OXIDATION OF INDOLES WITH TRIPLET OXYGEN

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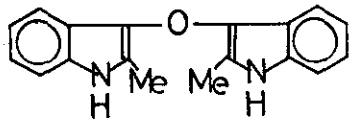
Autoxidation of indole derivatives provides 3-hydroperoxyindolenines as the initial product which collapse to a variety of products depending upon the structures and reaction conditions. The oxidation is discussed under the following headings.

1 Introduction

It has long been known that simple indole derivatives are sensitive to atmospheric oxygen especially in the presence of light. Baudisch and Hoschek[1] found in 1916 that oxygen had been consumed when a suspension of 2-methylindole in water saturated with oxygen was exposed to sunlight for several months in a closed vessel. From the reaction mixture they isolated N-acetylanthranilic acid and some yellow crystals to which they assigned structure 1. Oddo also found that 2-methylindole could be converted by air



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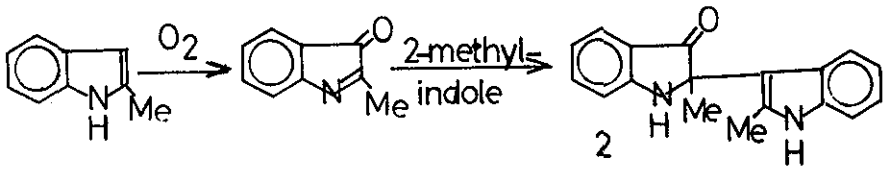
oxidation into a yellow compound $C_{18}H_{16}N_2O$ and assigned the same structure, 1. He further described that skatole and indole itself were also oxidized, but less easily, under similar conditions, though the structures of oxidation products were not described[2].

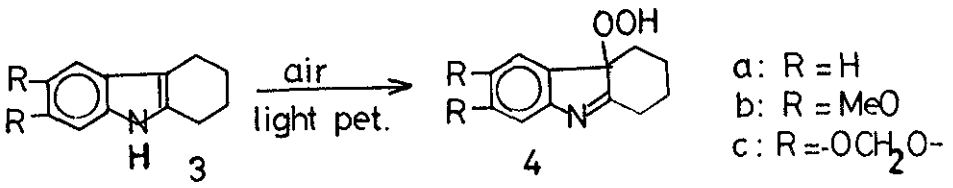
The structure 1 was first doubted by Toffoli[3] who claimed the structure(1) could not explain the yellow color of the compound. Later Witkop[4] revised the structure of the yellow compound to 2 utilizing UV and IR spectra, and the raction path for formation of 2 was proposed as follows.



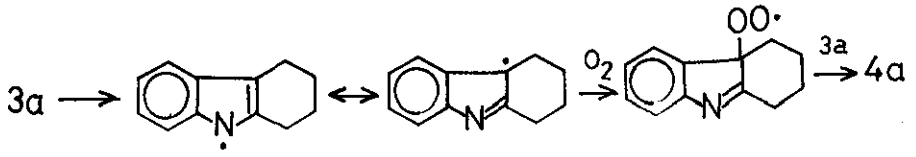
The same compound(2) was obtained by the oxidation of 2-methylindole with a variety of oxidants such as H_2O_2[5] and dye-sensitized photooxygenation[6]. In this review we have summarized the results of oxidation of indoles with triplet oxygen which have appeared since 1950.

II Autoxidation of Tetrahydrocarbazoles

Beer and coworkers reported the autoxidation of tetrahydrocarbazoles(3) to 4 during purification, and succeeded in the isolation of the hydroperoxide(4).[7] The hydroperoxide



(4a) liberates iodine on treatment with acidified aqueous potassium iodide and reverts to 3a on catalytic hydrogenation with Pd-C. The hydroperoxide decomposed vigorously with a blue fash at the melting point, the first indication of the chemiluminescence of indole derivatives. As the autoxidation of 3 was inhibited by N-methylation or N-acetylation, the reaction was assumed to proceed as follows.



Independently Witkop[8] also obtained the same hydroperoxide(4a) by catalytic oxidation of 3a with Pt. Both groups explained the reactivity of the hydroperoxide(4a) as shown in Chart 1. And these are the typical reactions of the 3-hydroperoxyindolenine. Recently McCapra has pointed out that if the peroxide is prepared by keeping a solution of 3a at room temperature for 24 hr, the compound first isolated has the structure 10 (the stereochemistry is not known), and it decomposed to 4a and 5 on boiling in ethyl acetate.[9] Thus attempted recrystallization above room temperature gives 4a as the least soluble component.

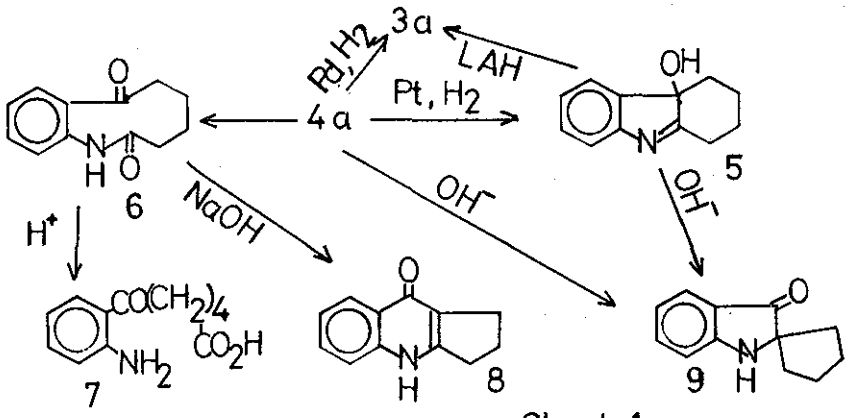
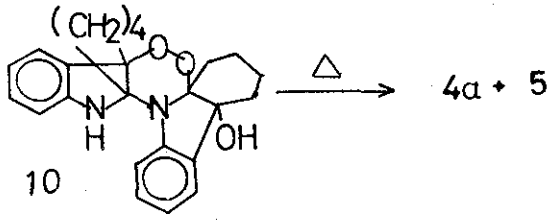


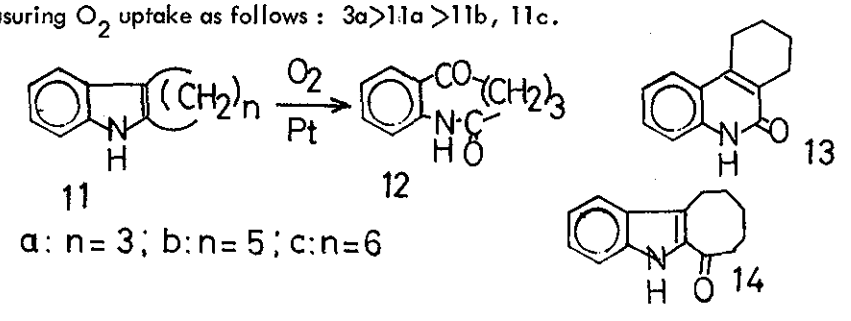
Chart 1



After disclosing the facile autoxidation of tetrahydrocarbazole, the Beer group[10] verified that the by-products obtained in the indolyzation of the o-bromophenylhydrazone of cyclohexanone by Barns[11] were the autoxidation products (4, 6, and 8) of the expected 8-bromotetrahydrocarbazole. Beer's group[12] also investigated the effect of the substituent on the autoxidation of tetrahydrocarbazoles. Electron-donating groups such as 6-methoxy accelerate the autoxidation in benzene solution, while electron-attracting groups such as 6- and 8-nitro retard the autoxidation. Relative rates for the autoxidation of methoxycarbonyl derivatives are shown to be in the following order. 6-MeO>unsubstituted>5-CO_2Me, 6-CO_2Me>7-CO_2Me≫8-CO_2Me. However the autoxidation of 6-benzyloxy or 6-hydroxytetrahydrocarbazole was inhibited due to the chain breaking action of the substituent in the

radical chain reaction. Furthermore aqueous solutions of carboxytetrahydrocarbazoles were oxidized in the presence of sodium hydroxide. In aqueous alkaline media 5-, 6- and 7-carboxytetrahydrocarbazoles gave the indoxylic compounds(9), or 4-quinolone compounds (8), while the 8-carboxy derivative was found to be stable under these conditions. Relative rate : 5-CO_2H>6- and 7-CO_2H≫8-CO_2H.

