxide[53,157]:

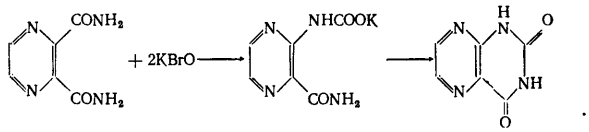


With a chloroformate ester, the methylamide of 2-methylaminoquinoxaline-3-carboxylic acid is converted into 1,3-dimethylalloxazine[53]. Alloxazine is also obtained from quinoxaline-2,3-dicarbonamide using the Hofmann reaction, by treating it with two moles of sodium hypobromite followed by alkali[158].

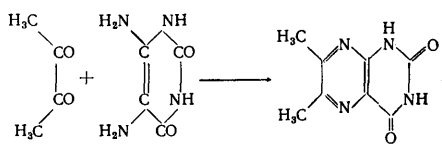


The synthesis of alloxazines and isoalloxazines from lumazines is of interest. Research was undertaken in this direction because of the suggestion that the biosynthesis of riboflavin in cells of microorganisms is achieved through lumazine derivatives[159]. The cells of *Eremothecium ashbyii* produce 6,7-dimethyl-8-ribityllumazine and a number of other substances[160]. It is curious that this compound, obtained synthetically, forms riboflavin on treatment with enzyme-containing extracts of microbic cells of *Ashbya gossypii*[161,162] but this is not the principal direction of the biochemical reaction[159].

Lumazine can be obtained by the Hofmann reaction from pyrazine-2,3-dicarbonamide and potassium hypobromite with subsequent treatment with alkali[163]:

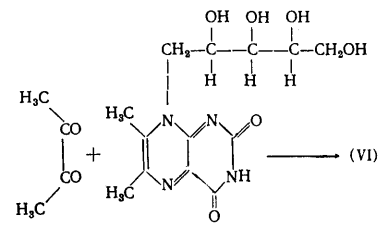


The principal method for synthesising lumazine and its derivatives, is however, the reaction of 4,5-diamino-2,6-dihydroxypyrimidines with the appropriate α-dicarbonyl compounds[164]. Thus, 6,7-dimethyllumazine was obtained from diacetyl and 4,5-diaminouracil[164]:



and 2,4-dihydroxy-6,7-dimethyl-8-*D*-ribitylpteridine (6,7-dimethyl-8-ribityllumazine) from diacetyl and 5-amino-4-*D*-ribitylaminouracil[161].

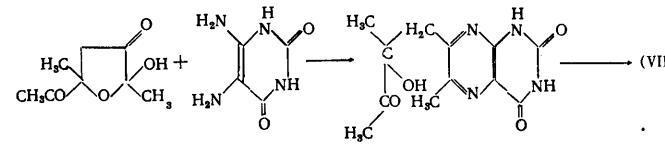
Riboflavin is obtained by the condensation of 6,7-dimethyl-8-ribityllumazine with diacetyl (130°, 6 h)[165]:



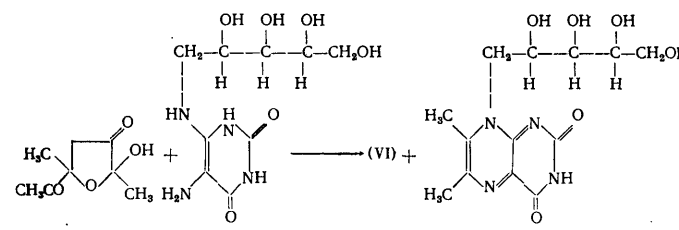
and lumiflavin from 6,7,8-trimethyllumazine by a similar condensation[165].

It has been established that in the cells of *Eremothecium ashbyii* and *Ashbya gossypii* the pyrimidine ring of riboflavin is derived from a purine precursor[166,167] and the benzene ring with *o*-dimethyl groups originates from diacetyl[167]. In connection with this, alloxazines and isoalloxazines were synthesised from 5-acetyl-2-hydroxy-2,5-dimethyl-3-oxotetrahydrofuran (a dimer of diacetyl) *via* substituted lumazines[159,167,168].

