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The Autoxidation of Azo-compounds and Certain Aspects of Associated Biochemical Processes†

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CONTENTS

I.	Introduction	121
II.	The mechanisms of oxidation under the influence of molecular oxygen	121
III.	The autoxidation of amines	122
IV.	The reactions of amides with molecular oxygen	125
V.	The oxidation of imines and enamines	127
VI.	The autoxidation of compounds with a double bond and a nitrogen atom in the ring	128
VII.	The oxidation of hydrazones	138
VIII.	The base-catalysed autoxidation of azo-compounds via an ionic mechanism	138
IX.	The interaction of hydrazines with oxygen	139
X.	The intermediate formation of peroxides in the bioluminescence process	140

I. INTRODUCTION

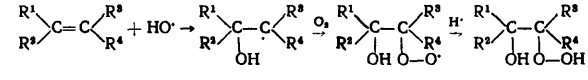
There is much interest at the present time in the role of organic peroxides in biochemical processes. After the discovery by Latarjet et al.[1] concerning organic peroxides in radiobiology, a study was published[2] on the biochemical importance of lipid peroxides, which subsequently served as a basis for a large review on this subject[3]. In recent years particular attention has been devoted to the oxidation of azo-compounds under the influence of molecular oxygen (in the triplet or singlet states). The studies published in recent years are concerned with the sensitised photochemical oxidation of aliphatic amines and oxides, various pyrrole, imidazole, oxazole, and isoindole derivatives, and also the oxidation of nucleic acid derivatives in the aqueous phase initiated by ionising radiation. Apart from the numerous original studies, the action of molecular oxygen on azo-compounds has been examined in a review[4] (containing 143 references to studies published up to 1967), while nucleic acids are dealt with in a major article[5] (70 references to studies published up to 1964). All these considerations led the present author to write a survey on the subject[132], combining all the latest and older studies on the autoxidation of aliphatic amines (in the gas phase), indoles, tetrahydrocarbazoles, dihydro-oxazines, tetrahydropyrazines, and hydrazones (in the liquid phase). Furthermore, in the studies published after 1967 (44 publications) the properties of the peroxides formed have been described in detail and an attempt has been made to relate, as far as possible, their formation to biological processes such as the decomposition of enzymes, the formation of pigments (kynurenine and melanin), the structural changes in alkaloids, and changes at the cellular level.

The results of 30 similar studies carried out in recent years, seven of which were published in 1975, are analysed in the present review. In particular, the review is concerned with the problem of the intermediate formation of peroxides in bioluminescence.

In the section dealing with oxidation mechanisms (oxidation by molecular oxygen), it was thought unnecessary to include the description of the classical chain mechanism of autoxidation.

II. THE MECHANISMS OF OXIDATION UNDER THE INFLUENCE OF MOLECULAR OXYGEN

The classical mechanism of the oxidation of hydrocarbons under the influence of O_2 is applicable to aldehydes, ethers, and esters[6-10]. Initiation may be due to the radical generated from a source other than the substrate; for example, in the presence of ionising radiation, the autoxidation of unsaturated compounds in the aqueous phase is initiated by HO· radicals formed from H_2O. It is terminated by formation of hydroxyhydroperoxides via the mechanism



The H· atom is also formed from H_2O. The reaction involving nucleic acids proceeds in this way.

The oxidation of nitriles, hydroxylamines, (ketones and branched esters), and pyrazolones is very strongly accelerated in the presence of bases. It is suggested[12,13,183] that this type of oxidation proceeds via a mechanism similar to that described above but with participation of the anion R^- (rather than the radical R·):

$$RH + HO^- \rightarrow R^- + H_2O;\ R^- + O^3 \rightarrow RO{-}O^-;$$
$$RO{-}O^- + HR \rightarrow RO{-}OH + R^- .$$

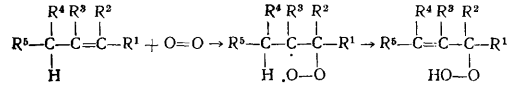
Sensitised photochemical oxidation proceeds in the presence of light and certain dyes (Methylene Blue, Rose Bengal, haematoporphyrin, and chlorophyll). In certain cases, for example in the presence of anthracene hydrocarbons, the substrate itself plays the role of the sensitiser. The sensitisation can be achieved via two different mechanisms.

1. In the first mechanism, the dye in the excited (biradical) state plays the role of a dehydrating agent, leading to the formation of a radical R·, which is then oxidised via the classical mechanism (involving O_2 as the triplet $^{\cdot}O{-}O^{\cdot}$).

†This review was written specially for the journal "Uspekhi Khimii". It was translated from French into Russian by T.V. Chernysheva.

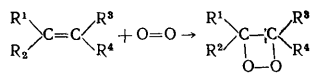
2. In the second mechanism, O_2 is involved in the singlet form O=O (formed in a certain amount under the conditions described above), which is capable of adding to ethylenic double bonds.

(a) In the oxidation of a mono-olefin having hydrogen atoms in the α-position relative to the double bond, a hydroperoxide is usually formed in accordance with the equation



Many unsaturated hydroperoxides, for example those of α- and β-pinenes [14] and of carvomenthene [15] have been obtained by this method. One should note that, in the presence of even one α-methylene hydrogen atom at the double bond, two peroxide isomers are usually formed.

(b) In the absence of an α-methylene hydrogen atom, O=O may add to the double bond with formation of a 1,2-peroxide:



This reaction proceeds more readily in the presence of nucleophilic substituents.

(c) In a system with conjugated double bonds, the addition in the 1,4-positions is stereospecific and proceeds only in the *cis,cis*-configuration. Numerous endoperoxides have been obtained in this way as a result of the sensitised photochemical oxidation of the corresponding 1,3-dienes (for example of ascaridole—from α-terpinene in the presence of chloropyll [16]).

The mechanism of sensitised photochemical oxidation has been discussed in a number of publications [17-21,181,184]. The stereospecificity of the reaction has also been considered [21]. Schaap and Faler [22] and Hasty and Kearns [23] examined the photochemical oxidation of alkenes and dienes.

The biological importance of the photochemical oxidation sensitised by various dyes, inducing the decomposition of aminoacids (aromatic and heterocyclic), nucleic acids, and various proteins, as well as the inactivation of viruses and cells of multicellular organisms has been discussed by Spikes [176].

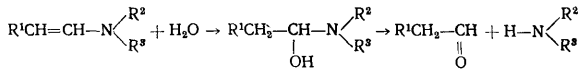
III. THE AUTOXIDATION OF AMINES

1. The Reactions of Aliphatic Amines with Hydroperoxides

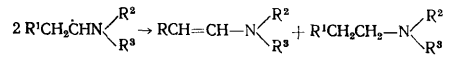
These reactions proceed via a mechanism different from that operating in the oxidation of amines by peracids (involving electrophilic attack by the oxygen of the peracid on the nitrogen atom of the amine). In the reactions with hydroperoxides, the dominant feature is the dehydrogenation of the amines simultaneously at the C and N atoms (when this is possible), which leads to the formation of an alcohol, water, or an imine. The hydrolysis of the latter leads to a carbonyl compound and the dealkylated amine:

$$RO{-}OH + R^1CH_2NHR^2 \rightarrow ROH + H_2O + R^1CH{=}NR^2,$$
$$R^1CH{=}NR^2 + H_2O \rightarrow R^1CHO + H_2NR^2.$$

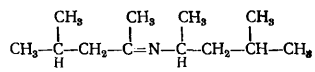
The molecules of the carbonyl compound may condense with one another (this reaction is favoured in an alkaline medium), with the initial amine, or with the dealkylated amine, forming respectively unsaturated carbonyl compounds and aldimines (or ketimines). The formation of a secondary amine and a carbonyl compound from a tertiary amine apparently proceeds as a result of the hydrolysis of the intermediate imine:



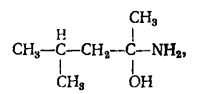
which is probably obtained as a result of the disproportionation of the radical $R^1CH_2CHNR^2R^3$:



The action of O_2 at 60–100°C on 4-methyl-2-pentylamine (I), 2,4,4-trimethyl-2-pentylamine (II), di-isopropylamine (III), and tri-n-propylamine (IV) has been considered [3] and it has been shown that $(CH_3)_3COH$, H_2O, and NH_3 (or RNH_2) are formed in satisfactory yields. In the reaction with the amine (I), the yields were 100, 82, and 60%; in addition, the compound



was isolated in 24–40% yield. The first compound, identified by infrared spectroscopy, is an aminoalcohol:



the subsequent decomposition of which to a carbonyl compound and NH_3 is facilitated by the formation of a hydrogen bond.

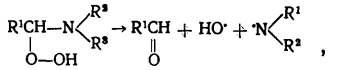
In the reaction with the amine (III), the yields of $(CH_3)_3COH$, H_2O, $(CH_3)_2CHNH_2$, and acetone were 85, 45, 88, and 95% respectively. The yields of t-butyl alcohol and dipropylamine from the amine (IV) were 80 and 32%.

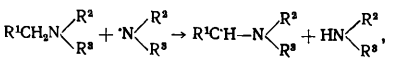
We may note that the corresponding nitro-derivative is formed in 2% yield from compound (II), which has no hydrogen atoms in the α-position relative to the nitrogen atom, and that the reaction is very slow. The mechanism of the action of hydroperoxides on amines has been examined in detail [24,25] and the mobility of the hydrogen atom linked to the nitrogen atom and the carbon atom in the α-position relative to the former has been discussed [26,27].

2. The Autoxidation of Aliphatic Amines in the Gas Phase

The autoxidation of aliphatic amines in the gas phase has been considered [28-34]. Studies have shown that the temperature of their oxidation (300°C) is lower by 200°C than the pyrolysis temperature. In contrast to hydrocarbons, ethers, and aldehydes, their oxidation is self-inhibited, but there is no appreciable induction period. The rate of oxidation depends on the structure of the amine and increases greatly as a result of branching both at the nitrogen and carbon atoms [30]. Table 1 presents the relative rates of oxidation K of various amines at 310°C, the relative rate of oxidation of CH_3NH_2 having been adopted as unity.

The products of the reaction consist of carbonyl compounds and dealkylated amines, apparently formed from the intermediate hydroperoxides,



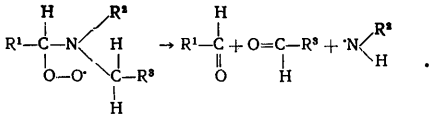


whose presence has been demonstrated in the oxidation of CH_3NH_2 at 350°C; their content reaches a maximum of 2×10^{-6} mole/mole of amines after 2 min, decreasing subsequently and reaching zero after 4 min. In the light of the above, one may assume that the carbonyl compound and the dealkylated amine may be formed as a result of the decomposition of the intermediate aminoalcohol $R^1CH(OH).NR^2R^3$ produced by the action of the hydroperoxide $R^1CH(OOH)NR^2R^3$ on the initial amine. The absence of alcohols ROH shows that the hydroperoxide cannot be cleaved in the β-position.

Table 1. [30]

Primary amine	K	Secondary amine	K
Methylamine	1	Dimethylamine	19
Ethylamine	5.6	Ethylmethylamine	150
Propylamine	48	Diethylamine	255
Butylamine	230	Methylpropylamine	580
Isopropylamine	107	Dipropylamine	760
Isobutylamine	170		

There is a possibility of the direct formation of a primary amine from the tertiary amine via the reaction [33]



The reactions of C_1-C_9 primary amines have also been discussed [28,29], while other workers considered secondary amines [31] and tertiary amines [32-34].

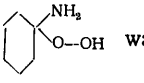
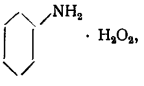
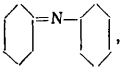
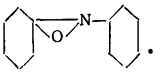
3. The Sensitised Photochemical Oxidation of Aliphatic and Aromatic Alkylamines in the Liquid Phase

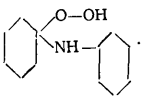
It has been shown [14] that primary amines (methyl-, ethyl-, propyl-, isopropyl-, and isobutyl-amines), secondary amines (diethylamine, pyrrolidine, and piperidine), and tertiary amines (triethylamine) are capable of absorbing oxygen and forming peroxides as a result of photochemical oxidation in the presence of chlorophyll, eosin, and haematoporphyrin. The amounts of absorbed O_2 (in moles per mole of the amine) are respectively 1, 2, and 2.6. On the other hand, $(CH_3)_3.CHNH_2$ does not absorb oxygen under these conditions owing to the absence of hydrogen atoms at the carbon atom in the α-position relative to the nitrogen atom. These findings indicate attack on the carbon atom in the α-position with the formation of a hydroperoxy-group in this position (as in the oxidation of amines in the gas phase).

The photochemical oxidation of the primary amines $C_3H_7NH_2$, $C_6H_5NH_2$, and $C_6H_5CH_2NH_2$, the secondary amine $(C_3H_7)_2NH$, and the tertiary amines $(C_2H_5)_3N$, $(C_3H_7)_3N$, $(C_6H_5CH_2)_3N$, $C_6H_5N(CH_3)_2$, and $C_6H_5N(C_2H_5)_2$, sensitised by benzophenone and dyes (Methylene Blue, eosin, and Rose Bengal) at room temperature in benzene or methanol solution, has been investigated in detail [35]. Primary and secondary amines proved to be relatively inactive and their decomposition products were not detected. In the reactions of tertiary amines, aldehydes and aldimines, formed as a result of the condensation of the aldehydes with initial amines or amines produced by dealkylation, were identified.