Beer's group also investigated the autoxidation of cyclopentano- (11a) and cycloheptanoindole(11b) under similar conditions to those used for tetrahydrocarbazole. However, they could not isolate the corresponding hydroperoxide, but obtained an amorphous powder which gave a weak KI-test[7]. On the other hand Witkop's group[13] clearly demonstrated that the catalytic oxidation of 11 gave different product dependand upon their ring size. They obtained 12 from 11a, 13 from 11b, and 14 from 11c. In contrast to tetrahydrocarbazole, the hydroperoxyindolenines of 11 were not isolated. However, a solution of 11c in benzene-hexane provided the corresponding hydroperoxyindolenine on exposure to air, which was readily converted to 14 on standing in AcOEt-AcOH[14]. This shows the first example of 2-acylindole formation which was later found to be a common autoxidation product of 2,3-dialkylindoles. Although the reason for the ring size effect on the oxidation products is not clear, it is suggested that the initial product for the oxidation of 11 is the hydroperoxyindolenine. They also showed the relative rate of the autoxidation by measuring O_2 uptake as follows : 3a>11a >11b, 11c.



III Autoxidation of 2,3-Dialkylindoles

1. Isolation of hydroperoxyindolenines.

The Witkop group[15] had succeeded in isolating the stable hydroperoxyindolenine(16), mp 154°(without decomp), from the catalytic O_2 oxidation of 3-methyl-2-phenylindole. The hydroperoxide is stable and forms a hydrochloride, but can be converted to 18 by heating with an acid. The reaction of the hydroperoxide is shown in chart 2.

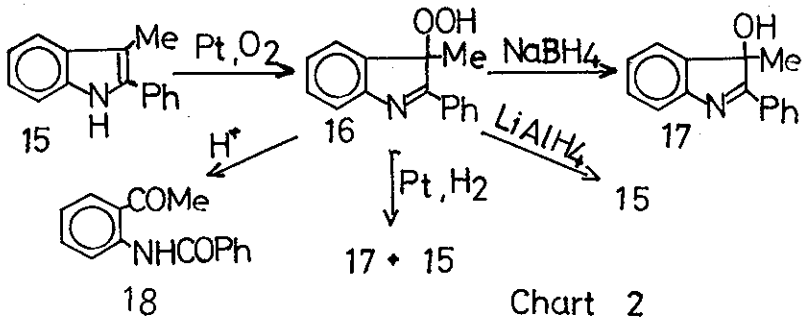
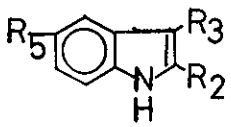


Chart 2

The hydroperoxide(16) was also precipitated by stirring a solution of 15 in benzene and hexane in an open vessel for several days[14]. On the other hand the Beer group[16] investigated the autoxidation of various 2,3-disubstituted indoles(19) in light petroleum and classified these compounds into hydroperoxide forming indoles and stable indoles.



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A : Hydroperoxide forming indoles

a: R_5 = MeO, R_2 = Ph, R_3 = Me

b: R_5 = MeO, R_2,R_3 =Me

c: R_5 =H, R_2,R_3 = Me

B : Stable indoles

a:R_2 = Me, R_3 =Ph, R_5 = H

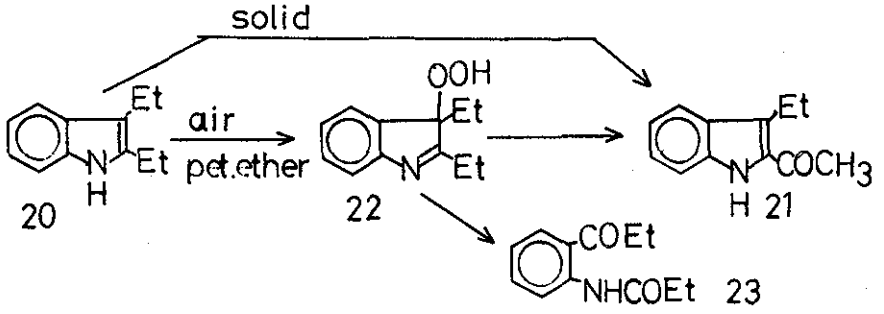
b: R_2,R_3 = Ph, R_5 = H

c : R_5 = MeO, R_2 =Me, R_3 = Ph

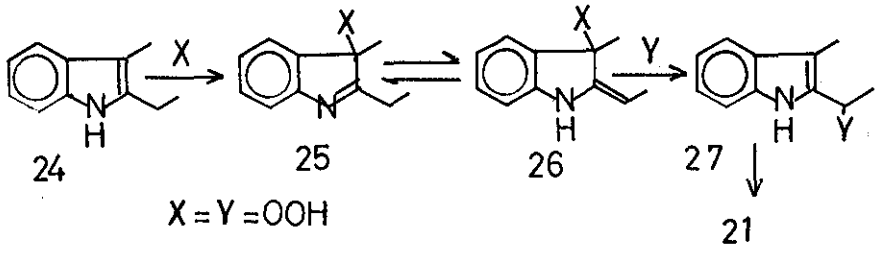
d : R_5 = MeO, R_2,R_3 = Ph

2. Various types of autoxidation

When freshly prepared 2,3-diethylindole(20) was exposured to air and room light for several days, the crystals were converted 2-acetyl-3-ethylindole(21) in good yield[17]. On the other hand, a solution of 20 in light petroleum produced the hydroperoxide(22) in excellent yield on standing in an open vessel for 24 hr, which was then rearranged to 21 in AcOH or AcOEt-AcOH, or converted to a ketoamide(23) by boiling its aqueous solution, demonstrating the probable course of this remarkable transformation of 2,3-dialkylindole to 2-acylindole.

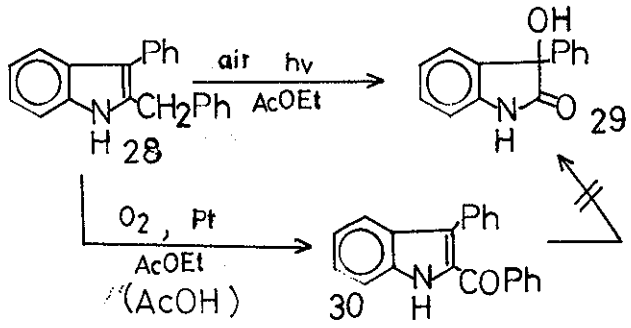


As a possible explanation, Taylor[18] suggested the so-called Taylor mechanism involving the enamine tautomer(26) as an intermediate followed by an internal rearrangement of the hydroperoxy group to give 27 which collapses to 21. Supporting this mechanism is the isolation of 2-formyl-3-methylindole from the autoxidation of 2,3-dimethylindole.

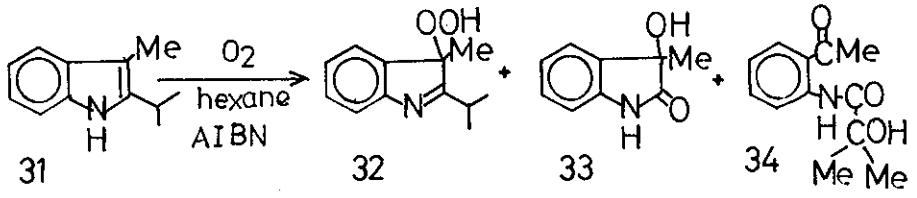


Following his proposal two groups chose the substrate for the autoxidation having substituents which stabilized the exocyclic double bond(26) in the above mechanism. Thus, exposure

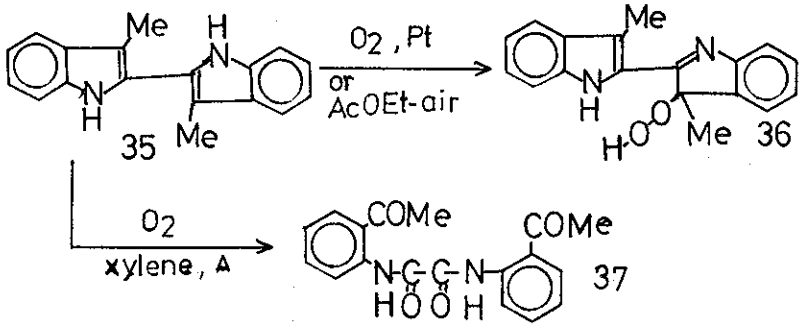
of a solution of 2-benzyl-3-phenylindole (28) in AcOEt to light and air resulted in the formation of dioxindole (29) instead of 2-benzoyl derivative[19]. However, when a solution of 28 in AcOEt was shaken with O_2 in the presence or absence of Pt the only product isolated was 30. This provides the first example of the reaction conditions affecting on the nature of the products. The corresponding hydroperoxide was not isolated under either set of conditions. When 30 was exposured to light and air in AcOEt, 29, a higher oxidation state, was not formed, eliminating 30 as an intermediate to 29[19].