From the diacetyl dimer and 4,5-diaminouracil, 7-(2-acetyl-2-hydroxypropyl)-6-methyllumazine is obtained and under the action of 1 *N* sodium hydroxide this undergoes ring closure to lumichrome[168]:



The condensation of 5-amino-4-methylaminouracil with the same diacetyl dimer with subsequent ring closure in the presence of polyphosphoric acid gives lumiflavin[168]. A mixture of riboflavin and 6,7-dimethyl-8-ribityllumazine is obtained by the reaction of 5-amino-4-*D*-ribitylaminouracil with the diacetyl dimer followed by ring closure under the action of 0.1 *N* sodium hydroxide[159,167]:

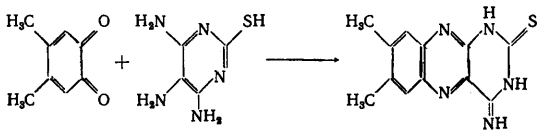


XI. SYNTHESIS OF ANALOGUES OF ALLOXAZINES AND ISOALLOXAZINES

Analogues of alloxazines and isoalloxazines are obtained by replacing the oxygen atoms of the oxo-groups in positions 2 and 4 by a sulphur atom or an imino-group. The condensation of aromatic *o*-diamines with alloxan derivatives containing sulphur or an imino-group in place of oxygen in positions 2, 4, and 6 is not used to synthesise analogues of alloxazine because the corresponding 5-oxopyrimidines are not easily available. However, it was

found possible to obtain some analogues of lumichrome by synthesising the pyrazine ring from the amino-groups of a pyrimidine compound and 4,5-dimethyl-1,2-benzoquinone.

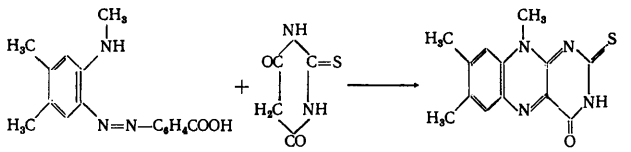
2- and 4-iminolumichrome are obtained from 2,4,5-triamino-6-hydroxy- and 4,5,6-triamino-2-hydroxy-pyrimidine, 2,4-diiminolumichrome from 2,4,5,6-tetraaminopyrimidine, and 4-imino-2-thiolumichrome from 4,5,6-triamino-2-mercaptopyrimidine [122] *e.g.* :



The reactions are carried out in boiling acetic acid; the yields are 66-90% [122].

2-Iminolumiflavin is obtained by condensation of the corresponding primary-secondary aromatic *o*-diamine with 5,5-dibromo-2-iminobarbituric acid in the presence of alkali [108].

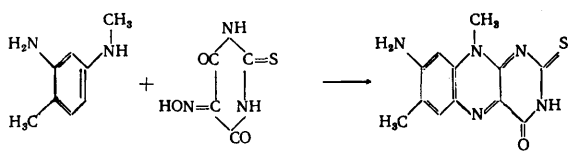
Condensation of aromatic *o*-aminoazo-compounds with barbituric acid was found suitable also for obtaining some of the simplest 2-thio- and 2-imino-analogues of isoalloxazine compounds. The condensation of 6-(*p*-carboxyphenylazo)-*N*,3,4-trimethylaniline with 2-thiobarbituric acid in the presence of acetic acid gives 2-thiolumiflavin, as reddish violet crystals, in good yield [156,169]:



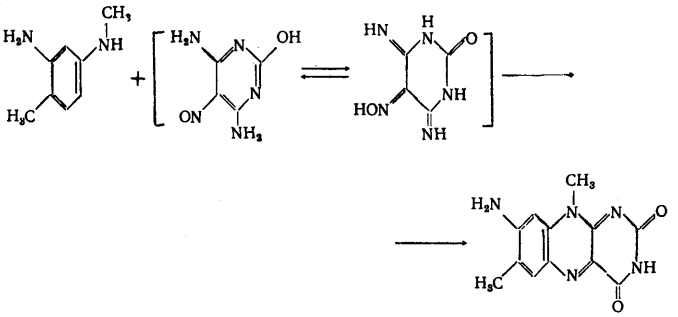
Condensation of *N*-(3,4-dimethyl-6-phenylazophenyl)-*D*-ribitylamine, 3,4-dimethyl-6-(3,4-dimethylphenylazo)-aminobenzene, 4-methyl-6-(4-tolylazo)aminobenzene, and *N*-(3,4-dimethyl-6-phenylazophenyl)-2′-deoxy-*D*-ribitylamine with 2-thiobarbituric acid gives respectively 2-thioriboflavin (60.4% yield), 2-thiolumichrome (79.7%), 6-methyl-2-thioalloxazine (73.5%) [170], and 2-thio-2′-*D*-deoxyriboflavin (69.6%) [149].

Replacement of the oxygen atom in position 2 of barbituric acid by an imino-group has a strong inhibiting effect on the condensation with *o*-aminoazo-compounds. 2-Iminobarbituric acid does not react with those compounds even when kept in pure acetic acid for 20 hours at boiling point, but if the original *o*-aminoazo-compound is converted into the hydrochloride, then 2-iminolumiflavin is formed [156].