The formation of aldimines, corresponding to the formation of primary amines in the photochemical oxidation of tertiary amines, suggests the direct formation of the former from the latter (via a mechanism similar to that operating in the gas phase). Analogous results were obtained [36] in a study of the tertiary amines $(C_3H_7)_3N$, $(C_2H_5)_3N$, and $C_6H_5N(CH_3)_2$ using polycyclic aromatic hydrocarbons (naphthalene, perylene, anthracene, and phenanthrene) as sensitising agents. These investigations showed that the initial stage of the reaction involves the dehydration of the amines by the sensitiser and the formation of the radical $R^1CH_2\dot{C}HNR^2R^3$, the subsequent behaviour of which should be similar to but not identical with its behaviour in the gas phase.

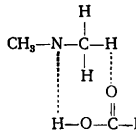
Indeed, apart from the cleavage in the α-position, there is also a possibility of the cleavage in the β-position as a result of the addition of singlet O_2 to the double bond of the enamine produced by the disproportionation of the radical. In a study of the autoxidation [37] of mono-, di-, and tri-butylamines, it was shown that, apart from the postulated products (butylidenebutylamine, butylaldehyde, and propylamine), produced as a result of cleavage in the α-position, considerable amounts of mono- or di-formamides are formed, indicating cleavage in the β-position. The reaction mechanism is discussed and the formation of reaction products as a function of the type of amine and solvent (ethanol, acetone, acetonitrile, and methyl methacrylate) is explained [37].

In certain cases it has been possible to isolate the corresponding hydroperoxide. In a study [28] of the benzophenone-sensitised photochemical oxidation of cyclohexylamine at temperatures between −20° and 20°C using ether and its mixtures with alcohol as solvents, the hydroperoxide  was isolated together with some of the decomposition products: the adduct , the cyclohexylideneamine , and the oxaziran . Under conditions identical to those described above, the hydroperoxide



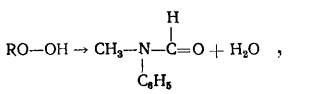
was also isolated from dicyclohexylamine [38].

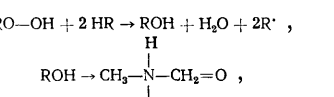
Aromatic alkylamines can also be oxidised in the absence of sensitisers. The autoxidation of *NN*-dimethylaniline (DMA), which has been investigated in particular detail by Horner and Knapp[40], has been described[29]. The autoxidation of DMA is catalysed by radical initiators—benzoyl peroxide[39], azobisisobutyronitrile[40], and particularly cobalt salts (manganese salts are less active and nickel and copper salts are completely inactive). Carboxylic acids also exhibit a catalytic activity, which is probably a consequence of the neutralisation of the amine and partly the formation of a cyclic complex in which a C–H bond in CH_2 is weakened, which favours attack by O_2 at this site:

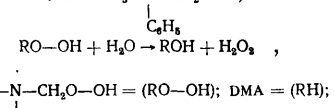


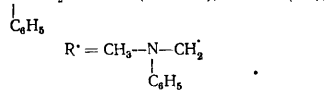
At 20°C, 80 mole % O_2 is absorbed in 90 min in the reaction catalysed by 0.2 mole % (relative to DMA) of cobalt stearate using a mixture of acetic acid, acetic anhydride, and benzene as solvent. The product consists of 50 mole % of peroxides (40% of H_2O_2 and 60% of organic peroxide), 90 mole % HCHO (45% in a free state), and 88 mole % $C_6H_5NHCH_3$. Apart from the compounds enumerated above, $(CH_3)_2NC_6H_4CH_2C_6H_4N(CH_3)_2$ can also be formed (as a result of the condensation of HCHO with DMA).

The nature of the products obtained and their relative amounts suggest the following mechanism of their formation from the hydroperoxide:

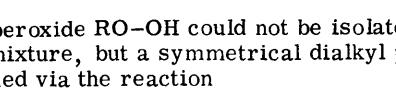


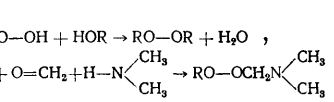




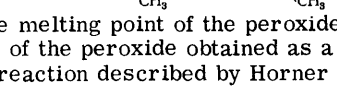


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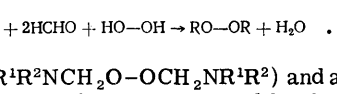




The hydroperoxide RO–OH could not be isolated from the reaction mixture, but a symmetrical dialkyl peroxide RO–OR, formed via the reaction



was isolated. The melting point of the peroxide RO–OR is identical with that of the peroxide obtained as a result of synthesis via the reaction described by Horner and Knapp[41]:



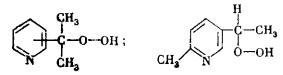
Symmetrical ($R^1R^2NCH_2O-OCH_2NR^1R^2$) and asymmetric ($R^1R^2NCH_2O-OR$) peroxides, synthesised by the action of secondary amines on formaldehyde in the presence of H_2O_2 or RO–OH respectively, are also known[42].

Similar results were obtained with certain DMA derivatives substituted in the benzene ring. We may note that nucleophilic groups increase and electrophilic groups decrease the rate of absorption of O_2.[39,40] On the other hand, aliphatic amines do not absorb O_2 in the presence of cobalt salts even at 40°C. All the methods and the complete composition of the products of the reactions are quoted by Horner and Knapp[40].

Primary aromatic amines absorb oxygen at room temperature only in a highly alkaline medium (in the presence of alkali metal alkoxides). The dominant process is dehydrogenation, leading to the formation of the corresponding diazo-compounds. This reaction may be inhibited by benzene derivatives disubstituted in the *ortho*- and *para*-positions; α- and β-naphthylamines yield the corresponding phenazines. This reaction has been discussed in detail by Horner and Dehnert[43].

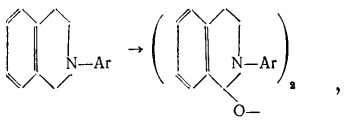
Non-hydrogenated or partly hydrogenated heterocyclic amines can also yield hydroperoxides or dialkyl peroxides as a result of autoxidation.

The stable crystalline hydroperoxides

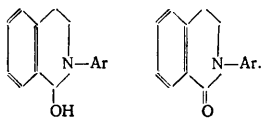


have been obtained by the autoxidation at 100–120°C of isopropylpyridines (the 2-, 3-, and 4-isomers) and 5-ethyl-2-methylpyridine.[46] Here the decomposition products are the alcohols $CH_3\diagdown\!\!\diagup CH_3\!-\!COH$ (Py) and the ketone $CH_3-\overset{\overset{O}{\|}}{C}-Py$. Preferential migration of the CH_3 group (in relation to pyridine) from carbon to oxygen always takes place in the cation $CH_3\diagdown\!\!\diagup CH_3\!-\!CO^+$ (Py). The synthesis and decomposition of hydroperoxides of this type have been described[44–46].

In other instances, dialkylperoxides were obtained. Thus *N*-aryltetrahydroisoquinolines yield, as a result of autoxidation, the peroxides

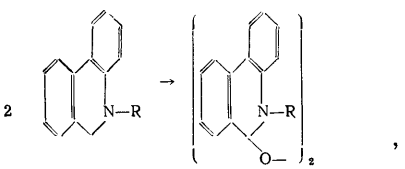


where Ar = C_6H_5, C_6H_4, or naphthyl. On boiling in $CHCl_3$, they undergo homolytic cleavage as a result of the rupture of the oxygen bridge. The radicals formed in this way disproportionate to a hydroxy-derivative and a ketone:



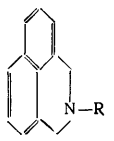
α-Substituted derivatives of these compounds do not react with oxygen. The properties of peroxides and the methods used to synthesise them have been described[47].

As a result of autoxidation, dihydrophenanthridines also give rise to dialkyl peroxides:

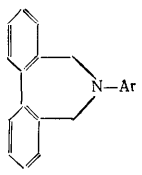


where R = CH_3 or C_6H_5 (they decompose on heating as in the previous case).

N-Substituted dihydroisoquinolines do not react[48]:



N-Aryldihydrobenzoazepines



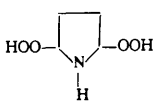
(Ar=C_6H_5, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$)

form peroxides whose properties have been described[49].

We may note that these three types of dialkylperoxides can also be synthesised by treating the corresponding α-bromo-derivatives with H_2O_2 and that α-aminated hydroperoxides $R^1R^2C(COH)NHR$ have been obtained by treating the corresponding ketimines $R^1R^2C = NR$ with H_2O_2.[60] The simultaneous action of H_2O_2 and NH_3 on cyclic ketones gives rise to aminoperoxides of different structures[51].

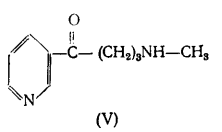
The different ways of obtaining peroxides from amines and related compounds have been described recently[52].

Pyrrolidinone absorbs two moles of O_2 at room temperature as a result of sensitised photochemical oxidation, forming a dihydroperoxide [14]:

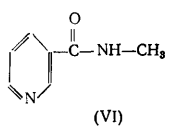


The sensitised photochemical oxidation of nicotine in an aqueous medium at 37° and 40°C has been investigated[53,54]. The structural changes apparently involve only the pyrrolidine ring, but the reaction goes beyond the hydroperoxide stage. Indeed the ring is cleaved, which entails the decomposition of the t-amino-group, resulting in a decrease of pH. The pyrrolidine ring is probably initially dehydrated with subsequent attack by O_2, causing the rupture of the ring owing to the formation of the very unstable intermediate 1,2-peroxide. This can probably account for the absorption of one mole of O_2 instead of two moles, as in another investigation[14]. The only peroxide detected was H_2O_2.

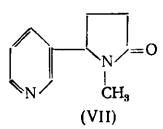
Methylaminopropyl pyridyl ketone (V), methylnicotinamide (VI), cotinine [1-methyl-5-(3-pyridyl)-2-pyrrolidinone] (VII), and methylmyosmine (VIII) have been isolated from tobacco leaves subjected to aerobic fermentation:



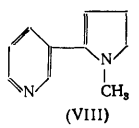
(V)



(VI)

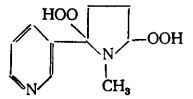


(VII)



(VIII)

The nature of these compounds suggests attack on the 2- and 5-positions of the pyrrolidine ring with formation of the corresponding mono- or di-hydroperoxides:



Compound (V) is probably obtained as a result of the decomposition of the monohydroperoxide with rupture of the ring between N and $C_{(2)}$, compound (VI) is produced by the decomposition of the dihydroperoxide with rupture of the ring between N and $C_{(2)}$ and between N and $C_{(5)}$, compound (VII) is formed by the dehydration of the hydroperoxide without the rupture of the ring, and compound (VIII) results from the dehydration of the alcohol without the rupture of the ring. The last compound is formed by the reactions

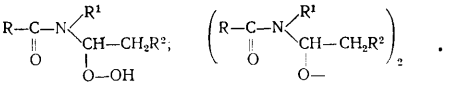
$$RO{-}OH \rightarrow RO^{\cdot} + {\cdot}OH\ ,$$
$$RO^{\cdot} + HR \rightarrow ROH + R^{\cdot}$$

(RH = nicotine).

IV. THE REACTIONS OF AMIDES WITH MOLECULAR OXYGEN

1. The Autoxidation and Sensitised Photochemical Oxidation of Aliphatic Amides

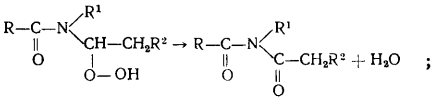
These reactions, involving aliphatic amides having the general formula $R{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R_1}{|}}{N}{-}CH_2{-}CH_2{-}R^2$, have been the subject of an extensive investigation[57]. It has been shown that in all cases the carbon atoms in the α-position with respect to N are attacked with formation of a hydroperoxide or a dialkyl peroxide depending on the reaction conditions:



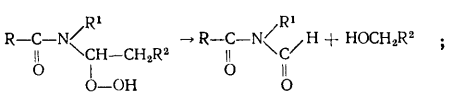
Using ^{14}C, it had been shown earlier[58] for *N*-pentylhexanamide that valeraldehyde is formed from the carbon chain linked to the nitrogen atom and caproamide is formed from the chain linked to C=O.