An alternative explanation for the formation of the 2-acylindole was provided by Wasserman, who obtained a hydroperoxyindolenine (32) as an unstable crystalline compound, dioxindole (33), and 34, by the typical autoxidation of 2-isopropyl-3-methylindole(31) in hexane in the presence of azobisisobutyronitrile(AIBN). Instead of 2-acylindole or 2-(1,1-dimethyl-hydroxymethyl)-3-methylindole expected from the Taylor mechanism higher oxidation products (33 and 34) were obtained. In neither example was the simple ketoamide derived from oxidative cleavage of the 2,3-double bond obtained.

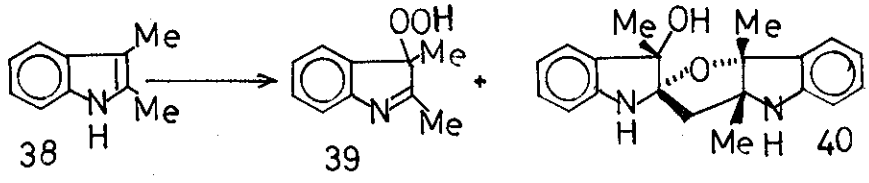


Furthermore, autoxidation of 2,2'-bis(3-methylindole) (35) under various conditions was reported to give the mono-hydroperoxide (36) which was stable in acidic solution and in polar solvents, and not converted to the corresponding ketoamide. However, when O_2 was bubbled through a boiling solution of 35 in xylene, oxidative cleavage of both 2,3-double bonds did occur to give 37 in 81% yield[21].



3. Autoxidation of 2,3-dimethylindole

After Beer's observation that 2,3-dimethylindole(38) gave 3-hydroperoxyindolenine(39) and an unidentified non-peroxidic product (mp 225°) on peroxide-catalyzed autoxidation[16], several workers[22-29] obtained besides 39 the non peroxidic compound under various conditions. Two structures tentatively assigned for this compound have been revised to the correct structure (40) based on mechanistic considerations and spectral data[25,28,29], x-ray analysis[26], and chemical reactions[26,28]. These investigations lead to the finding of a new rearrangement in indoline derivatives[25,27,28]



Dave and Warnhoff [28] reinvestigated the autoxidation of 38 under various conditions in some detail. When a solution of 38 in $CHCl_3$ was exposed to air undisturbed, the dimeric compound(40) was formed, whereas the hydroperoxide(39) was obtained as the major product when O_2 was bubbled into a solution of 38 in pet. ether at 0°. Furthermore, the dimer(40) was obtained in 60% yield when a solution of 38 in benzene was stored for several days[25]. On the other hand, catalytic oxygenation and reduction of 38 in AcOEt gave o-acetamido-acetophenone(8.2%), 2-formyl-3-methylindole(2%), 40(36%), and 2-hydroxymethyl-3-methylindole(4.5%). The dimer(40) was also produced by the reaction of 39 and 38 in $CHCl_3$, thermal decomposition of 39 in benzene, and the reaction of 3-hydroxy-2,3-dimethylindolenine with base. The dimer formation is restricted to 2-methyl-3-alkylindoles such as 2,3-dimethyl or 3-ethyl-2-methylindole[29,30], and autoxidation of 2-ethyl-3-methylindole resembles 2,3-diethylindole in behaviour and forms 2-acetyl-3-methylindole via the 3-hydroperoxyindolenine.

Oxidation of 2,3-dimethylindole having substituents on the benzene ring with oxygen in the presence of hydrogen peroxide was also reported to give hydroperoxyindolenine in good yields[31].

4. Mechanism of the autoxidation of 2,3-dialkylindoles

Autoxidation of 2,3-dialkylindoles gave a variety of oxidation products as described above. However, McLean and Dmitrienko[29] proposed the reaction path for these oxidation products in an unified manner and in mechanistic terms which consistently assign nucleophilic character to enamines and electrophilic character to the carbon atom of imines (Chart 3).

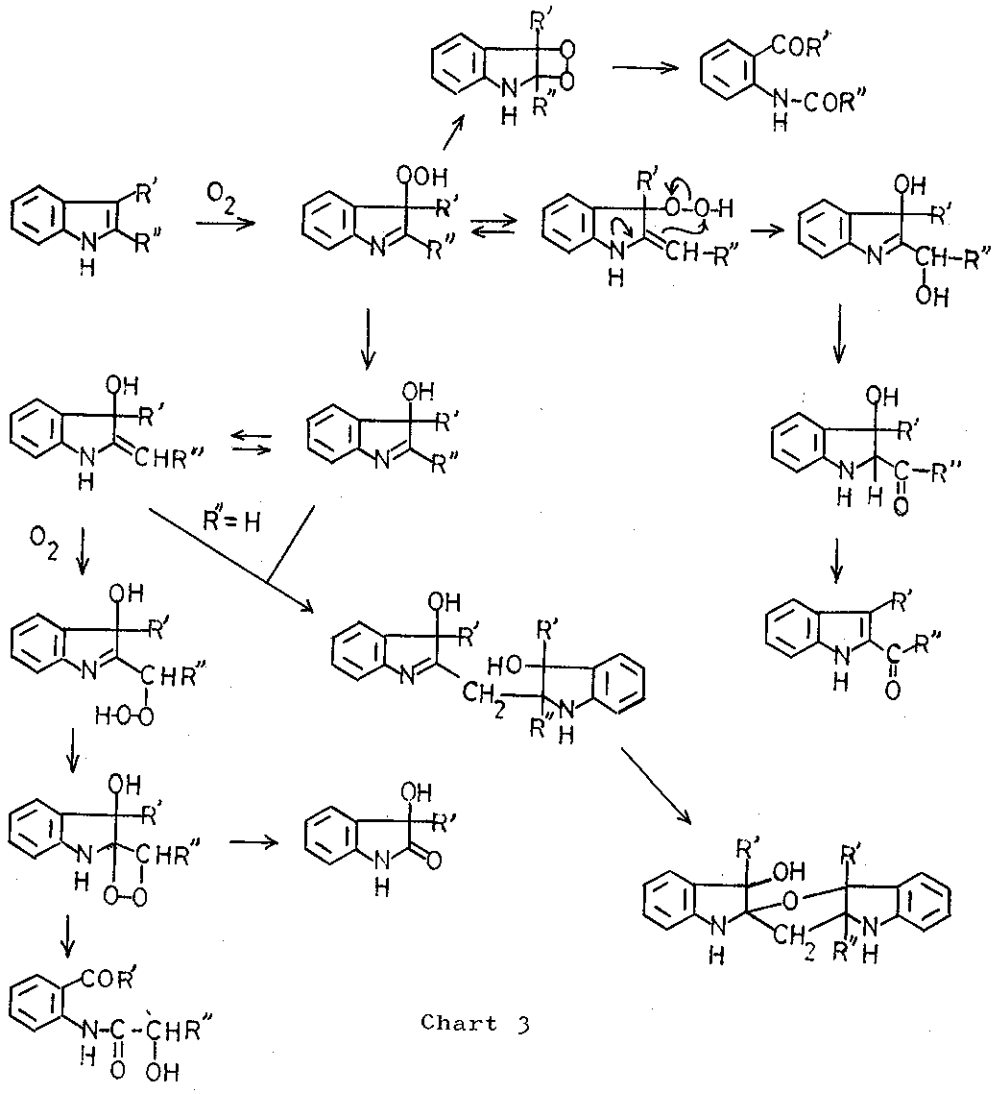
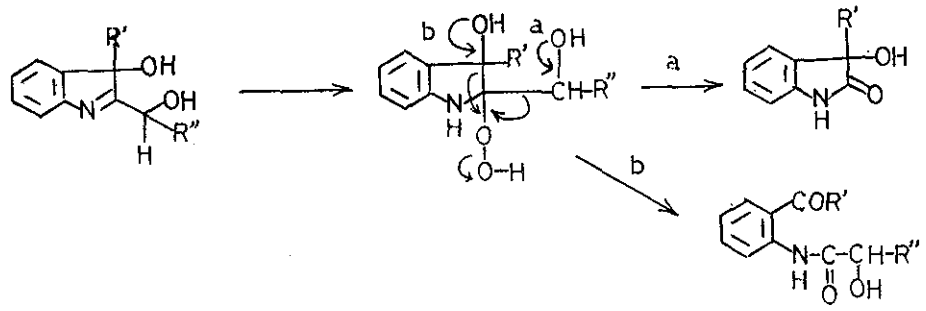
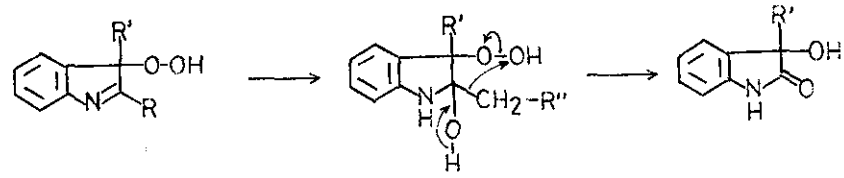


Chart 3

The reaction path to 2-acylindole in Chart 3 is the same as that originally proposed by Wasserman[20], who explained the reaction path to dioxindole and hydroxyketoamide in different way from that shown in Chart 3.