The following have been obtained by condensation of *m*-phenylenediamines with thio- and imino-analogues of violuric acid (5-nitrosopyrimidines): from 2-thioviolurie acid, 7-amino-2-thioalloxazine [57], and also 7-amino-6,9-dimethyl-2-thioisoalloxazine [136]:



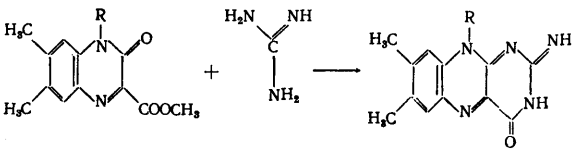
7-amino-2-imino-6,9-dimethylisoalloxazine from 2-iminoviolurie acid, 7-amino-4-imino-6,9-dimethylisoalloxazine from 4,6-diamino-2-hydroxy-5-nitrosopyrimidine, and 7-amino-2,4-diimino-6,9-dimethylisoalloxazine from 2,4,6-triamino-5-nitrosopyrimidine [136].

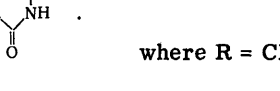


In the last two cases the pyrazine ring is closed as a result of the reaction between the secondary amino-group of the aromatic compound and the imino-group of the tautomeric form of the pyrimidine.

2-Thiolumichrome was obtained in 58% yield by the condensation of 4,5-dimethyl-*o*-phenylenediamine with 2-thioviolurie acid in an alcoholic solution of hydrogen chloride [138].

2-Iminoriboflavin and 2-iminolumiflavin were prepared by condensing esters of *N*-methyl or *N*-ribityl derivatives of 1,2-dihydro-6,7-dimethyl-2-oxoquinoxaline-3-carboxylic acid with guanidine [136,171] :

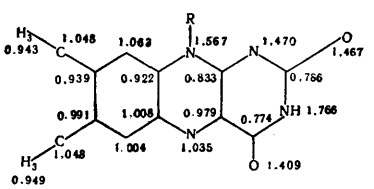


where R = CH_3 or .

XII. PROPERTIES OF ALLOXAZINES AND ISOALLOXAZINES

All compounds of the alloxazine and isoalloxazine series are high-melting crystalline substances with melting points above 200° and often above 300°. They contain a chromophore in the forming of the azomethine grouping $\rangle C{=}N-$, which explains their colour — yellow with shades from pale straw-yellow to bright orange; 7-amino-substituted alloxazines and isoalloxazines are red.

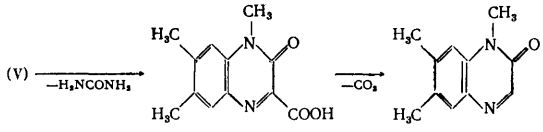
The electron density distribution in the molecule has been calculated for isoalloxazine compounds [172,173]:



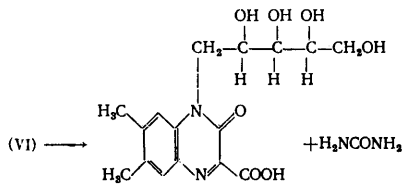
A characteristic peculiarity of compounds of the alloxazine and isoalloxazine series is the instability of the heterocyclic ring of the molecule. In alkaline solutions the

pyrimidine ring of alloxazines and isoalloxazines undergoes cleavage, particularly easily on heating, to form quinoxalines. Cleavage of alloxazine produces 2-hydroxyquinoxaline-3-carboxylic acid[45,174]. When 6,7-dimethylalloxazine is heated in sodium hydroxide solution, 2-hydroxy-6,7-dimethylquinoxaline-3-carboxylic acid is obtained[175].

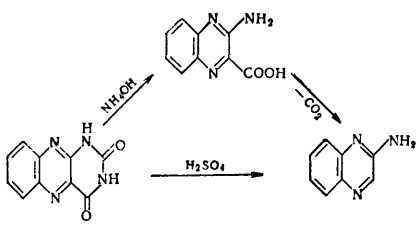
On heating with baryta water, lumiflavin gives urea[176] and 1,2-dihydro-1,6,7-trimethyl-2-oxoquinoxaline-3-carboxylic acid[21], which forms 1,2-dihydro-1,6,7-trimethyl-2-oxoquinoxaline on decarboxylation:



Riboflavin is completely decomposed by 1% sodium hydroxide in 24 h. After heating for a short time at 100° in 4% sodium hydroxide, urea and 1,2-dihydro-6,7-dimethyl-2-oxo-1-(1-*D*-ribityl)quinoxaline-3-carboxylic acid are formed[49,177]:

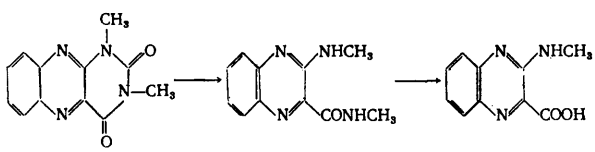


The mode of cleavage of the pyrimidine ring of alloxazine by aqueous ammonia differs from that by sodium hydroxide or baryta water; from alloxazine 2-aminoquinoxaline-3-carboxylic acid is obtained and this is decarboxylated to 2-aminoquinoxaline[175,178]:



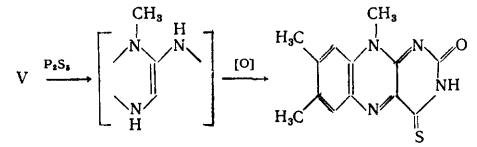
The last is also obtained directly from alloxazine by heating with concentrated sulphuric acid[175,178].

1,3-Dimethylalloxazine undergoes cleavage by sodium hydroxide in two stages[53]:

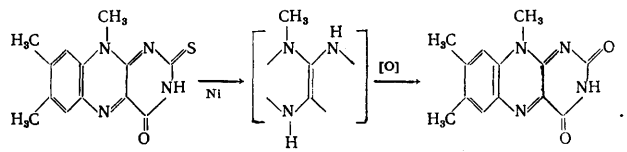


Substitution of the oxygen atom in positions 2 and 4 of the isoalloxazine molecule by a sulphur atom is evidently possible only if alloxazine is in the form of a leuco-compound[120]. 4-Thiolumiflavin is formed in good yield by the action of phosphorous pentasulphide on lumiflavin in pyridine; the lumiflavin is first reduced by the sulphide to a leuco-compound, substitution taking place only after this.

The intermediate 4-thioleucolumiflavin is then oxidised by atmospheric oxygen to 4-thiolumiflavin[120]:



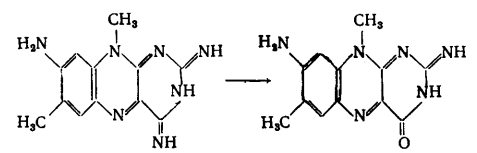
The sulphur atom in thioalloxazines is easily replaced by oxygen, alloxazines being formed. 7-Amino-2-thioalloxazine loses the sulphur atom on treatment with mercuric oxide[57]. 2- and 4-thioisoalloxazines are oxidised to isoalloxazines by atmospheric oxygen. By the action of Raney nickel on 2-thiolumiflavin its leuco-compound was first obtained; in the latter the sulphur atom is not replaced by hydrogen with Raney nickel at 20°, but on heating with access of air the sulphur is removed and lumiflavin is formed[120]:



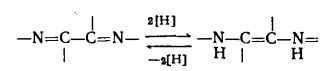
Under the action of dilute hydrogen peroxide or atmospheric oxygen, 2-thioriboflavin, 2-thio-2′-deoxyriboflavin, 6-methyl-2-thioalloxazine, and 2-thiolumiflavin are easily oxidised to riboflavin[170], 2′-deoxyriboflavin[149], 6-methylalloxazine[170], and lumiflavin[151] respectively.

An attempt to replace the oxygen in positions 2 and 4 of lumiflavin by chlorine using phosphoryl chloride or thionyl chloride led to breakdown of the isoalloxazine ring[120].

In 7-amino-2,4-diimino-6,9-dimethylisoalloxazine the 4-imino-group is selectively hydrolysed; the compound gives, on brief treatment with warm alkali, 7-amino-2-imino-6,9-dimethylisoalloxazine in which the 2-imino-group is stable towards alkali[136]:



Isoalloxazines possess characteristic redox properties because of the presence, in the molecule, of the redox system:

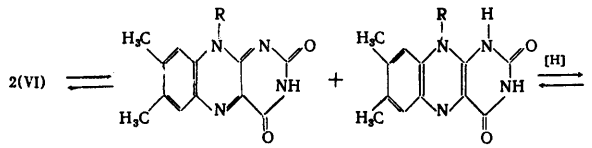


They can be easily reduced chemically or catalytically to colourless leuco-compounds which give coloured compounds again on oxidation.

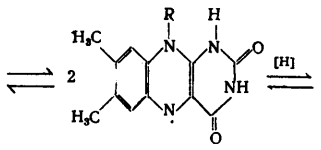
For example, riboflavin is easily reduced by two hydrogen atoms to leucoriboflavin, the yellow-orange colour of the substance and its fluorescence in solution disappearing[179]. Under the action of atmospheric oxygen or other oxidising agents the leuco-compounds is easily reconverted into riboflavin.