The peroxides formed and decomposed into

(a) a diacylamide and water:

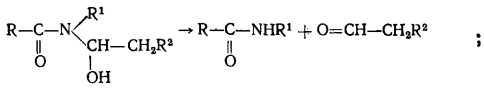


(b) an acylformamide and an alcohol:

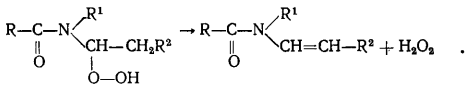


(c) an acylamino alcohol $R{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R_1}{|}}{N}{-}\underset{\underset{OH}{|}}{CH}{-}CH_2R^2$, the

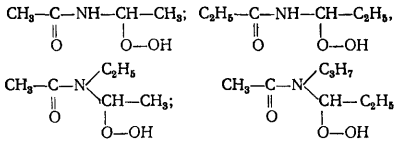
subsequent decomposition of which yields an amide and an aldehyde:



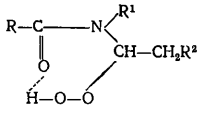
(d) an unsaturated amide and hydrogen peroxide:



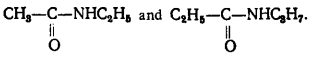
The hydroperoxides



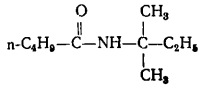
may be isolated in a pure state in a yield of the order of 2%. The autoxidation is carried out at 130° for 30 to 60 min. The excess amide is removed in a high vacuum at room temperature, the crude hydroperoxide being recrystallised from an appropriate solvent. These compounds are stable for several weeks at 0°C. Infrared spectroscopic and NMR data showed that they have a cyclic structure:



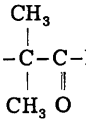
The photochemical oxidation at 0°C leads to the formation of dialkyl peroxides, which were isolated in a pure state in two instances:

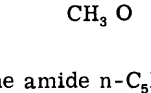


It is noteworthy that the rate of oxidation depends mainly on the structure of the carbon chain at the nitrogen atom and not at C=O; the oxidation does not occur in the presence of a tertiary carbon atom attached to the nitrogen atom; thus the amide

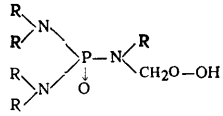


does not absorb oxygen in photochemical oxidation at 50°C,



while the amide  absorbs it at the same rate as the amide .[58]

The quite likely presence of the peroxide and the hydroperoxide

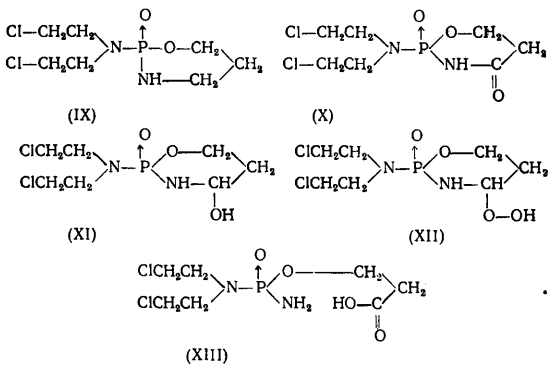


(R=CH$_3$)

was proved[177] by iodometric and polarographic methods in the photochemical oxidation of hexamethylphosphoramide (HMP); owing to its instability, the hydroperoxide was not isolated in a pure state. The formation of formaldehyde following its thermal decomposition was demonstrated.

The phosphoramide (IX) is used in the treatment of various types of cancer. The reactions of this compound *in vivo* involve the carbon atom in the α-position relative to the nitrogen atom. Indeed the mixed amide (X) and the open-chain acid (XIII) have been found in the urine of animals receiving intravenous injections of the amide (IX) [178, 179]; however, when compounds (X) and (XIII) were injected, they proved to be less active than the amide (IX), while the hydroxy-compound (XI) and the hydroperoxide (XII) exhibit a strong cyclotoxic activity both *in vivo* and *in vitro*.

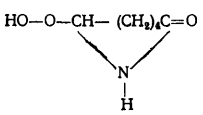
The hydroxy-compounds and mixed amides are probably formed via the intermediate hydroperoxide (XII), which can be obtained by treating the hydroxy-compound (XI) with Fenton's reagent[180]:



(IX) (X) (XI) (XII) (XIII)

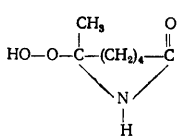
2. The Photochemical Oxidation of Lactams and Polyamides

The photochemical oxidation of ε-caprolactam (95°C, 48 h) led to the formation of the hydroperoxide



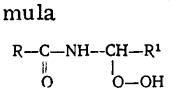
in 5% yield[59], the compound decomposing on heating in benzene solution into water and adipamide.

Under conditions identical with those described above, the lactam ring in methylcaprolactam is opened with formation of acetylvaleramide; the intermediate hydroperoxide

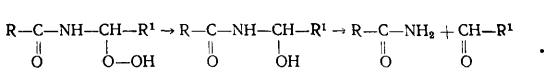


could not be isolated.

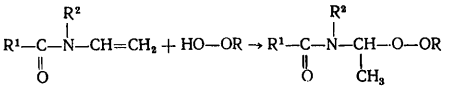
It is interesting to note that, when various polyamides are heated in the presence of oxygen, hydroperoxides having the general formula



are also formed. Depending on the experimental conditions, they give rise to the cross-linking of the chains accompanied by the formation of bridges with and without oxygen atoms, or to degradation of the type

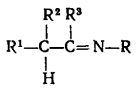


The autoxidation of polyamides has been discussed[60-62]. We may note that certain amide peroxides can be obtained by treating vinyl derivatives of amides with hydroperoxides[185]:

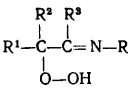


V. THE OXIDATION OF IMINES AND ENAMINES

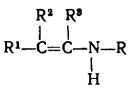
Imines having the general formula



with a hydrogen atom in the α-position relative to the nitrogen atom and in the β-position relative to the double bond, undergo autoxidation with conversion into the corresponding hydroperoxides:

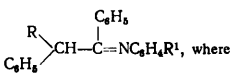


The same may be said of the enamines



containing a hydrogen atom linked to the nitrogen atom, which give rise to the same hydroperoxides after their isomerisation to the corresponding imines.

There are also several examples where the double bond and the nitrogen atom are outside a ring; these are the anils[63] derived from *p*-methoxyaniline, methylphenylacetaldehyde (XIV), and diphenylpropionaldehyde (XV) and the anils of *p*-methylaniline and diphenylacetophenone (XVI):[64]

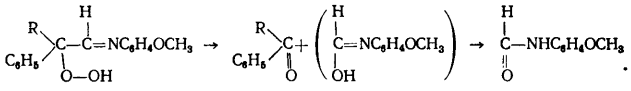


R=CH$_3$, R^1=OCH$_3$; (XIV)

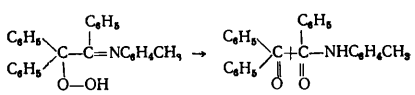
R=C$_6$H$_5$, R^1=OCH$_3$; (XV)

R=C$_6$H$_5$, R^1=CH$_3$. (XVI)

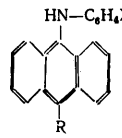
At room temperature in ether or ethyl acetate, compounds (XIV) and (XV) rapidly absorb one mole of O_2, forming hydroperoxides (iodine is liberated from iodides), which decompose fully into the corresponding ketone and formylamisidine (R = CH_3 or C_6H_5); in the case of compound (XV), the peroxide vanishes completely after 2 h at room temperature:



The same may also be said of the anil (XVI) from which only benzophenone and *p*-methylphenylbenzamide could be isolated:

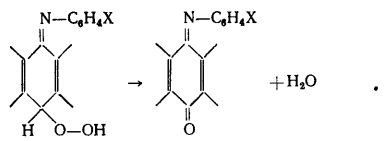


Derivatives of 9-aminoanthracene



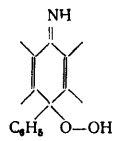
are of considerable interest. The rate of autoxidation depends on the nature of the substituent X in the *para*-position in the benzene ring linked to the nitrogen atom. For example, at room temperature (in ethereal solution) when R = C_6H_5 and X = NO_2 the absorption of O_2 is not observed for 7 days, while with X = OCH_3 or $N(CH_3)_2$ one mole of O_2 is absorbed after 4 days or after several hours respectively[65].

The stability of the hydroperoxide obtained depends not only on the nature of X but also on that of R. Thus, with R = H and X = OCH_3 or $N(CH_3)_2$, it was possible to obtain only quinone imines, formed as a result of the decomposition of the corresponding hydroperoxides:



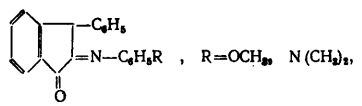
With R = C_6H_5, the corresponding hydroperoxides were isolated, but the hydroperoxide with X = $N(CH_3)_2$ was obtained only in a crude form and were not purified owing to its instability and low solubility in organic solvents. The hydroperoxide with X = OCH_3 was obtained in a pure form in a yield of 65%.

The hydroperoxide[66]

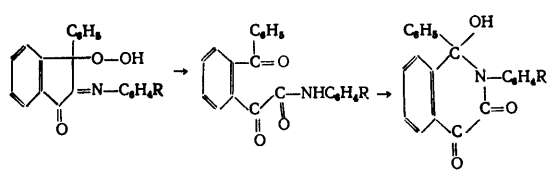


without substituents at the nitrogen atom, was isolated in 35% yield; the autoxidation was carried out in an ethereal solution at 0°C. The hydroperoxide decomposes fully into the corresponding quinone imine and phenol in several hours at 0°C. The methods of synthesis are described and the reaction is discussed in detail by Cauquis[65].

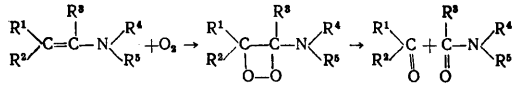
The autoxidation of the indandione anil



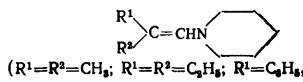
leads to the formation of the corresponding hydroxyisoquinolinedione.[67] Although the presence of the peroxide has not been established chemically, nevertheless one can postulate the intermediate formation of a very unstable hydroperoxide, the decomposition of which is probably due to the corresponding isoquinoline derivative:



Enamines without a hydrogen atom linked to the nitrogen atom can combine with singlet O_2 in certain cases and give rise to a carbonyl compound and a substituted amide via the intermediate formation of a very unstable 1,2-peroxide:



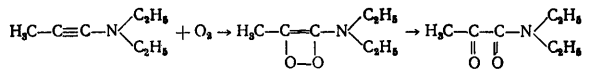
It has been shown[68] that the sensitised photochemical oxidation of the compound



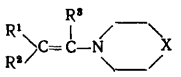
($R^1=R^2=CH_3$; $R^1=R^2=C_2H_5$; $R^1=C_6H_5$, $R^2=CH_3$)

(solvent—benzene, sensitiser—haematoporphyrin) at room temperature leads to the rapid absorption of one mole of O_2 with formation of the ketone $R^1R^2C=O$ (in a high yield) and formylpiperidine.

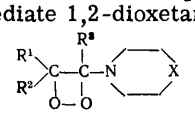
Under the same conditions, *NN*-dimethylpropynylamine yields the *NN*-dimethylamide of pyruvic acid:

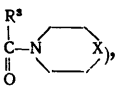


The photosensitised oxidation at room temperature of enamines of the type

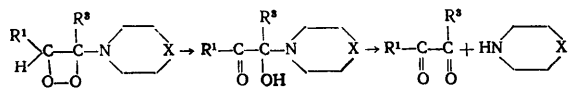


where X = CH_2 or O, has been examined[186]. It involves the rapid absorption of 1.2 moles of O_2 with formation of a very unstable intermediate 1,2-dioxetan

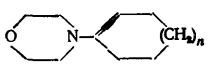
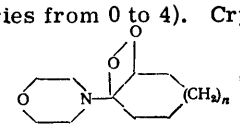
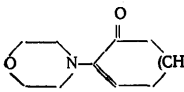
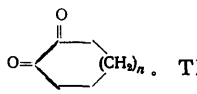
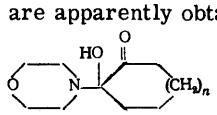


which may decompose as a result of the dissociation of the C–C bond, with formation of the monoketone $R^1R^2C=O$ and the amide, , or the C–N bond with formation of the α-diketone $R^1-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R^3$. The latter reaction depends to a large extent on the nature of R^3. For $R^1 = R^2 = CH_3$ and X = O, the degree of dissociation of the C–N bond is 32% when $R^3 = C_6H_5$, falling to zero when $R^3 = H$.

The presence of the hydrogen atom in the β-position relative to the nitrogen atom (R^1 or R^2 = H) also promotes the dissociation of the C–N bond in accordance with the β-elimination mechanism:

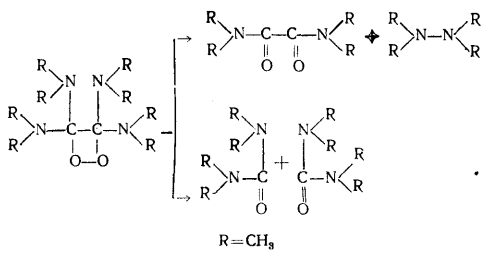


Thus, when $R^1 = CH_3$, $R^3 = C_6H_5$, and X = O, the degree of dissociation of the C–N bond increases from 32 to 71% following the replacement of $R^2 = CH_3$ by $R^2 = H$.

An interesting instance[187] of the sensitised photochemical oxidation of morpholine enamines  has been discovered (*n* varies from 0 to 4). Crystals of the intermediate dioxetans , were isolated at −78°C in dimethyl ether (for $n = 1$, 2, or 3), but at room temperature the main compounds are the monoketone enamines  and the diketone . They are apparently obtained from the aminohydroxyketone  by dehydrogenation in the former case and by the dissociation of C–N bond in the latter. The aminohydroxyketone may be formed from the dioxetan on dissociation of the peroxy-bridge and subsequent hydrogen transfer (the β-elimination mechanism).

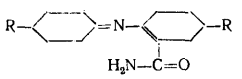
The photochemical oxidation of 3-morpholinocholest-3-ene in ether at −78°C leads to the formation of cholestane-2,3-dione and 3-morpholinocholest-3-en-2-one.[187]

The autoxidation of tetrakisdimethylaminoethylene in polar and non-polar solvents has been investigated[69]. The mechanism of this reaction is very complex, depends on the nature of the solvent, and has been investigated inadequately. The principal autoxidation products (the composition of the products varies depending on the nature of the solvent) are dimethylurea, tetramethyloximide, and tetramethylhydrazine. They are probably obtained from a very unstable intermediate peroxide:

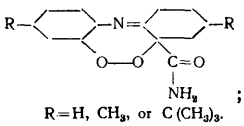


R=CH_3

Conjugated unsaturated imines, in which one nitrogen atom and one of the double bonds are outside the ring and which are described by the formula



constitute an interesting case[70]. At room temperature in chloroform they rapidly absorb one mole of O_2 (the reaction is appreciably accelerated by the addition of 0.1% of cobalt naphthenate) with formation of endoperoxides:



R=H, CH_3, or $C(CH_3)_3$.