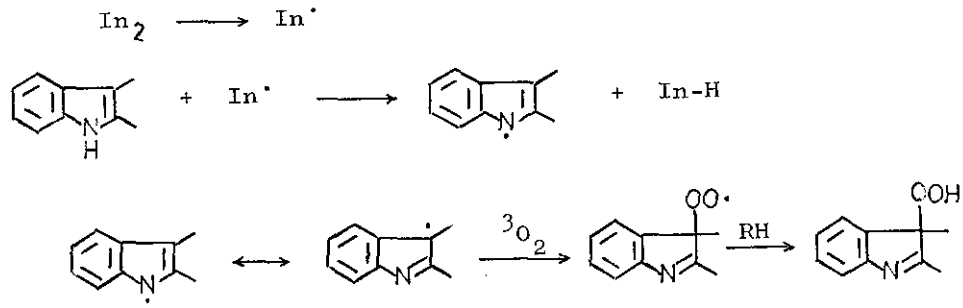


Another pathway to dioxindole was proposed by Leete[19].

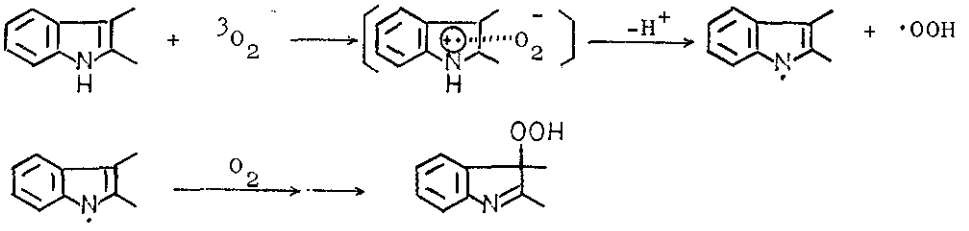


Little mechanistic study has been carried out on the formation of the 3-hydroperoxyindolenine. However, it can be understood in the following way from the knowledge of general O_2-oxidation , as indoles are electron-rich heterocyclic compounds[32].

i) In the presence of radical initiator:



ii) In the absence of the initiator:

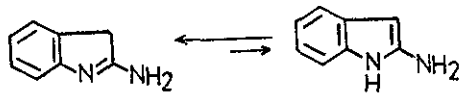


Distinguishing between above two mechanisms in actual examples is difficult, because it is not so easy to prove the absence of a radical initiator as an impurity in the indole subjected to the oxidation. Furthermore, light , even room light, may accelerate the oxidation through mechanisms such as radical formation via the excited state and excited charge transfer state[32].

IV Autoxidation of Indoles having a Hetero Atom Substituent at the 2-Position

1. Autoxidation of 2-aminoindoles

2-Aminoindole(41) was found to be susceptible to aereal oxidation, but none of the oxidation products has been reported[33].



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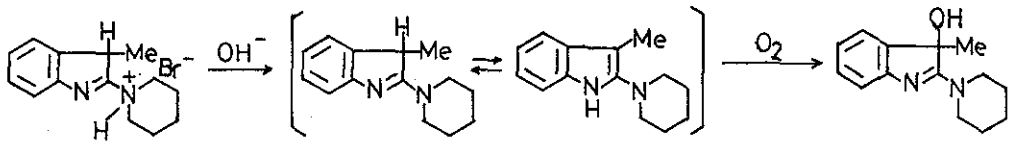
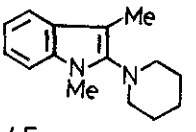
Facile autoxidation of a 2-aminoindole derivative in aqueous solution was found when 3-methyl-2-piperidinoindolenine hydrobromide(42), obtained by the catalytic hydrogenation of N-(3-methylindolyl-2-)pyridinium bromide was basified in aqueous solution and extracted with methylene chloride. Evaporation of the solvent gave the hydroxyindolenine (44) instead of the free base(43)[34].



42 43 44

The presence of the free base(43) as the intermediate was demonstrated by the nmr spectrum of 42 taken in $CDCl_3$ immediately after basification. On the other hand the 1-methyl derivative(45) is resistant to aereal oxidation under similar conditions and can be purified

in the usual manner[35]. In contrast with 2,3-dialkylindoles, 2-amino-3-methylindole(43)



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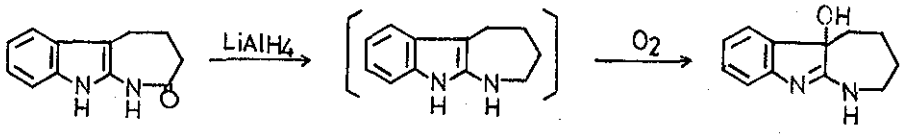
is too unstable to isolate, and immediately oxidizes to 3-hydroxyindolenine in good yield. Similar oxidation was observed when 46 was reduced with $LiAlH_4$. After isolation and purification the product was identified as the 3-hydroxyindolenine(48)[36].



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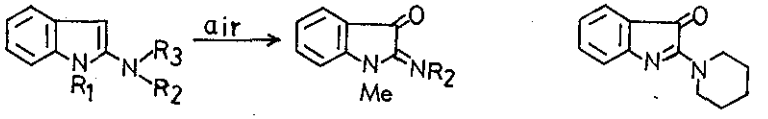
Autoxidation of some other 3-alkyl-2-aminoindoles has also been reported[37].

Several 2-aminoindoles(49) without any substituent at the 3-position are also oxidized by air to 3-oxo derivatives(50 or 51) if one of the substituents(R_1 - R_3) is a hydrogen, but a dimer similar to 2 obtained in case of 2-methylindole was not isolated. Again 49 can be purified only as salt form[35].

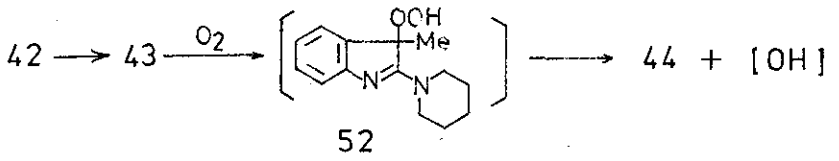


49 50 51

a: R_1= Me; R_2=CH_2CH_2OH; R_3=H ; b: R_1= Me; R_2= CH_2CH_2Cl; R_3= H
c: R_1= Me; R_2= Pr; R_3= H ; d: R_1= Me; R_2= i-Pr; R_3= H
e: R_1= H; R_2= Bu; R_3= H; f: R_1= H; R_2+R_3= -$(CH_2)_5$-

Oxidation of 49 was relatively slow and gave some other polymeric compounds besides 50 or 51. It is interesting to note that the oxidation state of 44 and 50 was different.