The reduction of riboflavin to the leuco-compound takes place through intensely coloured intermediate compounds[180], which are complexes of riboflavin or its leuco-form with

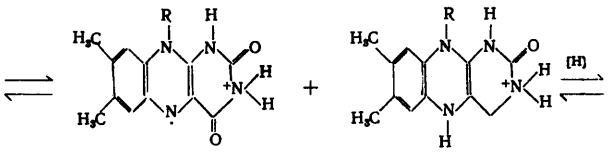
semiquinonoid radicals and which form a flavin cation on losing one electron or give leucoriboflavin on gaining a proton:



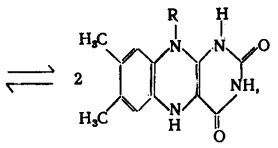
riboflavin (yellow-orange) verdoflavin (green)



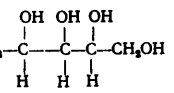
chloroflavin (green)



rhodoflavin (carmine red)



leucoriboflavin (colourless)

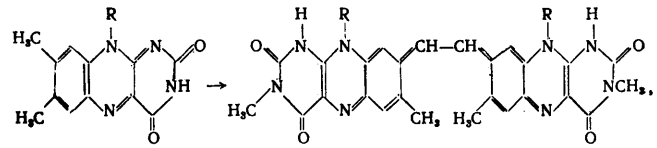
where R = 

According to new evidence, flavin enzymes are involved in the transfer of an electron in the respiratory chain in the form of the intermediate flavo-semiquinonoid compound of the free radical chloroflavin[181-189]. The extremely high activity of flavin enzymes as biocatalysts can be explained by this.

When isoalloxazines are exhaustively hydrogenated in the presence of a platinum catalyst under pressure the aromatic nucleus is reduced and colourless compounds are formed; for example, octahydro-9-(1-*L*-arabityl)isoalloxazine is obtained from 9-(1-*L*-arabityl)isoalloxazine[190].

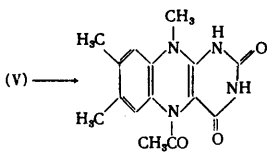
Alkylation and dealkylation reactions of alloxazines and isoalloxazines are of interest. 1,3-Dialkylalloxazines are formed rapidly and in good yield in the alkylation of alloxazines at 120°-150° with diazomethane[38] or a mixture of excess dialkyl sulphate and dimethylformamide, with potassium carbonate as a basic catalyst, for example, alloxazine gives 1,3-dimethylalloxazine[191] and lumichrome, 1,3-dimethyllumichrome[38]. In the isoalloxazine series the same reaction gives 3-alkyl derivatives — 3,9-dimethylisoalloxazine is obtained from 9-methylisoalloxazine[191]. 3-Methyllumiflavin is produced from lumiflavin under the action of dimethyl sulphate in the presence of sodium hydroxide solution[192].

7-Methylisoalloxazines, first and foremost lumiflavin and riboflavin, behave anomalously under the above methylation conditions; irreversible dimerisation occurs as well as methylation[191]:



where R = CH_3 or ribityl.

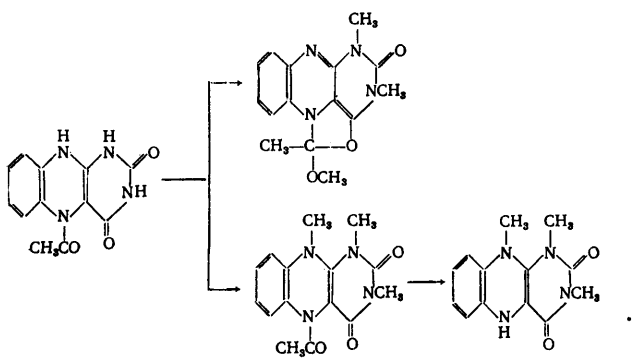
Stable 10-acetylleuco-compounds are formed on the reductive acetylation of alloxazines and isoalloxazines using zinc in a mixture of acetic anhydride and acetic acid[120], for example,



The acetyl group in position 10 inhibits the reverse oxidation of the leuco-compounds to alloxazines and isoalloxazines. It is hydrolysed by heating in dilute mineral acids[120].

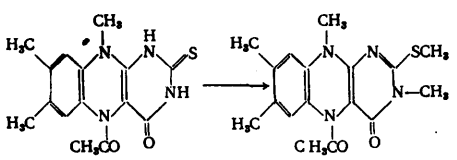
The alkylation reaction of leucoalloxazines is unusual. Methylation of 10-acetylleucoalloxazine with dimethyl sulphate and dimethylformamide plus potassium carbonate gives a complex mixture which, after acid hydrolysis and autoxidation, contains 1- and 3-methylalloxazines with 1,3-dimethylalloxazine and a small amount of 3,9-dimethylisoalloxazine[80].