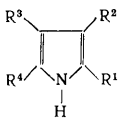
VI. THE AUTOXIDATION OF COMPOUNDS WITH A DOUBLE BOND AND A NITROGEN ATOM IN THE RING

1. Pyrroles

The pyrrole rings are important components of compounds which are of great biological significance: chlorophyll, haemoglobin, and certain alkaloids (chydrine and

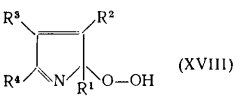
stachydrine). The various methods for their oxidation by oxygen are therefore of special interest. Numerous, very important studies have been devoted to them in recent years [72-84]. Non-sensitised autoxidation at room temperature yields only a mixture of compounds which are difficult to determine [71], the rate of absorption of O_2 increasing sharply in the presence of alkali metal alkoxides. Two moles of O_2 are absorbed and trimers with two pyrrole rings are formed [72]. Sensitised photochemical oxidation leads to the formation of readily identifiable compounds, which are probably obtained as a result of the isomerisation of the 1,4-endoperoxide, formed initially with or without the rupture of the pyrrole ring. The nature and proportions of the products depend on the structure of the pyrrole derivative and the conditions of preparation. In certain cases a hydroperoxide may be formed.

The tetrasubstituted pyrrole (XVII)



(XVII)

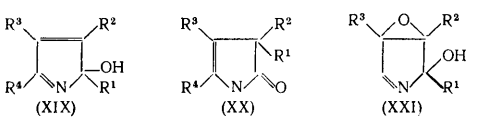
can lead to the formation of the hydroperoxides (XVIII)



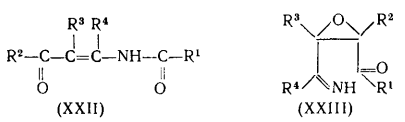
(XVIII)

(a) $R^1=R^2=R^3=$ t-Bu, $R^4=H$;
(b) $R^1=R^2=$ t-Bu, $R^3=R^4=H$;
(c) $R^1=R^2=R^3=R^4=C_6H_5$;
(d) $R^1=R^4=C_6H_5$, $R^2=R^3=H$,

as well as an alcohol (XIX), a lactam (XX), an epoxyalcohol (XXI), a chalcone (XXII), an epoxyketoimine (XXIII), and its hydrolysis product (XXIV):

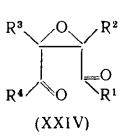


(XIX) (XX) (XXI)



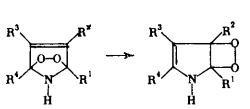
(XXII)

(XXIII)



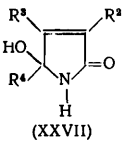
(XXIV)

In order to account for the formation of some of the above products, obtained in consequence of the dissociation of the $C_{(1)}-C_{(2)}$ bond, the formation of the intermediate 1,2-peroxide (XXVI) as a result of the isomerisation of the 1,4-endoperoxide (XXV) was examined:



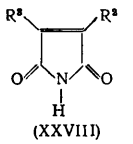
(XXV) (XXVI)

Pyrroles unsubstituted in the 1- and 4-positions can give rise to the formation of the hydroxylactam (XXVII)



(XXVII)

as a result of the base-catalysed rearrangement of the endoperoxide (XXV) and its more far-reaching oxidation products, for example derivatives of maleimide (XXVIII):



(XXVIII)

(in the case of pyrroles unsubstituted in both 1- and 4-positions).

Unsubstituted pyrrole (as well as its *N*-methyl derivative), subjected to photochemical oxidation at room temperature (with eosin as the sensitiser), yields a hydroxylactam (XXVII). [73] On photochemical oxidation in benzene solution, 2,4-dimethylpyrrole gives rise to the hydroxylactam (XXVII), $R^1=R^3-H$, $R^2=R^4=CH_3$) but with the OH group in the 2-position (the 4-position is blocked). It is apparently obtained on rearrangement of the 1,2-peroxide (XXVI). [74] The photochemical oxidation of 2,3-diethylpyrrole in solution in methanol (with Rose Bengal as sensitiser) gives a methoxy-derivative of the hydroxylactam (XXVII) and the corresponding maleimide (XXVIII) in a yield of the order of 35%. [75]

We may note that in certain cases the hydroxylactam and maleimide are formed as a result of the dealkylation of the $C_{(4)}$ atom. Thus the photochemical oxidation of 3-ethyl-2,3,4-trimethylpyrrole and 3-ethyl-2,4-dimethylpyrrole (in methanol solution with Rose Bengal as the sensitiser) gives rise to the hydroxylactam (XXVII) and the corresponding maleimides in yields of 40 and 3% respectively [75].

The sensitised photochemical oxidation of 1,4-di-t-and 1,2,4-tri-t-butylpyrroles (in methylene chloride with Methylene Blue as sensitiser) gives rise to hydroperoxides with a strong hydrogen bond [76].

The behaviour of 1,2,3,4-tetraphenylpyrrole, the photochemical oxidation of which has been investigated [77-79], is most characteristic of pyrroles. This compound is similar to lophine (1,3,4-triphenylimidazole), the sensitised photochemical oxidation of which gives rise to a hydroperoxide and not an endoperoxide, as was believed previously. The irradiation of a 2% solution of compound (XVII, $R^1=R^2=R^3=R^4=C_6H_5$) at room temperature or −50°C in CS_2, CH_3OH, $CHCl_3$, or ether for 10–15 min in the presence of 1% of the sensitiser (heterocoerdianthrone, dibenzoperylenequinone) leads to the formation of a hydroperoxide in 35% yield. It is noteworthy that this hydroperoxide, like that of lophine, can decompose into the initial pyrrole and O_2.

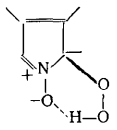
When compound (XVII) is subjected to autoxidation without a solvent at 120–130°C or refluxed in propanone, dioxan, or benzene, 2,4-substituted pyrroles are formed preferentially in yields of 66, 75, and 82% respectively. When the compound is refluxed in methanol, the main products are compounds (XXI) and (XXII) in yields of 30 and 15% respectively.

The reduction of the hydroperoxide (XVIII) at room temperature (KI solution in acetic acid) gives rise to

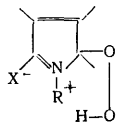
compound (XIX) (90% yield). Decomposition in a sealed tube in benzene solution with added anhydrous KOH results in the formation of compounds (XX) and (XXII) in yields of 28 and 10% respectively. The formation of a hydrogen bond between the H atom of the HO–O group and the nitrogen atom of the pyrrole ring facilitates the dissociation of the CO–OH and HO–O–C linkages with evolution of O_2, which proceeds more readily the lower the degree of association of the solvent. We may note that compounds (XXI) and (XXII) are formed in the sensitised photochemical oxidation of compound (XVII) without the preliminary isolation of the hydroperoxide (XVIIIc).

The sensitised photochemical oxidation of 1,4-diphenylpyrrole also leads to the corresponding hydroperoxide (XXVIId), but the latter is very unstable, which makes it impossible to reduce it by iodides. Its thermal decomposition *in vacuo* at 80°C leads to the formation of a tarry residue with slight evolution of O_2.[79]

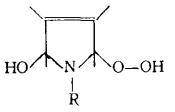
The sensitised photochemical oxidation of 1,2,3,4-tetraphenylpyrroles substituted at the nitrogen atom by OH,[80] C_6H_5,[81] benzoyl,[82] and NH_2 [83] groups has been investigated. When R = OH, the product is a nitrone peroxide



which is converted into the corresponding hydroxynitrone on reduction with KI solution in acetic acid. Similar results were obtained for R = C_6H_5 [81] and benzoyl.[82] In both cases the initial product (a 1,4-endoperoxide) isomerises to the 1,2-peroxide, which was detected iodometrically in the course of photochemical oxidation in ethereal solution at −65°C. In the first instance, the peroxide may be isolated as the hydroperoxide salt, which readily hydrolyses to compound (XIX) and H_2O_2 (X = halogen or $CH_3C_6H_4SO_3$):

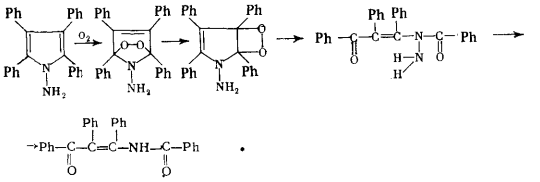


If R = benzoyl, treatment with the above acids leads to the hydrolysis of the initial hydroperoxide and the formation of a hydroxyhydroperoxide



The decomposition products of these two peroxides are similar to the products obtained from tetraphenylpyrrolyl hydroperoxide (XVIIc) unsubstituted at the nitrogen atom. In both cases the chalcone (XXII) is formed in chloroform solution with C_6H_5 and C_6H_5COO groups respectively at the nitrogen atom; when R = C_6H_5COO, the second reaction product is the epoxyoxoimine (XXIII); when R = C_6H_5, the epoxyoxoimine hydrolyses with formation of the epoxyketone (XXIV).

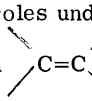
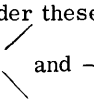
If R = NH_2, [83] the formation of a peroxide could not be observed even at −60°C regardless of the solvent. The main products of this sensitised photochemical oxidation were benzoyltriphenylpyrazole and tetraphenylpyridazine. The former compound is apparently formed from a very unstable intermediate peroxide:



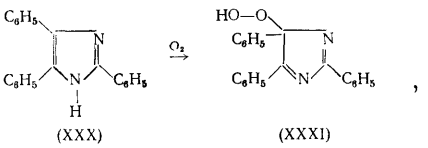
The sensitised photochemical oxidation of *N*-phenylpyrrole unsubstituted at the carbon atoms, which is used to synthesise the hydroxylactam (XXVII, $R^1 = R^2 = R^3 = R^4 = H$), necessary for the synthesis of various mitomycins, has been investigated[87].

The sensitised oxidation of pyrroles substituted and unsubstituted at the nitrogen atom has also been examined[85,86].

2. Imidazoles

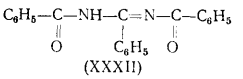
The behaviour of imidazoles under autoxidation and sensitised photochemical oxidation conditions is similar to that of pyrroles under these conditions except that compounds with  and  bonds are formed respectively in the two cases.

Triphenylimidazole (lophine) (XXIX) gives rise to a hydroperoxide,



(XXX) (XXXI)

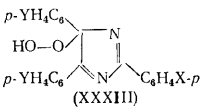
as a result of non-sensitised (in CS_2) [87] or sensitised (in chloroform) photochemical oxidation[88] in yields of 20 and 68% respectively. The hydroperoxide is relatively stable at room temperature in the solid state but is very unstable in solution (particularly in acid or alkaline solutions). On heating, it decomposes into lophine (with a yield of 50%) and O_2. This reaction is accompanied by luminescence and the formation of *MN*-dibenzoylamidine (XXXII):



(XXXII)

The latter compound is also formed as a result of the oxidation of compound (XXX) in organic solvents.

Certain hydroperoxides derived from lophine, described by the formula



(XXXIII)

have been obtained by the photochemical oxidation of compound (XXXIII) in solution in a mixture of methylene chloride (95%) and ethanol (5%).[89]

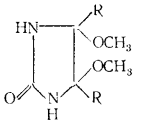
The pure hydroperoxides have been obtained for X = H_3CO, Y = H and X = H_3CO, Y = H_3CO; for X = $(CH_3)_2N$, Y = H and X = $(CH_3)_2N$, Y = H_3CO, the hydroperoxides proved to be very unstable[89]. The luminescence of hydroperoxides

of this type has been discussed[89]. It is probably associated with the formation of *NN*-dibenzoylamidine in an excited state.

The luminescence in the case where the substituents in the three benzene rings of compound (**XXXIII**) are chlorine atoms (one chlorine atom in the *ortho-*, *meta-*, or *para*-position and two chlorine atoms in the 2,4- and 3,4-positions) has been discussed in another investigation[90].

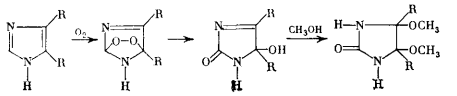
We may note that the sensitised photochemical oxidation of *N*-phenyl-lophine in solution gives rise to a very unstable peroxide, which was detected iodometrically at −60°C. The product in this instance is probably a 1,4-endoperoxide, the hydrolysis of which results in the formation of hydroperoxide salts, similar to those of *N*-substituted pyrroles[91].

The sensitised photochemical oxidation (in solution in methanol) of unsubstituted imidazole and 1,2-diphenylimidazole has been examined[92]. The final reaction products are methoxyimidazolidinones (**XXXIV**) (in 45% yield):



(XXXIV)

Their formation with participation of the solvent can be represented as follows on the basis of the formation of a 1,4-endoperoxide:

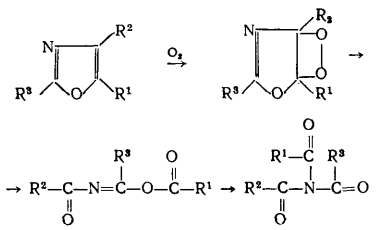


The decomposition of the imidazoline ring of histidine on sensitised photochemical oxidation of enzymes in the aqueous phase is associated with a decrease of their activity. A relation between the degree of decomposition of the imidazole ring of histidine in bovine insulin and the biological activity of this hormone can be established[93]. We may note that the absorption of 2.25 moles of O_2 lowers the histidine content from 5.4 to 0.1%, while the content of other aminoacids remains almost constant [93].