The autoxidation of 43 was rapid and gave the 3-hydroxyindolenine as a sole product which was not observed in the autoxidation of 2,3-dialkylindoles, and the hydroperoxyindolenine could not be isolated even under mild conditions. Therefore, we investigated the oxidation of 43 in detail[38]. On mole of oxygen was absorbed during 30 min when an ethanolic solution of 42 was stirred under O_2 atmosphere in the presence of base. Increasing the base from 1 mole equivalent to 4 mole equivalents does not increase the oxidation rate, indicating that the oxidation is not a base-catalyzed. A similar oxygen-uptake was observed when the reaction was carried out in dichloroethane-Et_3N. Uptake of one mole oxygen suggests that the primary intermediate of the oxidation is a hydroperoxyindolenine, and 44 is not derived from the reaction of 52 and 43 which was sometimes proposed for the formation of 3-hydroxyindolenine. Therefore, reductive cleavage of the O-O bond should occur during the reaction or some species which has oxidizing power



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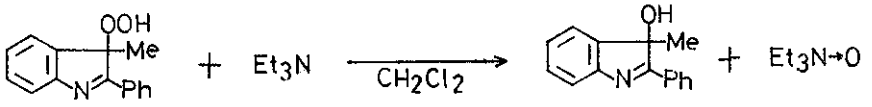
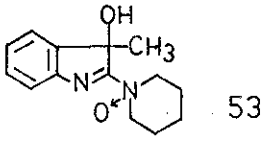
should be present in the reaction mixture. To prove the presence of an oxidizing agent the reaction was carried out in isopropyl alcohol instead of ethanol. Acetone was isolated in low yield and identified as its 2,4-dinitrophenylhydrazone. Furthermore when the reaction was carried out in ethanol in the presence of Hantsch ester, the corresponding pyridine derivative was obtained in 94% yield after 3 hr. Without 42 Hantsch ester was not oxidized under similar conditions.

As the instability of the hydroperoxyindolenine(52) is considered to be due to the nitrogen atom at 2-position, reaction of 3-hydroperoxy-3-methyl-2-phenylindolenine(16), a stable hydroperoxide, with triethylamine was carried out. Without triethylamine, 16 was stable in CH_2Cl_2 at room temperature for 3 days , but hydroxyindolenine(17) was



16 17

isolated in 64% yield when a solution of 16 and 0.7 mole equivalent of triethylamine in CH_2Cl_2 was stirred for 5 hr at room temperature. In the presence of an excess of triethylamine 17 was obtained in quantitative yield, and triethylamine N-oxide was isolated as the hydrochloride in 27% yield. As an N-oxide (53) was not obtained in the autoxidation of 43, the piperidino-nitrogen in 43 did not act as a reducing agent, but must have catalyzed the cleavage of O-O bond, though how is not clear. Also one mole of oxygen was absorbed in the oxidation of 49. However the hydroperoxide(54) was not reduced to the hydroxy derivative, but converted to the oxo derivative by an α-cleavage. Facile α-cleavage of secondary hydroperoxides is well known.



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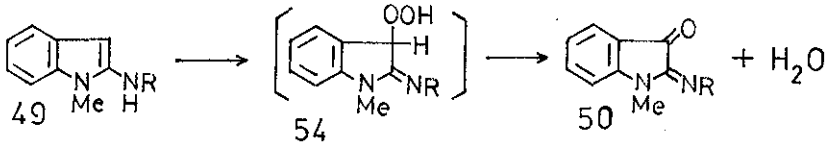
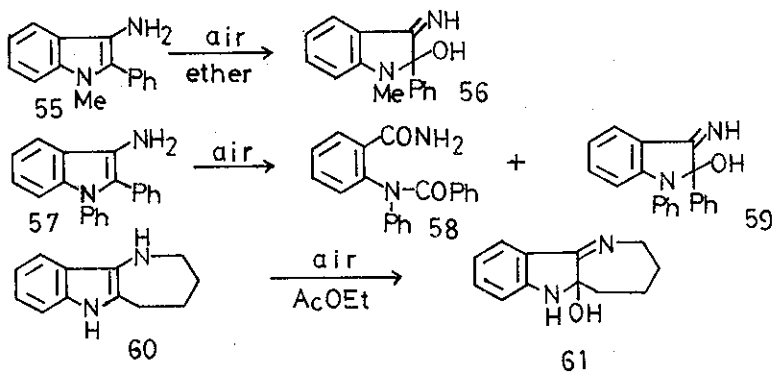
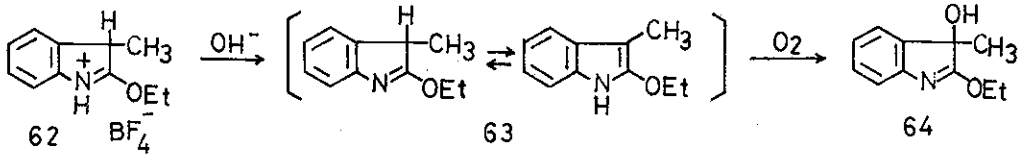


The 3-aminoindole derivatives(55, 57, and 60) were also reported to be oxidized by air to 2-hydroxy derivatives(56, 59, and 61) and ketoamide(58)[39,40].

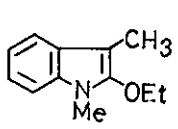


2. Autoxidation of 2-ethoxyindoles

2-Ethoxy-3-methylindolenine hydrogen tetrafluoroborate salt(62), prepared from 3-methyloxindole with Meerwein reagent, was also oxidized easily to the 3-hydroxyindolenine (64) quantitatively when treated with base[41]. Rate of oxygen uptake was similar to that



of the 2-amino derivative and one mole of oxygen was absorbed in 30 min.[38] The corresponding hydroperoxyindolenine(63) was not isolated in this case either, oxidation proceed as in the case of 43. As expected 2-ethoxy-1,3-dimethylindole(65) was stable to air. In contrast with the 2-aminoindole derivative(49), 2-ethoxyindole(66) was rather stable to air, but gradually oxidized to indirubin on long standing[42,43]. On the other hand, the 2-ethoxyindole(67) was reported to give hydroperoxyindolenine(68)[44].



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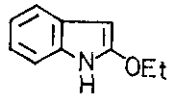

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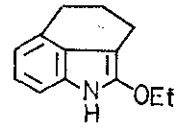

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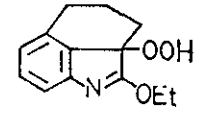
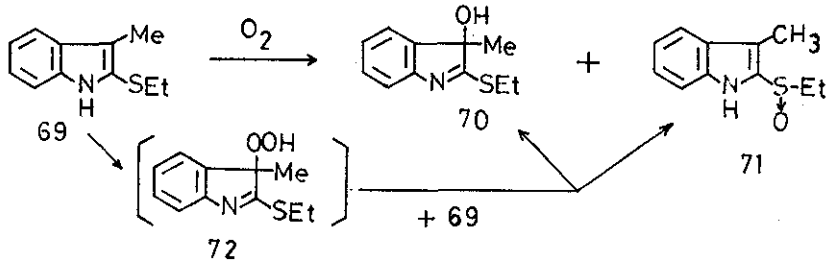


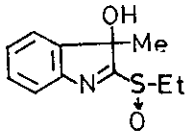
68

3. Autoxidation of 2-ethylthioindoles

Unlike 2-amino- and 2-ethoxyindole, 2-ethylthio-3-methylindole (69), prepared by ethylation of 3-methyl-2-indolinethione or reaction of skatole with ethanesulfenyl chloride, can be purified as itself. However, oxidation with O_2 did occur to give the 3-hydroxyindolenine(70) and sulfoxide(71) in equal amount when a hexane solution of 69 was stirred at room temperature[41].

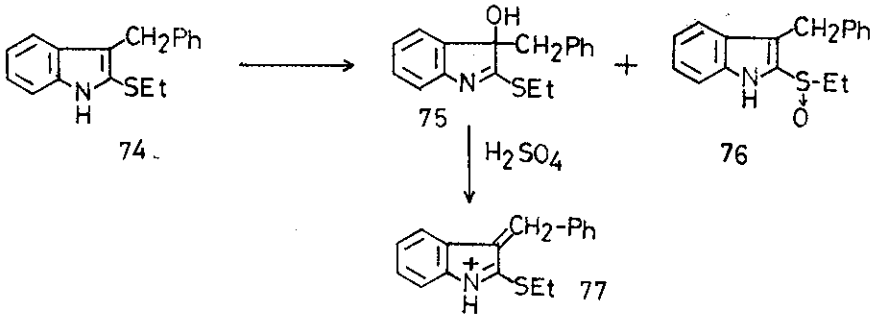


The oxidation did not proceed in ethanol or dichloroethane. Uptake of oxygen in cyclohexane was slower than that of the 2-amino- or 2-ethoxy derivatives, and stopped at slightly over a half mole after 6 hr[38]. Thus formation of 70 and 71 was understood by the reaction of the hydroperoxyindolenine(72) with unreacted indole(69). The hydroperoxide(72) might oxidize the thioether intramolecularly to form 73, but thioether of 69 was oxidized easier than that of 72 which is not simple thioether but a thioiminoether. Oxidation of 69 in cyclohexane in the presence of sodium ethoxide gave only the hydroxyindolenine, probably due to rapid reduction of 72 with base. On the other hand the sulfoxide(71) was the major product when the oxidation of 69 was carried out in the presence of 43, indicating hydroperoxyindolenine can oxidize the thioether of 69[38].