Methylation of 10-acetyl-1,3-dimethylleucoalloxazine using diazomethane leads to ψ-10-acetyl-*ONN*-trimethylleucoalloxazine and 10-acetyl-1,3,9-trimethylleucoalloxazine, from which 1,3,9-trimethylleucoflavin is formed on hydrolysis in the presence of hydrochloric acid.



The last is more stable than all known leucoisoalloxazines[80].

10-Acetyl-2-thioleucolumiflavin is methylated, using dimethyl sulphate, first at the sulphur atom and then at the nitrogen in position 3:[120]



while 2-thiolumiflavin in the normal form is methylated by methyl iodide or diazomethane at position 3, forming 3-methyl-2-thiolumiflavin[120].

Isoalloxazines containing 3- and 2-hydroxyalkyl groups in position 9 undergo photolysis under the influence of light particularly direct sunlight[18,19,60,63,64,193,194] and ultraviolet light[195]. In alkaline, neutral, and even acidic, solutions the hydroxyalkyl group is split off; this reaction is more vigorous at low concentrations. Such compounds as 9-(2-hydroxyethyl)- and 9-(2,3-dihydroxypropyl)-isoalloxazine are decomposed to alloxazine[60]. Photolysis of riboflavin in neutral and acidic solutions leads to complete dealkylation and the formation of 6,7-dimethylalloxazine (lumichrome)[196] and the breakdown of the pentose residue to hydroxyethanal and glyceraldehyde[197,198].

In alkaline solutions the main photolysis of the riboflavin molecule is connected with the splitting off of the side chain between atoms $C_{(1)}$ and $C_{(2)}$, with formation of 6,7,9-trimethylisoalloxazine (lumiflavin)[18,21]; there is at the same time partial decomposition to lumichrome. The photolysis of riboflavin in alkaline solution in the presence of hydrogen peroxide gives, besides lumichrome and lumiflavin, 6,7-dimethylisoalloxazine-9-acetic acid (7%)[199]. Metals catalyse the photolysis of riboflavin[200]. The ribityl group of riboflavin, which is unstable to light, is stabilised by passing oxygen through the solution[185,186,201].

Isoalloxazines with 3-hydroxyalkyl substituents in position 9 display less photosensitivity than compounds with 2-hydroxyalkyl groups. The photolysis of 9-(3-hydroxypropyl)- and 6,7-dimethyl-9-(*D*-2-deoxyribit-1-yl)-isoalloxazine is considerably more difficult[63].

2′,3′,4′,5′-Tetraacetylriboflavin and lumiflavin, the molecules of which do not contain free hydroxyl groups, do not decompose on irradiation[60].

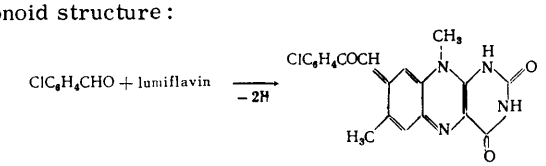
Lumiflavin is not dealkylated at 18°–20° but in hot neutral or weakly acid solution it decomposes photolytically to lumichrome[80]. The very slow reaction is accelerated by adding metal ions: Fe^{2+}, Sn^{2+}, or Co^{2+}. Decomposition does not occur if oxygen is passed through the solution.

Light is not a specific catalyst for the decomposition of 9-substituted isoalloxazines, which is catalysed by metal ions[185,186,200], and in some cases by bases[171] and by reagents for a carbonyl group[80].

9-Methylisoalloxazine, lumiflavin (9-methylflavin), and their 3-methyl derivatives were dealkylated (in good yields) to alloxazine, lumichrome, and their 3-methyl derivatives by boiling repeatedly with excess hydroxylammonium sulphate in glacial acetic acid. The same result was obtained with hydrazine and phenylhydrazine, but with lower yields[80].

Since the carbon atom in position 7 of the alloxazine molecule has a lower electron density than atoms $C_{(5)}$, $C_{(6)}$, and $C_{(8)}$,[172] a methyl group in that position must have an increased tendency to react with electrophilic reagents.