Similar phenomena have been observed for phosphoglucomutase [94] and chymotrypsin.[95] The change in the properties of lactoglobulin [96] is also associated with the decomposition of the imidazole ring in histidine.

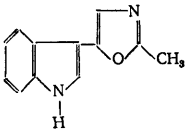
3. Oxazoles

The sensitised photochemical oxidation of oxazoles leads to the formation of triamides. A study[97] of the photochemical oxidation of 3-methyl-1,2-diphenyl- and 2-methyl-1,4-diphenyl-oxazoles (at room temperature in methanol) showed that the final product of the reaction is *N*-acetylbenzamide in both cases. It is probably formed as a result of a rearrangement of the 1,2-peroxide (which is apparently in its turn a product of the isomerisation of the 1,4-endoperoxide):

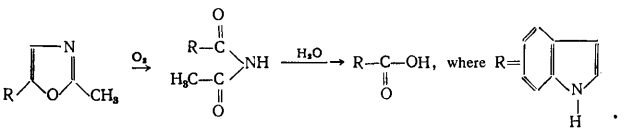


The mechanism of this reaction has been considered in detail[97,98].

The conversion of pimprinine

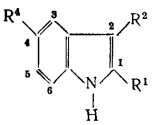


in sensitised photochemical oxidation into indolecarboxylic acid is a reaction of this type[97,99]:



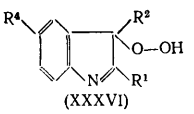
4. The Autoxidation of Indoles

Alkylindoles (**XXXV**) having the general formula



(XXXV)

give rise to the corresponding hydroperoxides (**XXXVI**)



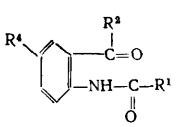
(XXXVI)

on autoxidation. Their formation requires the presence of a hydrogen atom linked to the nitrogen atom. The nature of the group R^2 in the pyrrole ring (in the β-position relative to N) is very important; for example, the reaction does not occur when $R^2 = C_6H_5$. The nature of the group R^4 in the 4-position of the benzene ring (in the β-position relative to the common double bond) also influences the reaction; the latter proceeds more readily in the presence of a nucleophilic group, for example OCH_3. The results are presented in Table 2.

Table 2. Data on the autoxidation of indoles.[100]

Группа			Yield of hydroperoxide
R^4	R^1	R^3	
H	CH_3	CH_3	25
CH_3O	CH_3	CH_3	50
CH_3O	C_6H_5	CH_3	100

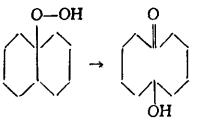
On being refluxed with dilute acids or alkalis, indolyl hydroperoxides are converted into amidoketones (**XXXVII**)



(XXXVII)

via two possible mechanisms:

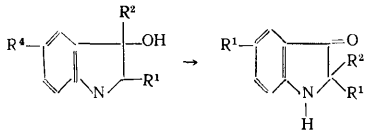
(1) The mechanism described by Criegee, which consists in the conversion of decalinyl hydroperoxide into hydroxycyclodecanone:



The reaction proceeds with heterolytic dissociation of the O–O bond followed by rupture of the $C_{(1)}$–$C_{(2)}$ bond and the migration of the OH group from O to $C_{(6)}$.

(2) The mechanism (operating in the case of tetraphenylpyrrolyl hydroperoxide) involving the heterolytic dissociation of the O–H bond (in RO–O–H), resulting in the formation of $RO-O^-$ and H^+, and the addition of the anion $RO-O^-$ and the proton H^+ to the $-N=C\langle$ double bond.

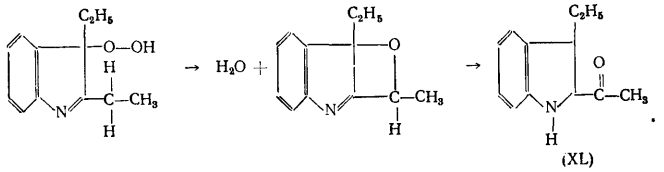
On being reduced with hydrosulphites, hydroperoxides are converted into the corresponding alcohols (XXXVIII), which are further converted into lactams (XXXIX) in an alkaline medium. This reaction is analogous to that which occurs with pyrrole derivatives:



(XXXVIII) (XXXIX)

The methods for the synthesis and decomposition of hydroperoxides of this type have been described [100].

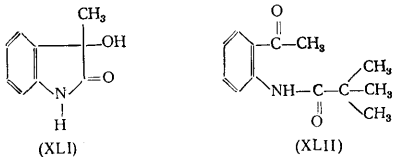
The behaviour of 1,2-diethylindole is interesting [102]. The hydroperoxide (XXXVI, $R^3 = H$, $R^1 = R^2 = C_2H_5$), with the OOH group in the 2-position, is converted into 1-acetyl-2-ethylindole (XL):



(XL)

(The presence of the N=C double bond renders the hydrogen atoms in CH_2 mobile). One should note that (XL) is formed from diethylindole at room temperature in the presence of atmospheric oxygen in the light.

The behaviour of 1-isopropyl-2-methylindole is more complex [103]. The resulting hydroperoxide with the OOH group in the 2-position, gives rise on decomposition to compounds (XLI) and (XLII):



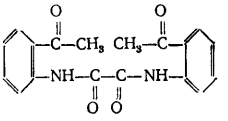
(XLI) (XLII)

The mechanism of these anomalous reactions has already been discussed [103–105].

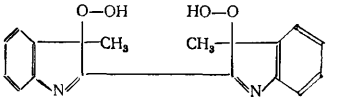
The formation of 1-acylindoles during the *in vivo* oxidation of derivatives of 1,2-dialkylindoles in alkaloids such as dregamine [106], voacafrine [107], and vobasine [108] apparently proceeds via a mechanism similar to that operating with 1,2-diethylindole.

A more complex instance involving indoles (XXXV, $R^4 = H$, $R^2 = CH_3$, R^1 = methylindolyl) has been examined [109].

The monohydroperoxide (XXXVI) is formed initially and its subsequent oxidation (on passing O_2 into a boiling xylene solution) yields the oxamide (XLIII):



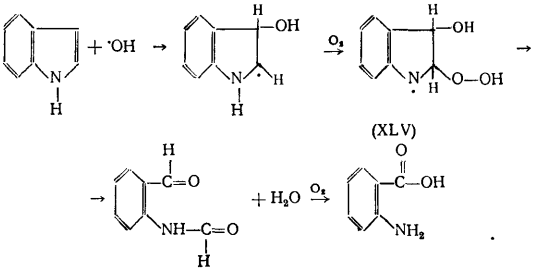
which is apparently formed from the intermediate dihydroperoxide (XLIV):



(XLIV)

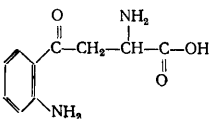
The formation of indolyl hydroperoxides is probably associated with the bioluminescence of certain marine organisms. This hypothesis has been confirmed by studies on the hydroperoxides (XXXVI, $R^4 = H$, $R^2 = CH_3$, $R^1 = CH_3$ of p-$CH_3OC_6H_4$). [110]

The action of γ-radiation in the presence and absence of O_2 on indole, *N*-methylindole, 2,*N*-dimethylindole, and 1,2-dimethylindole in aqueous solution has also been investigated [111]. It was shown that attack by the $^{\cdot}OH$ radicals formed from H_2O is initially directed to the 2-position (the β-position relative to the nitrogen atom) of the pyrrole ring (which does not in any way exclude attack on the benzene ring) and that, depending on the presence or absence of oxygen, different reaction products are obtained. In particular, anthranilic acid is formed from indole only in the former case—probably as a result of the formation of the intermediate hydroxyhydroperoxide (XLV) in accordance with the equation



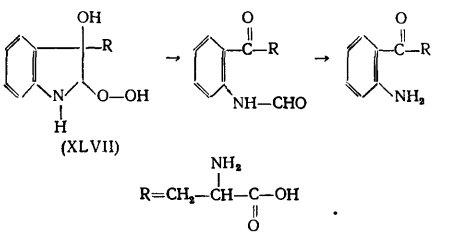
(XLV)

The formation of kynurenine (XLVI)



(XLVI)

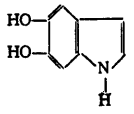
from tryptophan apparently proceeds via a mechanism similar to that involving the formation of the intermediate hydroxyhydroperoxide (XLVII):



(XLVII)

This reaction was achieved *in vitro* when an aqueous solution of tryptophan (at a concentration of 0.001 M) was exposed to X-rays at room temperature in the presence of oxygen[112]. Kynurenine is a product of the decomposition of tryptophan in living cells and in micro-organisms and is one of the controlling factors in transmitting hereditary information[113]. It has been shown[114] that the conversion of tryptophan into kynurenine in rat liver proceeds via the intermediate formation of formylkynurenine. Various metabolic aerobic transformations of tryptophan have been examined[192].

The role of indolyl hydroperoxides in the formation of melanin pigments has not been completely elucidated as yet. These pigments are formed as a result of the biological oxidation of tyrosine with intermediate formation of 4,5-dihydroxyindole:[115]

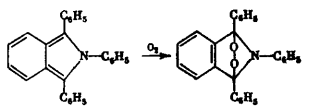


The attempts to oxidise 4,5-dihydroxyindole and its 1- and 2-methyl derivatives in an aqueous alkaline medium have shown[115] that O_2 is absorbed in all cases, but a black deposit is formed only from the 2-methyl derivative; the 1-methyl derivative gives rise to an amorphous blue precipitate, while the unsubstituted derivative is converted into a purple solution. Presumably these three indole derivatives are oxidised via different mechanisms.

5. The Autoxidation of Isoindoles

The non-sensitised photochemical oxidation of isoindoles has been the subject of several studies[116-119]. In the autoxidation of *N*-substituted isoindoles the intermediate is apparently an endoperoxide, the stability of which and hence the nature of the final product depend to a large extent on the nature of the 1,2-substituents in the pyrrole ring.

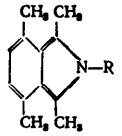
The corresponding endoperoxide (XLIX)



(XLVIII) (XLIX)

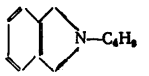
was isolated in the autoxidation of 2,3-*N*-triphenylisoindole (XLVIII). This endoperoxide decomposes on heating in oxygen up to 118°C; acid hydrolysis leads to the rupture of the pyrrole ring with formation of dibenzoylbenzene and aniline[116].

The autoxidation of *N*-alkyl-1,2,4,7-tetramethylisoindoles (L)

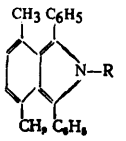


(L)
R=CH_3, C_2H_5, C_6H_5

has been examined[117]. The final oxidation products in boiling tetrahydrofuran (THF) are the corresponding phthalimides, which are believed to be formed on decomposition of the intermediate endoperoxides as a result of the elimination of CH_3 groups. The CH_3 groups are abstracted from the pyrrole ring (which is retained, in contrast to the previous case).

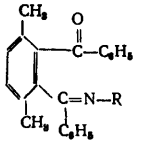
The autoxidation of *N*-butylisoindoline 

has been investigated[118] and it has been shown that the first reaction stage involves the dehydrogenation of the corresponding isoindole and depends to a large extent on the nature of the solvent. The products of this reaction are phthalimidines and a phthalimide. The reaction has a non-classical mechanism, which is believed to involve peroxy-radicals[118]. The autoxidation of the isoindoles

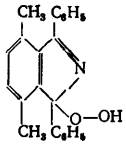


(R=H, CH_3, C_6H_5, or $C_6H_5CH_2$)

(in boiling THF) has been studied[188] and it has been shown that, owing to the greater difficulty of the elimination of C_6H_5 groups compared with CH_3 groups, the ketimines



are formed instead of phthalimides (R can be any group other than a hydrogen atom) as a result of the rupture of the pyrrole ring. When R = H, the product is the hydroperoxide

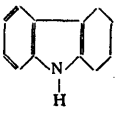


which is rapidly converted into the corresponding alcohol.

6. The Autoxidation of Tetrahydrocarbazoles

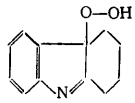
The autoxidation of tetrahydrocarbazole derivatives has been studied in detail[120-127]. It is to some extent similar to the autoxidation of dialkylindoles, in particular in view of the necessity for the presence of a hydrogen atom linked directly to the nitrogen atom and as regards the influence of the substituent in the benzene ring. The formation of hydroperoxides at the beginning of the reaction (which have been isolated in many instances) is accompanied by the formation of interesting products on their decomposition.

The unsubstituted tetrahydrocarbazole (LI)



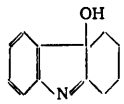
(LI)

gives rise, under conditions analogous to those in the reactions of dialkylindoles, to the hydroperoxide (LII)



(LII)

which may be reduced to the alcohol (LIII)

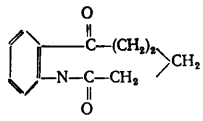


(LIII)

by an aqueous solution of $Na_2S_2O_4$ in the presence of NaOH.