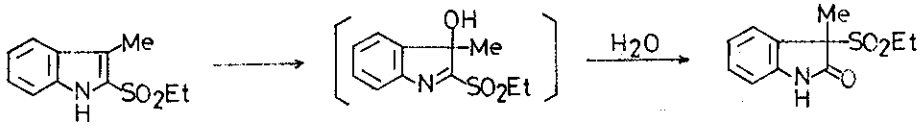


73

3-Benzyl-2-ethylthioindole(74) was similarly oxidized to the 3-hydroxyindolenine(75) and the sulfoxide(76) in chloroform solution[45]. The 3-hydroxyindolenine(75) was dehydrated to 3-benzylidene-2-ethylthioindolenine(77) on treatment with conc. sulfuric acid. This is the first example of oxidation of a 3-alkylindole to a 3-alkylideneindolenine[45].

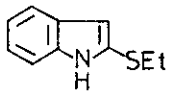


The indole ring in 69 thus oxidized easier than the thioether group with oxygen, but the thioether was preferentially oxidized with hydroperoxyindolenine. This was further confirmed by the oxidation of 69 with hydrogen peroxide in acetic acid which gave sulfoxide(69) and the proportion of sulfone obtained depends upon amount of hydrogen peroxide used and reaction temperature[46]. However, the indole ring of the sulfone(78) was oxidized with further mole of hydrogen peroxide to 80 via 79 accompanying rearrangement of the ethylsulfonyl group[46].



78 79 80

Unlike 2-aminoindole and 2-ethoxyindole, 2-ethylthioindole(81) was stable to air.

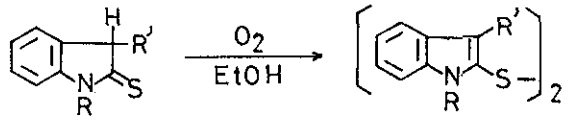


81

In summary the effect of a heteroatom substituent at the 2-position towards autoxidation decreases in the order N>O>S . The same effect was observed in the tautomerism between indole and indolenine, where the indolenine is prefered in 2-amino derivative and the indole form is prefered in 2-ethylthioindole[35].

4. Autoxidation of 2-indolinethiones

2-Indolinethione is tautomeric with 2-mercaptoindole. The former is predominant in most cases, but the presence of the thiol form has been observed in 3-aryl derivatives in solution[47]. Unlike the simple thiol, 2-mercaptotryptophan is reported to be easily oxidized by air to the corresponding disulfide in neutral condition[48]. We examined O_2-oxidation of various 2-indolinethiones(82) in ethanol without base.



82 83

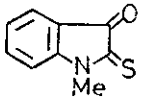
	a	b	c	d	e	f	g	h	i	j	k	l	m
R	H	H	H	H	Me	Me	Me	Me	H	Me	H	H	H
R'	Ph				Ph				H	H	Me		t-Bu

From the rate of O_2 uptake and the UV spectral change O_2-oxidation of 2-indolinethiones can be divided into four groups[47].

1) Rapid oxidation ; complete within 4-12 hr
   82b, 82d, 82h
2) Moderate oxidation ; complete within 24 hr
   82a, 82f, 82l, 82k
3) Slow oxidation ; complete within 48 hr
   82c, 82e, 82g
4) Resist to the oxidation ; practically no O_2 absorption within 24 hr
   82i, 82j, 82m

This order does not parallel the stability of the thiol form. The O_2^- oxidation of 82 did not proceed in dichloroethane, but was accelerated by the addition of NaOMe (4 mol equivalents), $FeCl_3$(0.1 mol equiv.), and $Cu(OAc)_2$(0.2 mol equiv.) in ethanol[49].

The oxidation of 1-methyl-2-indolinethione(82j) in ethanol under O_2 atmosphere for 2-weeks gave a small amount of 1-methyl-3-oxo-2-indolinethione(84) besides recovered 82j. The compound(84) corresponds to 50 obtained by the O_2^- oxidation of 2-aminoindole (49).

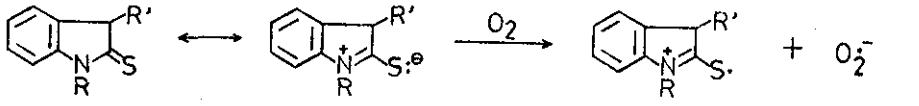


84

Uptake of oxygen during the oxidation of 2-indolinethiones ceased at a half mole of oxygen to one mole of 2-indolinethione, instead of a quarter mole, suggesing the following equation.

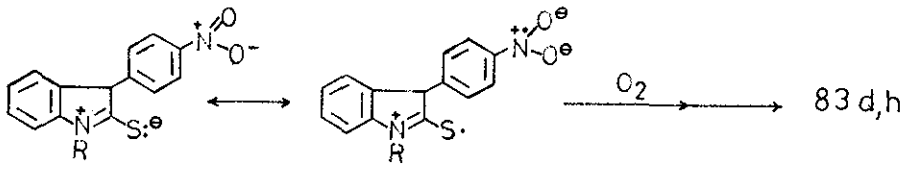
$$2\,RSH + O_2 \dashrightarrow R\text{-}S\text{-}S\text{-}R + H_2O_2$$

The detailed mechanism of the oxidation to the disulfide is not clear, but the following path may be considered.



82 85 86 83

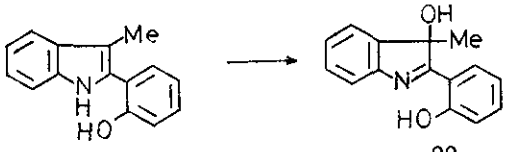
Acceleration by p-nitrophenyl group may be understood intramolecular electron-transfer in 85.



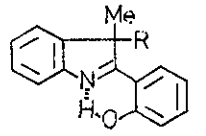
Acceleration of nitrobenzene derivatives in the O_2^- oxidation of carbanion is well known[50].

V Autoxidation of other Indole Derivatives

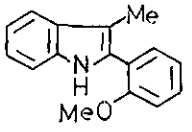
2-(2-Hydroxyphenyl)-3-methylindole(87) is oxidized with oxygen to hydroxyindolenine (88) upon boiling its solution in light petroleum exposed to the atmosphere. As the similar compounds such as 89, 90, and 91 did not oxidized under similar conditions, stabilization of 92(R=H, OOH, or OH) by the hydrogen bond shown may be responsible for the oxidation[51].



87 88



92



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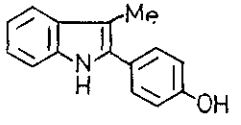

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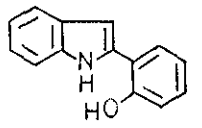
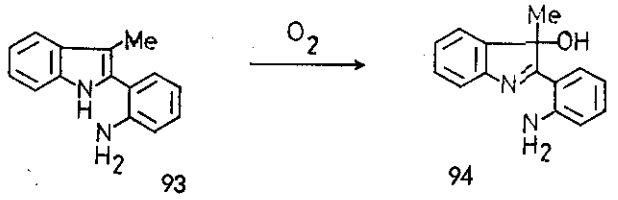


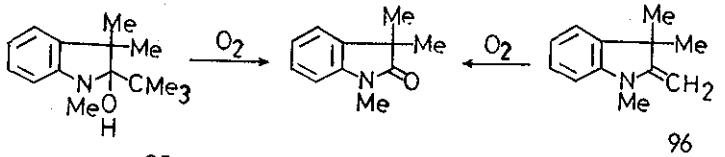
91

The aminoanalog(93) of 87 was also oxidized to the hydroxyindolenine in low yield on heating its solution in light petroleum for 9 weeks[52].



93 94

Since the parent compound, 3-methyl-2-phenylindole(16), is easily oxidized in non-polar solvents at room temperature upon exposure to the atmosphere, the inhibitory effects of hydroxy and amino groups on the benzene ring should be considered. The hydrogen bonding in 92 reduces the inhibitory effect. As O_2 oxidation at elevated temperature sometimes causes the reverse reaction, oxidation under milder conditions might give different results. The compounds(95 and 96) were reported to give the oxindole derivative(97) on exposure to air and sun light. In the former case C_2, C_3, and C_4-hydrocarbons and formaldehyde were detected in the reaction mixture[53].