Lumiflavin reacts with *p*-chlorobenzaldehyde at 20° in concentrated sulphuric acid containing phosphorus pentoxide; the compound obtained by Hemmerich *et al*[191] is considered to be an isoalloxazine derivative possessing a quinonoid structure:

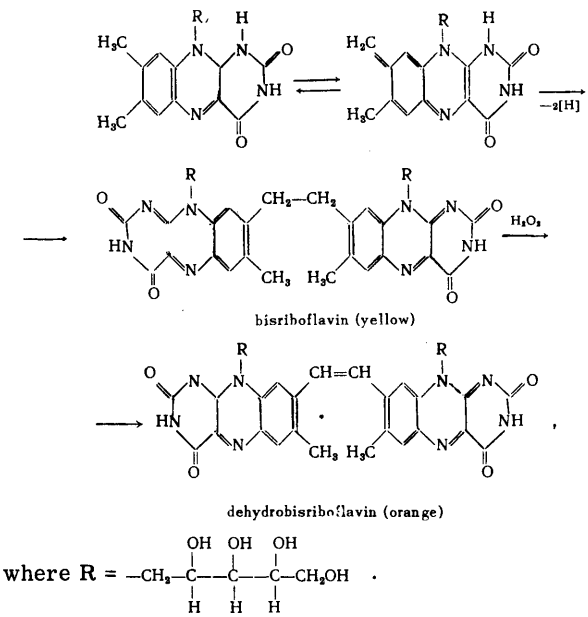


When lumiflavin is treated with excess nitrous acid in boiling acetic acid, the methyl group in position 7 is oxidised giving the hardly stable 6,9-dimethylisoalloxazine-7-carboxylic acid which is converted into 6-methylalloxazine-7-carboxylic acid under the action of alkali[191].

The particular activity of position 7 in the isoalloxazine system is shown by the chlorine in 7-chloro-6,9-dimethylisoalloxazine being rather easily replaced using such nucleophilic reagents as sodium methoxide and ethanolamine, with the formation of, respectively, 7-methoxy- and 7-(β-hydroxyethylamino)-6,9-dimethylisoalloxazine[191].

The amino-group in 7-amino-6,9-dimethylisoalloxazines is weakly basic and can, with difficulty, be acylated and diazotised[136]. However, the amino-group in 8-aminolumiflavin has aromatic character; it is diazotised in strongly acid solution, the diazonium cation takes part in azo-coupling and undergoes cleavage. Deamination results and lumiflavin is formed[108].

The ability of lumiflavin and riboflavin to dimerise through the methyl group in position 7 is also of interest. The reactions connected with the dimerisation can be represented by the following scheme[191]:



where R = $-CH_2-\overset{H}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{H}{C}}-CH_2OH$.

The dimers bisriboflavin and bislumiflavin were obtained by treating the flavins with potassium carbonate in hot dimethylformamide in a nitrogen atmosphere.

Where isoalloxazines containing a polyhydroxyalkyl group in position 9 are treated with lead tetraacetate or periodic acid, this side chain is split off; thus 9-formylmethyl-6,7-dimethylisoalloxazine was obtained from riboflavin[202,203]. Riboflavin is oxidised by chromic acid[204] and by potassium permanganate but bromine, hydrogen peroxide, and nitric acid have no effect on it.

The hydroxyl groups of the ribityl chain in riboflavin easily form ethers and esters. The primary hydroxyl in the 5′ position is the first to undergo esterification, and then the secondary hydroxyls in the 2′, 3′, and 4′ positions.

5′-Tritylriboflavin is produced by the action of triphenylchloromethane on riboflavin in pyridine[205]. With acetic anhydride or acetyl chloride, riboflavin gives 2′,3′,4′,5′-tetraacetylriboflavin[92]. Sulphate esters are obtained by

dissolving riboflavin in concentrated sulphuric acid[206] or by the reaction of chlorosulphonic acid in chloroform with a solution of riboflavin in pyridine[207,208]. The mono-, di-, tri-, and tetra-sulphate esters are isolated as the calcium salts. Riboflavin-5′ monosulphate is an antivitamin[207].

Phosphate esters are obtained by the action on riboflavin of various phosphorylating agents, such as phosphoryl chloride, phosphorochloridic acid, dialkylphosphorochloridic acids, etc.[209-216]. A mixture of mono-, di-, and poly-5′-phosphates is obtained; they are fairly stable. The riboflavin di- and poly-phosphates are partially hydrolysed to riboflavin-5′ monophosphate by hydrochloric acid[216-218].

Albert showed, in 1950, that riboflavin forms inner complexes (chelate compounds) with bivalent metals[219]. A series of these insoluble complexes of riboflavin with iron, nickel, cobalt, copper, zinc, and manganese was isolated[220]. They contain two metal atoms to each flavin molecule but it is not clear how these atoms are bound. It is probable that the biocatalytic activity of many flavin enzymes is connected with metal ions, such as iron molybdenum, copper, or manganese, contained in them[219-228].

A peculiarity of alloxazines and isoalloxazines is their ability to fluoresce in solutions exposed to light, particularly on excitation by ultraviolet light. Weak aqueous solutions of many flavins, including riboflavin, emit an intense yellow-green light. The fluorescence spectrum of riboflavin lies between 515 and 615 mμ with a maximum[229] at 565 mμ and it is most intense at pH 6–8; [204] the intensity of colour weakens in acidic and alkaline medium and depends on the concentration of the substance in the solution[230].