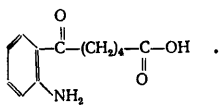
Here one should note that the catalytic hydrogenation of compound (LII) in the presence of palladium yields the tetrahydracarbazole (LI), while in the presence of PtO_2 the hydrogenation proceeds with formation of hexahydrocarbazole.

The formation of the lactam (LIV)



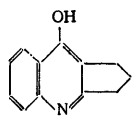
(LIV)

from compound (LII) proceeds at room temperature in polar solvents and is strongly catalysed by acids [121]. Under the influence of acids, the lactam is converted into *o*-aminobenzoylvaleric acid (LV):



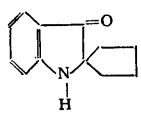
(LV)

Compounds of two types are formed in an alkaline medium (2 *N* NaOH) at room temperature: hydroxycyclopentanoquinoline (LVI)



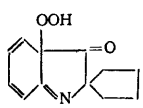
(LVI)

as a result of the internal condensation of the lactam (LIV) and the oxospiran (LVII)



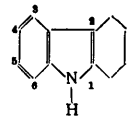
(LVII)

which is a product of the isomerisation of the hydroxy-derivative. As a result of catalytic hydrogenation, the oxospiran is converted into the corresponding dihydro-derivative, which yields the hydroperoxide (LVIII) on autoxidation [120,121]:



(LVIII)

The autoxidation of tetrahydrocarbazoles substituted in the benzene ring has been investigated [122-124]:



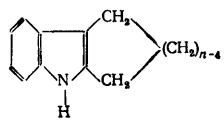
(LIX)

substituent	position
OCH_3	4,5
Br	4
NO_2	6
$H_2N-C-CH_2$ (O)	4
$COOCH_3$	3
$COOCH_3$	4

In the presence of the same substituent, the rate of autoxidation is a maximum for the isomer substituted in the 3-position and a minimum for the isomer substituted in the 6-position. Thus the reaction proceeds in a different manner when the 6-position is occupied by the NO_2 and $COOCH_2$ groups. Particular attention has been devoted to the study of derivatives with the $COOCH_3$ and COOH substituents in the 3-, 4-, 5-, and 6-positions.

In the first case, the autoxidation proceeds only in an organic solvent. The corresponding hydroperoxides have been isolated (except for the isomer substituted in the 6-position). In the second case the autoxidation occurs only in an aqueous alkaline medium and intermediate peroxides could not be isolated. The corresponding hydroxyquinolines have been obtained for 6- and 8-bromo-derivatives and the 3-methoxycarbonyl-derivatives.

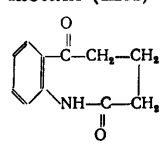
A study has been made of the influence of the size of the hydrogenated ring in compound (LX)



(LX)

(where n is the number of carbon atoms in the ring) on the rate of autoxidation and on the nature of the products [125]. It was found that the rate decreases with increase of n and the corresponding hydroperoxides could not be isolated in any of the instances considered (except for $n = 6$).

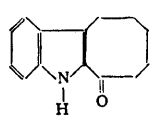
The corresponding lactam (LXI)



(LXI)

formed from the compound with a five-membered ring is readily hydrolysed to *o*-aminobenzoylbutyric acid, but the corresponding hydroxyquinoline (LVI) could not be isolated. The hydroxyquinoline is formed from the compound with a seven-membered ring, but the OH group is in the α- and not the γ-position as in compound (LVI).

It is interesting to note that attack by O_2 on the compound with the eight-membered ring is directed to the α-position of the hydrogenated ring relative to the nitrogen atom with formation of the corresponding cyclic ketone (LXII)



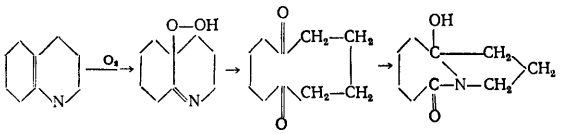
(LXII)

probably via a mechanism similar to that of the formation of 1-acetyl-2-ethylindole from 1,2-diethyl-2-hydroperoxyindole.

The rearrangements occurring in the series of indoles and tetrahydrocarbazoles in connection with structural changes in alkaloids such as quinamine and cinchonamine has been examined in a major article [126].

7. The Autoxidation of Octahydroquinoline

The autoxidation of octahydroquinoline (LXIII) [127] at room temperature in ethyl acetate leads to the absorption of 0.9 mole of O_2 per mole of compound with formation (in 87% yield) of the crystalline hydroperoxide (LXIV), which is relatively unstable at room temperature but is fairly stable at −5°C. In polar solvents, it is transformed into 7-hydroxy-1-azabicyclo[5,3,0]decan-2-one (LXVI)

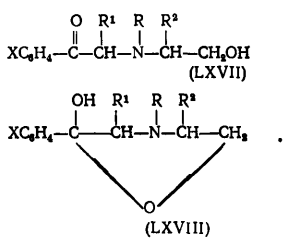


(LXIII) (LXIV) (LXV) (LXVI)

as a result of the rearrangement of the intermediate lactam (LXV).

8. The Autoxidation of Dihydro-oxazines

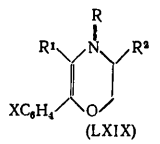
β-Hydroxyethylaminoacetophenones can exist in linear and cyclic forms. This tautomerism and its dependence on steric and polar factors have been discussed [128,129]:



(LXVII)

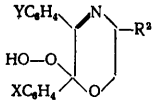
(LXVIII)

Some of these compounds have antimalarial and carcinolytic properties [128]. They readily split off H_2O, being converted into dihydro-oxazines [129]:

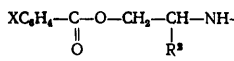


(LXIX)

When R = H and R^1 is a *para*-substituted phenyl group *p*-YC_6H_4, compounds (LXIX) readily give rise to hydroperoxides under the influence of atmospheric O_2:



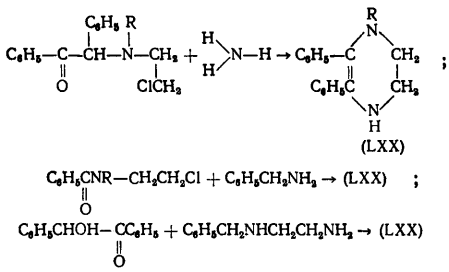
The hydroperoxides are unstable and decompose rapidly close to their melting points. On heating in an acid medium, they are converted into esters:



The hydroperoxides were isolated for the following substituents: $R^1 = CH_3$, X = Y = H or Cl; $R^2 = C_2H_5$, X = Y = H or Cl; $R^2 = C_6H_5$, X = Y = H, Cl, or CH_3O; $R^2 = C_6H_5CH_2$, X = CH_3O, Y = H. On the other hand, they could not be obtained in the presence of the following substituents: $R^2 = C_2H_5$, X = CH_3O, Y = H; $R^2 = C_6H_5CH_2$, X = CH_3O, Y = H, X = Y = Cl or X = Y = CH_3O.

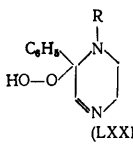
9. The Synthesis of 1,2-Dehydropiperazinyl Hydroperoxides

The attempts to synthesise *N*-alkyl(or aryl)-1,2-diphenyl-1,2-dehydropiperazines (in ethereal solution at 70–80°C) in the presence of atmospheric oxygen according to the mechanisms



(LXX)

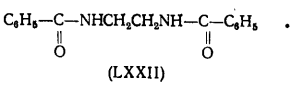
led to the formation of the hydroperoxides (LXXI) [130]:



(LXXI)

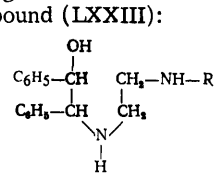
which are crystalline compounds, rapidly decomposing close to their melting points when R = C_2H_5, $C_6H_5CH_2$, or C_6H_5.

Their decomposition in an acid medium (3 *N* HCl) leads to dibenzoylalkylethylenediamines, e.g.



(LXXII)

Catalytic hydrogenation results in ring opening with formation of compound (LXXIII):



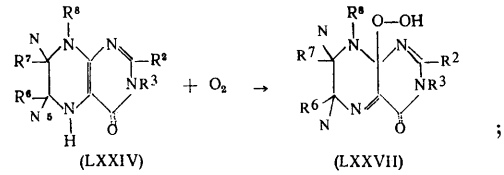
(LXXIII)

while reduction with $LiAlH_4$ yields the corresponding piperazine. The experiment has been described and discussed [130].

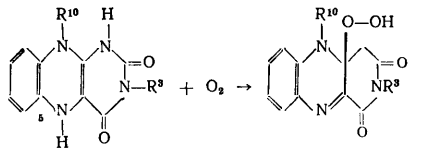
The attempts to synthesise compound (LXXI) with R = H by treating 1,2-diphenyl-4,5-dihydropyrazine with H_2O_2 led to the synthesis of its decomposition products only, which included, apart from the expected dibenzoylethylenediamine, a multiplicity of compounds, the nature and content of which varied as a function of the experimental conditions (for example, depending on the presence of water). It is interesting to note that in certain cases the ring may contract with formation of imidazolines [131].

Partly hydrogenated pyrazines and isoalloxazines, such as tetrahydropteridines (LXXVI) or dihydroisoalloxazines (LXXV), also give rise to the intermediate hydroperoxides

(XXVI) and (XXVII) as a result of autoxidation[132] (their presence has been established chemically and polarographically in some instances). An exception is the case where the nitrogen atom in the 5-position has a substituent:

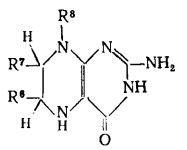


(LXXIV) (LXXVII)



(LXXV) (LXXVI)

In the pteridine series, 2-amino-4-hydroxy-derivatives have been investigated:



(1) $R^6=R^7=CH_3$ and $R^8=H$;
(2) $R^6=R^7=CH_3$ and $R^8=C_2H_5$ or $CH_2—CH_2OH$;
(3) $R^6=R^7=C_6H_5$ and $R^8=C_2H_5$.

The first case has been investigated in particularly great detail. The initial solid compound is stable at room temperature, but in solution absorbs O_2 rapidly. The intermediate hydroperoxide interacts with the initial compound, forming a dihydro-derivative via the mechanism

$$H_3PterO—OH + H_4Pter \rightarrow 2H_2Pter + 2H_2O .$$

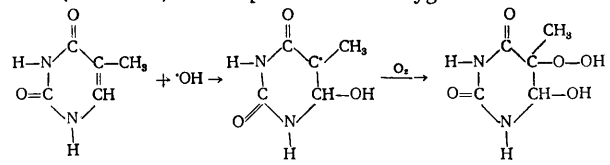
Tetrahydropteridines (cases 2 and 3) and the corresponding isoalloxazine with R = H behave similarly. In the presence of an appropriate reducing agent, H_2Pter can be reconverted into H_4Pter. It has been noted that H_4Pter has an accelerating effect on the oxidation of various compounds, for example thiols (β-mercaptoethanol, cysteine) as well as more complex compounds, for example dihydronicotinamide-adenine nucleotide. This effect has been examined in detail[132]. The possible involvement of tetrahydropteridine and dihydroisoalloxazines in biochemical hydroxylation is discussed in the same report[132].

5,6,7,8-Tetrahydrofolic acid and its 5-methyl derivative have been recently reinvestigated[189]. Traces of an organic peroxide could not be detected, but H_2O_2 was found in the distillation products. Hence one can apparently conclude that the oxidising radicals (chain-transfer agents) are HO–O· and not RO–O·, which leads to the formation of H_2O_2 and not ROOH.

10. Nucleic Acid Derivatives

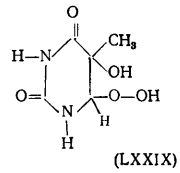
The influence of ionising radiation on the organism causes cell damage such as aberrations in chromosomes, mutation, and carcinogenesis, which are a result of changes at the molecular level. Radiation has a particular influence on the cell nucleus, since it has been established that the latter is twenty times more sensitive to radiation than cytoplasm. It is now believed that exposure to ionising radiation leads mainly to the formation of ·OH radicals, produced by the radiolysis of the aqueous medium. It was found previously that, in the radiolytic process, attack by the ·OH radicals is directed to the extent of 80% towards the pyrimidine base and only to the extent of 20% towards the sugar component of DNA. Purine bases are apparently more resistant to this attack. The foregoing findings suggest that the action of ionising radiation on pyrimidine bases *in vitro* in an aqueous medium is of considerable interest: since 1966, it has been the subject of numerous studies[133-150]. In particular, much attention has been devoted to thymine.[139-147]

The studies have shown that attack is directed mainly to the $C_{(5)}=C_{(6)}$ double bond; the preferred site of the initial attack by ·OH radicals is the 6-position, with formation of a hydroxy-radical, which gives rise to the hydroxyhydroperoxide (LXXVIII) in the presence of oxygen:



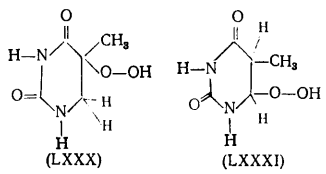
(LXXVIII)

Apart from the hydroxyhydroperoxide (LXXVIII) (consisting of a mixture of the *cis*- and *trans*-isomers), compound (LXXIX) was also obtained (as a result of attack by ·OH radicals in the 5-position):



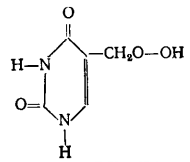
(LXXIX)

and the hydroperoxides (LXXX) and (LXXXI) as a result of attack by H· atoms in the 5- or 6-position:



(LXXX) (LXXXI)

Apart from the $C_{(5)}=C_{(6)}$ double bond, the CH_3 group in the side chain can also be attacked by ·OH radicals, which leads to the formation of the primary hydroperoxide (LXXXII):

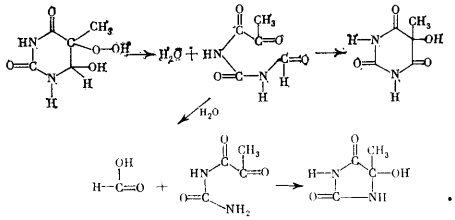


(LXXXII)

In a neutral medium, the rate of this reaction is very insignificant, but increases with increase in alkalinity owing to the aromatisation of the pyrimidine ring[143,147].