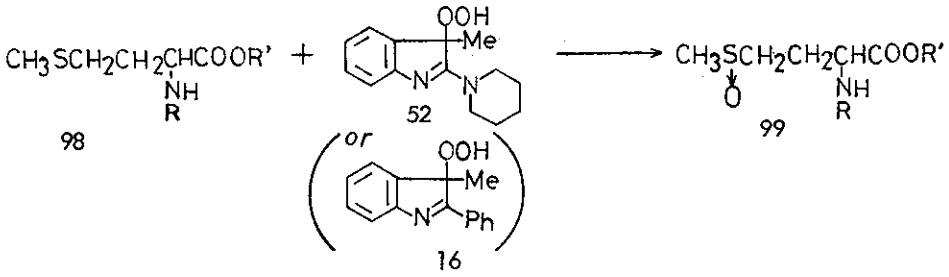


95 97 96

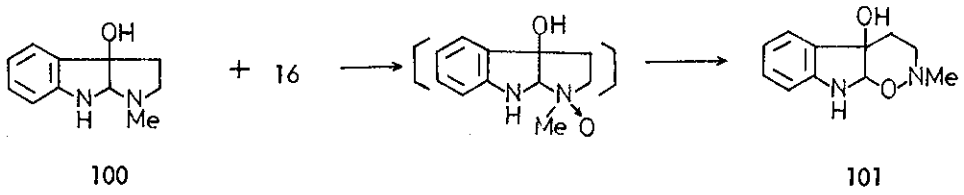
VI 3-Hydroperoxyindolenines as Oxidizing Agents

As described above, 3-hydroperoxyindolenine(52) oxidized isopropyl alcohol, triethylamine, and Hantsch ester, so hydroperoxyindolenines seem to be interesting mild oxidizing

agent. Examples of the oxidation are limitted at present, though oxidation with alkyl hydroperoxide is widely known[54]. Methionine derivatives(98) were oxidized to the sulfoxide(99) with 52 or 16 in methanol at room temperature[55]. Oxidation with 52 was carried out by the addition of NaOMe to a methanolic solution of 98 and 3-methyl-2-piperidinoindole(42) under O_2 atmosphere. Oxidation of benzoylmethionine methyl ester (98, R= PhCO ; R' = Me) with 16 gave the sulfoxide(99, mixture of diastereomers(ca 1:1)) in quantitative yield. With an excess of reagent the corresponding sulfone was scarcely observed.

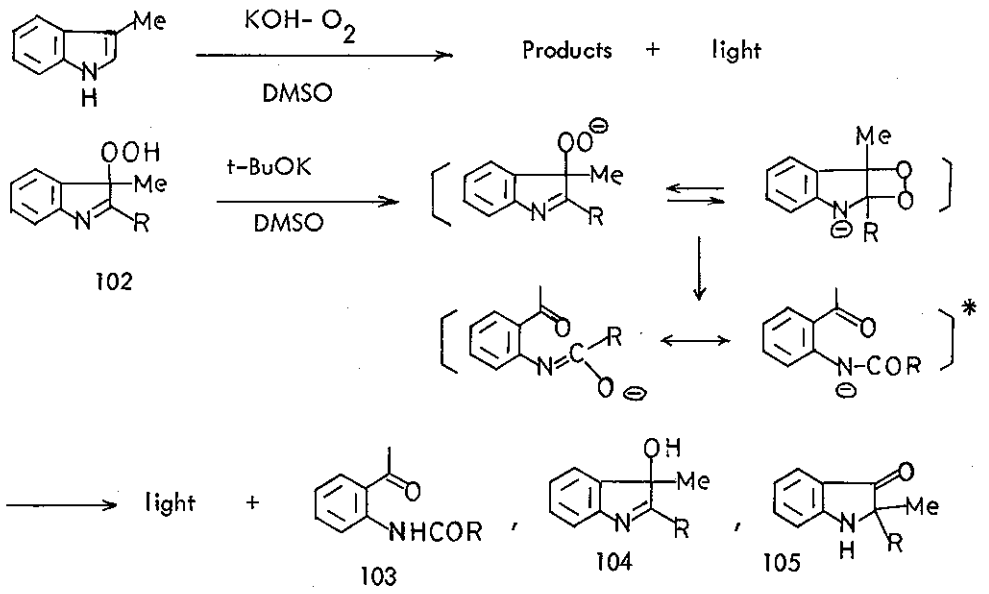


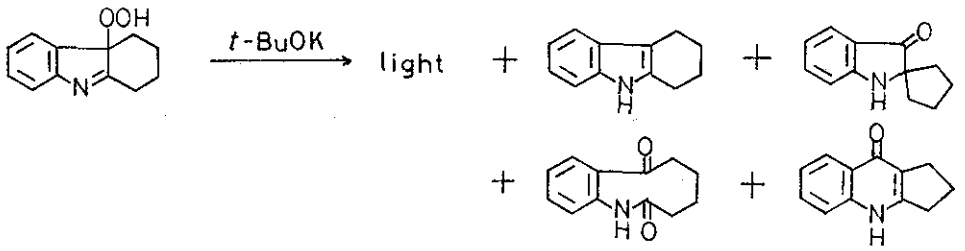
3a-Hydroxypyrroloindole(100) was smoothly oxidized with 16 in $CHCl_3$ to 1,2-oxazino-indole(101) via N-oxide[56].



VII Oxidation of Indoles with Oxygen in Basic Media

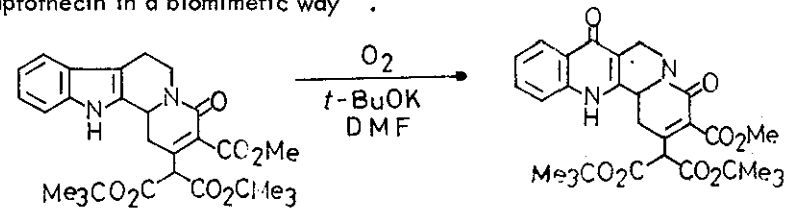
Oxidation of carbanions and sulfides($R-S^-$) with oxygen proceeds more rapidly than does that of the hydrocarbons and thiols themselves, and numerous data are available[57]. On the other hand, oxidation of indoles with oxygen in basic media was interesting in relation to chemiluminescence and bioluminescence. When a pellet of potassium hydroxide was added to a DMSO solution of skatole in the dark, blue chemiluminescence was observed[58]. Chemiluminescence of many indole derivatives has been reported[58,59,60,61]. Base catalyzed decomposition of the 3-hydroperoxyindolenine has been proved to be the origin of the chemiluminescence[59,60]. Furthermore, decomposition of the dioxetane intermediate derived from 3-hydroperoxyindolenine is proposed as a key step in the chemiluminescence[62]. The most strong chemiluminescent emitters in the indoles so far studied are 102, and products obtained are 103, 104, and 105[62]. In these studies the products after chemiluminescence were not investigated thoroughly except for a few examples, in which many compounds were obtained.

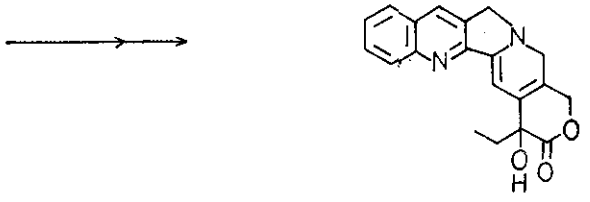




The research on the chemiluminescence of indole derivatives has declined since 1967, as the origin of bioluminescence in the crustacean Cypridina has been shown to be the imidazolopyrazine part of the Cypridina luciferin and not the indole ring. However, chemi- and bioluminescence are an active field in bioorganic chemistry[63]. During this research, indole derivatives which are rather stable towards O_2 in neutral media, such as 3-mono-alkylindoles, were found to be oxidized in basic conditions.

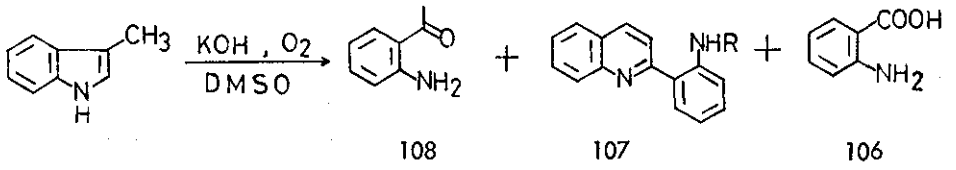
Winterfeldt ingeniously applied this oxidation in basic media to the total synthesis of camptothecin in a biomimetic way[64].