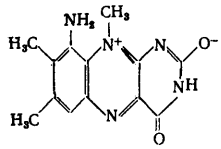
It has been shown that the ability of isoalloxazines to fluoresce is accounted for by the conjugated system $-N=\overset{|}{C}-\overset{|}{C}=N-$ and the intensity of fluorescence depends on the coplanarity of this system with the plane of the nucleus of the molecule[76]. The fluorescence is reduced to 20–23% when a methyl group is substituted in the 5-position[76].

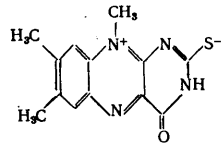
It is of considerable interest to establish how the fluorescence of alloxazines and isoalloxazines depends on different substituents and their position. However, a systematic study of the effect of substituents, under comparable conditions, on the fluorescence has not been made.

Change of the position of the methyl groups in the benzene ring of alloxazine and an increase in their number causes the fluorescence colour to deepen from violet through dark blue-violet, greenish blue, yellow to purple-yellow[40,41,186] in the following sequence: unsubstituted alloxazine < 6- or 7-mono- < 6,7-di- < 8-mono- < < 6,7,8-tri- < 5,7,8-tri- < 5,6,7,8-tetra-.

The isoalloxazine molecule with the simplest $N_{(9)}$-methyl substituent has a yellow-green fluorescence; introduction of a methyl group into positions 5, 6, and 7, a carboxy- or methoxy- group in position 7, a nitro-group in position 8, or hydroxyalkyl groups in position 9 has hardly any effect on the spectrum[58,108,191,196]. However, some substituents in position 8, such as a methyl group, cause a bathochromic effect, the colour deepening to brownish yellow[66]. An imino-group in position 2 or 4 causes a small increase of colour (a hypsochromic effect)[120,136,151].

Lumiflavin with an amino-group in position 8 (brownish red) and 2-thioflumiflavin (reddish violet) and its derivatives do not possess fluorescence[120,136]. It can be assumed that the absence of fluorescence is connected with the nitrogen atom in position 9 possessing a high positive charge, the isoalloxazine compounds being in a polar form in which evidently they mainly exist in solution[108,151]:

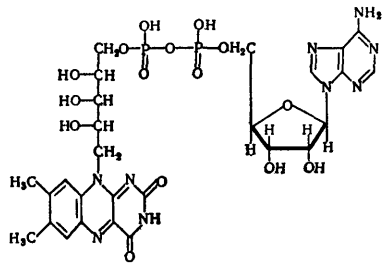




XIII. NATURALLY OCCURRING ALLOXAZINES AND ISOALLOXAZINES AND COMPOUNDS WITH ANTIMETABOLITE AND PHARMACOLOGICAL PROPERTIES

Besides riboflavin (vitamin B_2), *L*-lyxoflavin is possibly found in animal organisms; its isolation from cardiac muscle has been reported[231], but reliable confirmation of this has not been obtained[232]. Lumiflavin and lumichrome have been isolated together with riboflavin from the retina of the eye.

Riboflavin-5′ monophosphate and flavin-adenine dinucleotide



are coenzymes containing riboflavin. They represent the prosthetic group of flavin enzymes[17,18,233-237].

Of riboflavin analogues, 2-thioriboflavin possesses the full activity of vitamin B_2.[170]

In their biological action, many alloxazine and isoalloxazine compounds are antivitamins; the strongest are: araboflavin[238], galactoflavin[239], 5′-deoxyriboflavin[148], isoriboflavin[93], and riboflavin-5′sulphate[207]. 6,7-Dichloro-9-(1-*D*-ribityl)isoalloxazine[99,100], 7-chloro-6-methyl-9-(1-*D*-ribityl)isoalloxazine, and many other halogen-substituted isoalloxazines[100,102,105] are bacterial inhibitors of riboflavin. It was found that 7-chloroalloxazine possesses diuretic action[55].

6-(5-Dialuryl)-7-methyl- and 6-chloro-9-(4-diethylamino-1-methylbutyl)-isoalloxazine possess antimalarial action[106,240]. 2-Thiolumiflavin and 2-iminolumiflavin display bacteriostatic action on Gram - positive bacteria and, in experiments on animals, inhibit the growth of cancerous tissue[171]. 1,2-Dihydro-6,7-dimethyl-2-oxo-1-(1-*D*-ribityl)-quinoxaline-3-carboxylic acid, a decomposition product of riboflavin, lowers the blood pressure and depresses the activity of cardiac muscles[177].

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CATALYTIC HYDROGENATION AND HYDROGENOLYSIS OF FURAN COMPOUNDS

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