Hydrogen peroxide is also formed as a result of the dimerisation of ·OH radicals and the hydrolysis of the hydroxyhydroperoxides (LXV). The existence of these different peroxy-compounds has been established chromatographically[146] and spectroscopically (mass spectrometry, infrared and ultraviolet spectroscopy, NMR, ESR)[144]. NMR and particularly ESR made it possible to demonstrate the existence of intermediate radicals.

At 12°C, pH 5, and an irradiation dose of 9×10^3 rad min^{-1}, a reaction time of 1 h, and a concentration of 0.001 M, the contents of the hydroperoxides (LXXVIII), (LXXIX), (LXXX), and (LXXXI) were respectively 4.0, 4.4, 2.4, and 2.1%. The hydroperoxides (LXXVIII) and (LXXIX) were synthesised (by treating the corresponding glycol with H_2O_2). The hydroperoxide (LXXVIII) is fairly stable, decomposing slowly at 30°C. When thymine is radiolysed in an aqueous medium in the presence of O_2, the decomposition products of the hydroperoxide (LXXVIII) are formed, namely 5,6-dihydroxy-5,6-dihydrothymine, pyruvylurea, 5-hydroxy-5-methyl-barbituric acid, 5-hydroxy-5-methyl-hydantoin, urea, and formic and pyruvic acids:

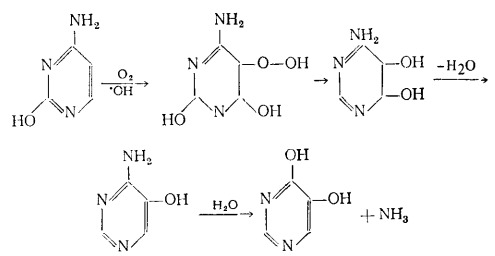


The results of a study of the radiolysis (^{60}Co γ-radiation) of an aqueous solution of thymine (12°C, pH 5, dose 9×10^3 rad min^{-1}) have been published[145] and the kinetics of the formation of various compounds as a function of the irradiation dose (between 2×10^2 and 10^6 rad) under the above conditions have been investigated[143,144].

Under analogous conditions, uracil also yields a hydroxyhydroperoxide, since the O–OH group is likewise located in the 5- or 6-position, but it is much more unstable than in the case of thymine; its presence has been detected by NMR.[148] Its decomposition products are similar to those of the hydroperoxide derived from thymine (with the CH_3 group replaced by an H atom); they include hydroxybarbituric acid, hydroxyhydantoin, formylglyoxylurea, and products of more extensive oxidation—alloxane, parabanic acid, and dialuric acid.

The complete list of compounds and the methods for their isolation in the radiolysis of uracil in an aqueous medium (at room temperature, pH 6, a concentration of 0.001 M, and a γ-radiation dose of 90 rad) has been published[148].

The hydroxyhydroperoxide derived from cytosine is still less stable than that derived from uracil. Thus irradiation of this base (under conditions similar to those described above) leads to the formation of isobarbituric acid via the mechanism[136,149]



Products of more far-reaching oxidation are formed from isobarbituric acid: alloxan, dialuric acid, and parabanic acid.[150]

Pyrimidine nucleosides and nucleotides also form peroxides under conditions similar to those in the formation of the corresponding bases[133]. Attack by ·OH radicals is mainly directed to the 6-position, in the double bond of the 5,6-pyrimidine ring, and not to the bond between the nitrogen-containing base and the monosaccharide or between the monosaccharide and phosphoric acid.[154]

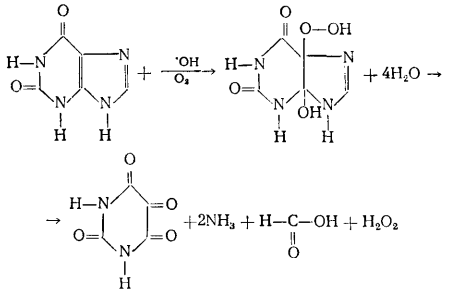
The radiolysis of thymidine has been investigated at 16°C, pH 6, and an irradiation dose of 8×10^3 rad.[152,190] Molecular asymmetry at the level of the sugar component indicates the occurrence of diastereoisomerism leading to the formation of two forms of the *cis*-peroxide derived from 5-hydroperoxy-6-hydroxy-5,6-dihydrothymidine and two forms of the corresponding *trans*-hydroperoxide. These hydroxyhydroperoxides have properties similar to those of the hydroxyhydroperoxide derived from thymine. In particular, they are readily hydrolysed to the corresponding glycols (with retention of the configuration), which are the main reaction products.

The presence of the sugar component makes the pyrimidine ring appreciably resistant to the dissociation of the $C_{(5)}=C_{(6)}$ bond. Indeed hydroxymethylribofuranylbarbituric acid, which can be obtained as a result of the rearrangement of formylpyruvylribofuranylurea, could not be detected[152].

The formation of organic peroxides and H_2O_2 was also established following the irradiation of an aqueous DNA solution (at 22°C, a concentration of 0.001 M, and a dose of 7×10^3 rad).[163] The kinetic curves for the decomposition of these peroxides at 52°C, 62°C, 72°C, and 79°C indicate the existence of two different peroxy-compounds[153], which are in all probability hydroxyhydroperoxides derived from thymine and cytosine nucleotides. These hydroperoxides probably play an important role in the development of the consequences of the irradiation of organisms as a result of their further decomposition into the products discussed above[153].

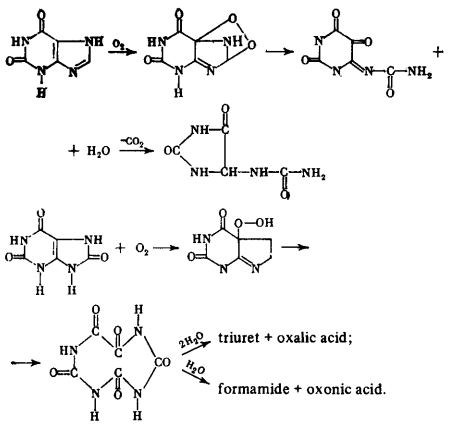
It is noteworthy that only pyrimidine compounds are formed. Indeed not even traces of a peroxide could be detected after the irradiation of an aqueous solution of quanine and adenine as well as their nucleosides and nucleotides[133].

However, purine bases can be subjected to oxidative degradation under the influence of γ-radiation in an aqueous solution with rupture of the imidazole ring. Thus xanthine is converted into alloxan, formic acid, NH_3, and H_2O_2. The preferred site attacked by the ·OH radical is apparently the $C_{(4)}=C_{(5)}$ double bond. In order to account for the formation of the above compounds[155], the formation of very unstable hydroxyhydroperoxides was postulated:



In addition, purine bases (in contrast to pyrimidine bases) decompose at room temperature as a result of sensitised photochemical oxidation. For example, in an aqueous alkaline medium containing added dyes, they absorb approximately one mole of O_2 following exposure to light with formation of various decomposition products consisting of allantoin in the case of xanthine and triuret in the case of uric acid.

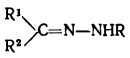
In order to account for the formation of these compounds, it was suggested that a very unstable endoperoxide (in the case of xanthine) and a very unstable hydroperoxide (in the case of uric acid) are formed as intermediates:



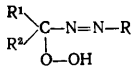
The compounds formed in accordance with the experimental conditions have been described and their formation discussed [156,157].

VII. THE OXIDATION OF HYDRAZONES

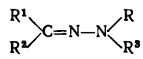
Hydrazones having the general formula



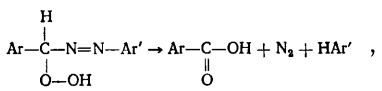
yield hydroperoxides on autoxidation at room temperature in an organic solvent:



Hydrazones disubstituted at the nitrogen atom are not oxidised under these conditions.

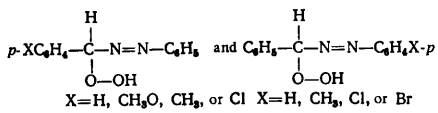


The hydroperoxides derived from hydrazones are yellow crystalline substances, which explode in the dry state, are more or less stable in solution, are soluble in alcohol and ether, and are sparingly soluble in petroleum ether. They decompose to a carboxylic acid, a hydrocarbon, and nitrogen,



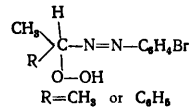
and on reduction (with KI in acetic acid) give rise to the corresponding hydroxy-derivatives, which rearrange to acylhydrazines.

Hydroperoxides of the type



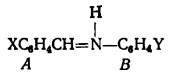
have also been investigated.

Apart from the above hydroperoxides, there exist a further two hydroperoxides:



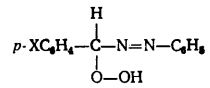
Hydrazone hydroperoxides were obtained for the first time by Bush and Dietz [158] and their structures have been established by Pausacker [159] and Criegee and Lohaus [160].

Any substituent in ring *A* of the hydrazone having the general formula



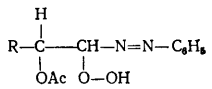
decreases the rate of autoxidation; the autoxidation is accelerated in the presence of nucleophilic substituents and is retarded in the presence of electrophilic substituents in ring *B*. [159]

The stability of the hydroperoxides

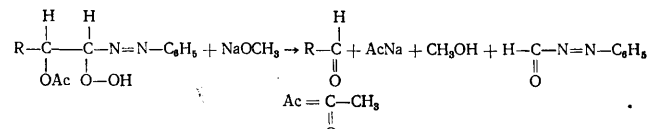


increases in the presence of nucleophilic substituents and diminishes in the presence of electrophilic substituents. For example, when X = CH_3O, the hydroperoxide decomposes very slowly at room temperature and can be stored for several weeks at 0°C, while in the case where X = Cl it decomposes already during crystallisation [161].

Interesting results have been obtained for hydrazones derived from monosaccharides. [162] Thus when a stream of O_2 is passed into a benzene solution of penta-acetylgalactose phenylhydrazone, the product is the hydroperoxide



which decomposes under the influence of sodium methoxide in methanol solution to lyxose and *N*-phenyldi-imine formate:



Deoxyarabinose is formed similarly from rhamnose.

Thus the above method can be convenient for the synthesis of C_{n-1} monosaccharides from a C_n monosaccharide.

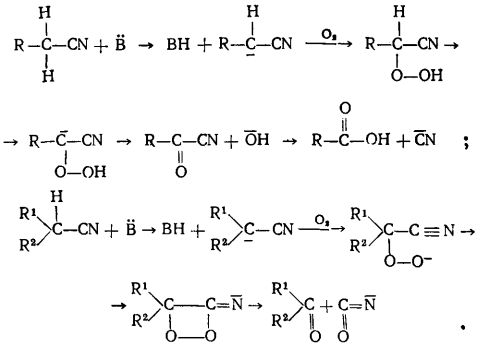
VIII. THE BASE-CATALYSED AUTOXIDATION OF AZO-COMPOUNDS VIA AN IONIC MECHANISM

Nitriles

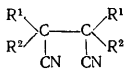
The autoxidation of a number of mono- and di-substituted nitriles (phenyl-, diphenyl-, and cyclohexylphenyl-acetonitriles) has been examined [163,164] and it has been established that there is no absorption of O_2 at room temperature even in solvents such as pyridine, but it begins rapidly after the addition of a strong base (sodium methoxide, benzyltrimethylammonium hydroxide), reaching a maximum

of 0.7–0.8 mole of O_2 in the course of several hours. Disubstituted nitriles lead to the formation of ketones and cyanates, while monosubstituted nitriles yield benzoic and hydrocyanic acids (in the form of alkali metal salts). The yield of benzophenone from diphenylacetonitrile is 65%.

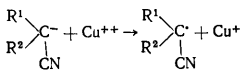
The following reaction mechanism has been proposed [164]:



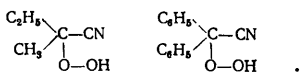
In the presence of copper ions (1–2 mole %), the acceleration of the absorption of O_2 is accompanied by the formation of the dinitriles



which are apparently a result of the dimerisation of the radicals formed via the mechanism

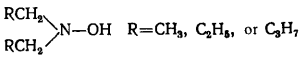


When the oxidation was carried out at −40° and −75°C with added $(CH_3)_3COK$ in solution in $CH_3OCH_2CH_2OCH_3$, pure hydroperoxides were obtained from the corresponding nitriles in 67% yield:



Hydroxylamines

The study of the autoxidation of symmetrical disubstituted aliphatic hydroxylamines (in the form of oxalates) [165,166]



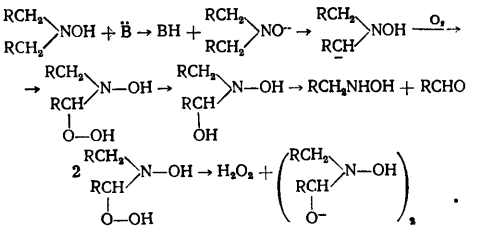
shows that alkalis have a marked accelerating effect on the absorption of O_2. Mn^{2+} and particularly Cu^{2+} ions greatly accelerate the absorption of O_2.

A monosubstituted hydroxylamine (RCH_2NHOH) aldehydes (RCHO), and peroxy-compounds are formed in the autoxidation reaction. The content of peroxides passes through a maximum, then falls, but does not reach zero. The formation of H_2O_2 and of an organic peroxide from the compound



has been demonstrated by the polarographic method [166]. However, the latter could not be isolated in a pure state.

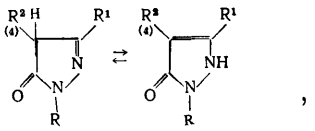
The following mechanism of the reaction involving the formation of a hydroperoxide, a dialkyl peroxide, and H_2O_2 is possible:



The accelerating effect of metal ions can probably be accounted for by the conversion of anions into radicals, as for nitriles.

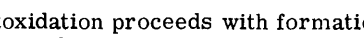
Pyrazolones

Pyrazolones, which exist in two tautomeric forms,

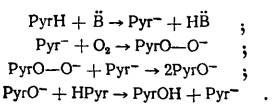


are converted in the presence of atmospheric oxygen into the corresponding dimers linked via the carbon atoms in the 4-positions. The study of the autoxidation of pyrazolones with R = C_6H_5, $R^1 = CH_3$, and a variable R^2 shows that one mole of O_2 is absorbed in an alkaline medium [167].

The primary autoxidation products are apparently pyrazolones hydroxylated in the 4-position, which yield dimers as a result of the reaction with the initial pyrazolone [167]:



The autoxidation proceeds with formation of intermediate pyrazolone anions in the following manner:



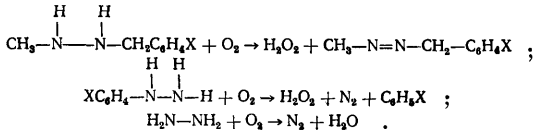
This mechanism has been discussed in detail with changes caused by any change in the nature of the base [167].

The autoxidation of 3,4-dialkyl-1-(methylpiperidinyl)-5-pyrazolones, which have interesting pharmacological properties, has been examined. A study has also been made of pyrazolidine-3,5-diones [169].

IX. THE INTERACTION OF HYDRAZINES WITH OXYGEN

Hydrazines containing at least one hydrogen atom linked to each nitrogen atom undergo autoxidation at room temperature (in the form of salts in aqueous solution) with dissociation of N–H bonds and the formation of H_2O_2 and a diazo-compound. The latter may decompose into N_2 and a hydrocarbon. The rates of the reactions of *N*-benzyl-*N'*-methylhydrazines [170], *N*-arylhydrazines [171], and

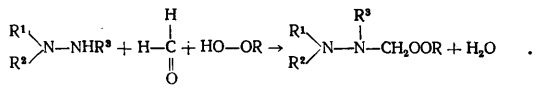
unsubstituted hydrazine [172] at room temperature are consistent with the following equations:



The reactions are vigorously catalysed by Cu^{2+} ions.

In the presence of O_2, hydrazines exhibit a cytotoxic activity owing to the possible formation of $^{\cdot}OH$ radicals (via the reaction between H_2O_2 and the initial hydrazine), which disrupt the structure of nucleic acids by adding to the $C_{(5)}=C_{(6)}$ double bonds of the pyrimidine bases. We may note that benzyl-*N*-isopropyl-*N*-methylcarbamoylhydrazine is present in the blood and in urine and is probably capable of being oxidised *in vivo*, exhibiting a cytotoxic activity [170,173-175].

Despite the absence of hydroperoxides from the autoxidation products of hydrazines, it has been possible to obtain several peroxides (derived from these compounds) by treating hydrazines with RO–OH in the presence of formaldehyde [191]:



We may note that in certain instances hydroperoxides can be obtained when RO–OH is replaced by H_2O_2.

X. THE INTERMEDIATE FORMATION OF PEROXIDES IN THE BIOLUMINESCENCE PROCESS

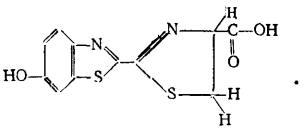
Since many substrates exhibiting bioluminescence contain nitrogen, it was thought useful to examine briefly the intermediate formation of peroxides at the instant of the manifestation of bioluminescence.

Luminescing organisms are frequently encountered among animals, particularly among the marine fauna. The only luminescing organisms among vertebrates and plants are fish and fungi respectively. Luminescence is also characteristic of certain bacteria. However, only a few of the many thousands of the existing species of organisms have so far been investigated owing to the difficulty of collecting them and the very low content of the active compound (several milligrams per tens of thousands of individuals).

All the reactions associated with the manifestation of bioluminescence require oxygen or a peroxide formed beforehand. In the presence of the enzyme luciferase, the substrate called luciferin is oxidised. During the last decade, bioluminescence has been the subject of serious research and development [195-200].

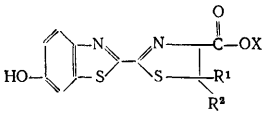
Luciferins

Particular attention has been devoted to the study of the luciferin of the North American *Photinus pyralis*, which emits a bright yellow light. The luciferin from *Photinus pyralis* was isolated in a pure form and characterised by elemental analysis infrared spectroscopy [201], and by the identification of the decomposition products [202]. It is a benzothiazole derivative having the formula



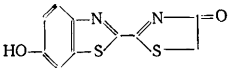
It was synthesised by treating cysteine with 2-cyano-4-hydroxybenzothiazole. [202] The corresponding luciferase was also isolated. Its molecular weight is 100 000 and it has an isoelectric point of 6.2–6.3. [203]

Numerous luciferin derivatives having the general formula [215]

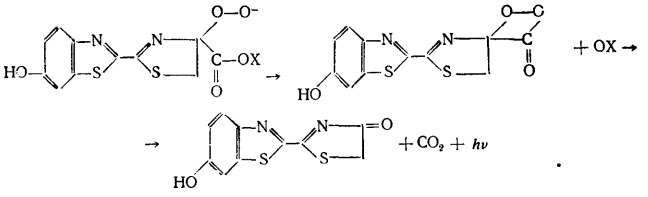


where X = C_6H_5 or adenyl, $R^1 = R^2 = CH_3$, or $R^1 = H$, and $R^2 = CH_3$, have also been synthesised. The disubstituted derivative ($R^1 = R^2 = CH_3$) is particularly interesting because it cannot decompose via dehydroluciferin (which is readily formed when $R^1 = R^2 = H$). The bioluminescence arises as a result of the enzymatic oxidation of luciferyl adenylate formed when adenosine triphosphoric acid is acted upon by luciferin in the presence of luciferase and Mg^{2+} ions.

The light emitting compound is the lactam

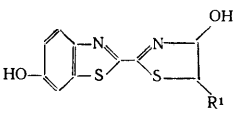


(in the excited state), which is probably formed via the very unstable dioxetan:

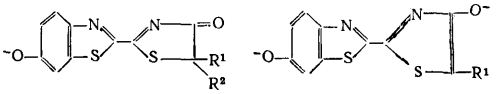


Indeed one mole of O_2 per mole of compound is absorbed and one mole of CO_2 per mole of compound is evolved in the bioluminescence process.

The above lactam was identified and isolated (in the form of the diacetate) from glow worm extracts [204]. Furthermore, the chemiluminescence spectrum of luciferin is identical with the fluorescence spectrum of the lactam, synthesised [204] by the condensation of the above nitrile with ethyl thioglycolate. Similar lactams have also been obtained from various substituted luciferin derivatives [205]. The chemiluminescence of these lactams varies with pH owing to the possibility of their existence in the enolic form



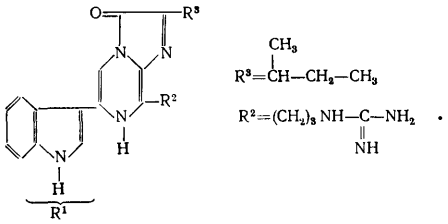
which can lead to the formation of a mono- or di-anion in an alkaline medium:



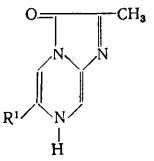
When $R^1 = R^2 = CH_3$ in the disubstituted derivative, only the monoanion can exist.

The Bioluminescence of Cypridina hilgendorfi

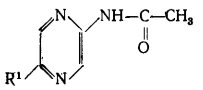
This crustacean lives in the Sea of Japan and near the shores of Jamaica. When the contents of two glands containing luciferin and luciferase respectively are introduced into air-saturated water, a blue glow is observed. The luciferin of this crustacean was identified[208] as an indolopyrazine derivative having the formula



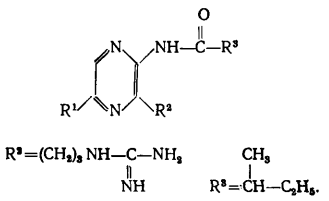
Simpler model compounds



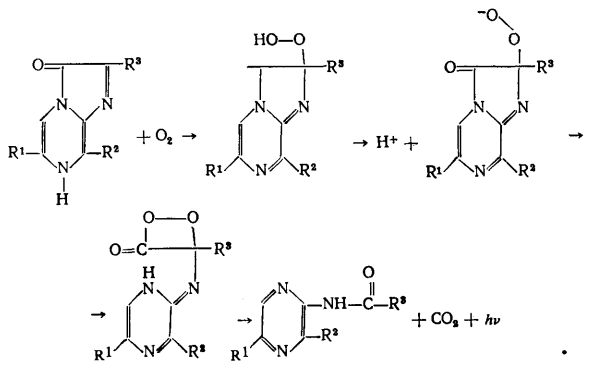
where $R^1 = C_6H_5$ [209] or β-indolyl [210], have also been synthesised. They inhibit luminescence and decompose after the absorption of O_2 into the corresponding amides:



Luciferin itself (obtained from natural extracts) absorbs O_2 in the presence of luciferase and evolves CO_2 in equimolar amounts[211,212]. The reaction yields the amide

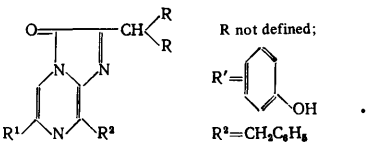


All the foregoing facts suggest the following sequence of reactions proceeding via an intermediate dioxetan, yielding an amide in an excited state:

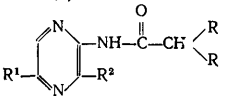


The Bioluminescence of the Jellyfish *Renilla* and *Aequorea*

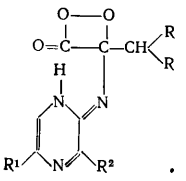
The mechanism of the bioluminescence of the jellyfish *Renilla* is similar to that of Cypridina, but is more complex. Since a photoprotein, containing a peroxide formed beforehand, is present in this organism apart from luciferin identical with that from Cypridina [213], light emission begins only after the addition of ions (in the presence of O_2). The luciferase from *Aequorea* [214] has the following structure:



In conformity with a sequence of reactions analogous to that described previously, the amide

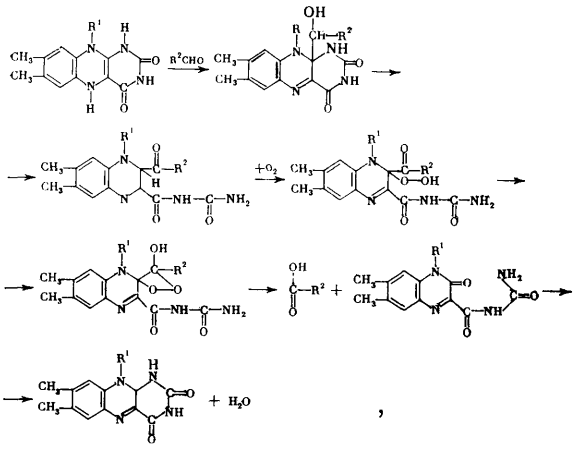


is obtained in an excited state via the intermediate dioxetan



The Bioluminescence of Bacteria

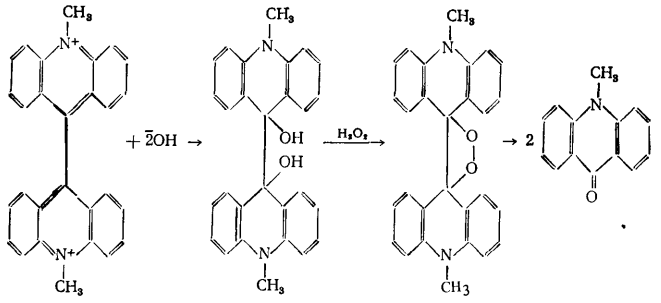
The luminescence of fish, dead animal tissues, and plants is caused by bacteria, various species of which have been described[215]. In this case, there is no luciferin or luciferase, but two other compounds are active: flavinmononucleotide (in a reduced form) ($FMNH_2$) and a linear long-chain aliphatic aldehyde. The aldehyde is apparently oxidised to the corresponding acid[217,218] in an excited state via the peroxide in accordance with the mechanism



where R^1 = ribosyl and R^2 = aldehyde group.

Synthetic Luminescent Compounds

Studies have shown that the conversion of lucigenin (*NN*-dimethyl-2,9-biacridinium dinitrate) under the influence of H_2O_2 in an alkaline medium into *N*-methylacridone (in an excited state), accompanied by the emission of a green light, proceeds via the formation of an intermediate peroxide[218]:



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