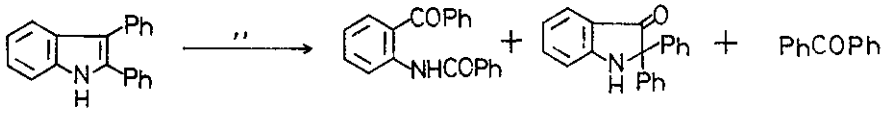


Camptothecin

Oxidation of skatole with DMSO-KOH-O_2(bubbling) at room temperature gave anthranilic acid(106) in 31% yield besides a small amount of the quinoline derivative(107) which was derived from the condensation of two moles of aminoketone(108). When a mixture of skatole-DMSO-KOH was stirred on exposure to atmosphere, oxidation ceased at the aminoketone(108) stage, and the quinoline derivative(107) was obtained as the major product instead of anthranilic acid[65].



108 107 106

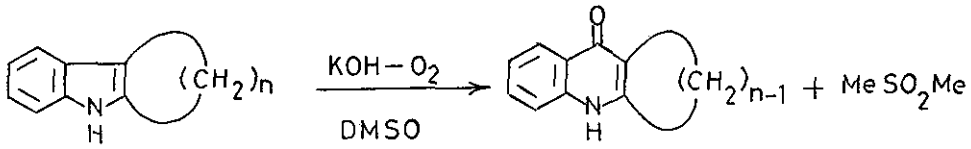


109 110

Oxidation of 2,3-diphenylindole with DMSO-KOH-O_2(bubbling) on the other hand, gave the ketoamide(109) in 68%, besides the indoxyl(110) in 14% and benzophenone in 4%. Oxidation of skatole was rapid and most of skatole disappeared within 20 hr, but 17% of 2,3-diphenylindole was recovered after 48 hr.

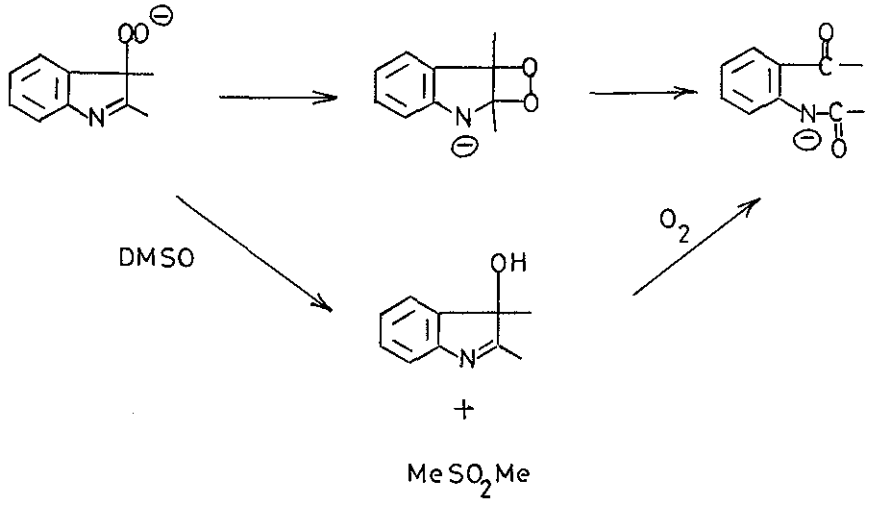
Oxidation of tetrahydrocarbazole(111, n=4) and cyclooctanoindole(111, n=6) under similar conditions gave 4-quinolone derivatives(112) in 41% and 47% respectively, indicating that the ring size effect was not observed in basic media. Another major product in these oxidations is dimethyl sulfone, which is not observed in the oxidation of 2,3-diphenylindole. Obviously the sulfone is derived from the oxidation of the solvent

with 3-hydroperoxyindolenine, but hydroxyindolenine or indoxyl were not obtained as major products. Therefore, oxidation of hydroxyindolenine derivative to 4-quinolone derivative(112) via the ketoamide may occur under the reaction conditions.

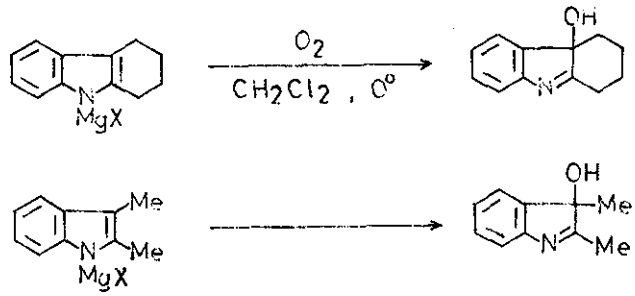


111 112 n = 4,6

These results showed that the reactivity of 3-hydroperoxyindolenine depends upon its structure. The cyclization of the hydroperoxy anion to form dioxetane might be rapid in 2,3-dipenylindole, but it might be slower than the reduction with DMSO in cycloalkanoindoles.



The Grignard reagents are known to give hydroperoxides or alcohols on treatment with oxygen. A few indole Grignard reagents are reported to give 3-hydroxyindolenines on treatment with oxygen[66]. Oxidation of Grignard reagents is believed to proceed in radical mechanism shown below.



$$RMgX + O_2 \longrightarrow R^{\cdot} + MgX^{+} + O_2^{-}$$

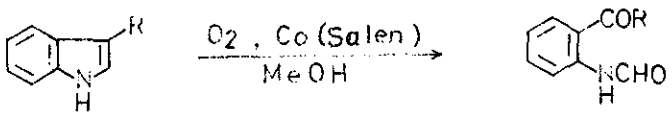
$$R\cdot + O_2 \longrightarrow ROO\cdot$$

$$ROO\cdot + RMgX \longrightarrow [ROOMg(R)X] \longrightarrow ROOMgX + R\cdot$$

$$ROOMgX + RMgX \longrightarrow 2\ R\text{-}O\text{-}MgX$$

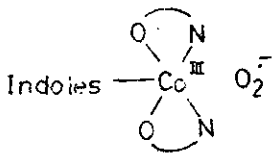
VIII Oxidation of Indoles with Oxygen catalyzed by Metal complexes

It is well known that autoxidation is catalyzed by metal ions such as Cu, Fe, or Co. However few examples are known in the indole derivatives. When oxygen was bubbled through a solution of 3-substituted indoles in methanol in the presence of bis(salicylidene) ethylenediaminatocobalt(II) (Co(salen)) at room temperature, ketoamides were obtained in good yields[68]. These indole derivative are rather stable to O_2 in neutral media without metal catalyst.



R = CH_3, CH_2CO_2Me, $CH_2CH_2CO_2Me$, CH_2CH_2NHAc, $CH_2CH(NHAc)CO_2Me$

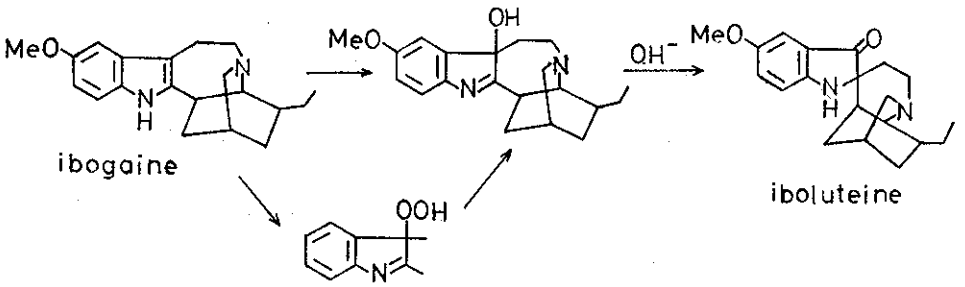
Although active species of oxygen in this oxidation is not thoroughly clarified, the following complex is proposed.



Similar oxygenation with porpyrin-Co complexes was also reported[69].

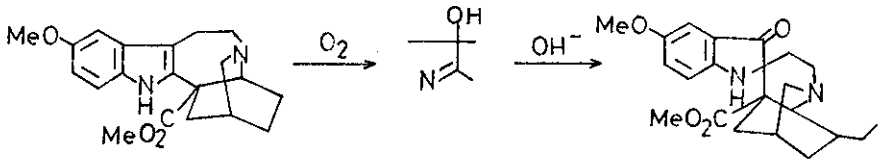
IX Examples of Autoxidation in Indole Alkaoids

Catalytic oxygenation of ibogaine gave the 3-hydroperoxyindolenine which was reduced catalytically to 3-hydroxyindolenine[70]. The same hydroxyindolenine was obtained when a benzene solution of ibogaine was aerated. The oxidation virtually did not proceed in ethanol. The hydroxyindolenine was converted to iboluteine on treatment with alkali[71].



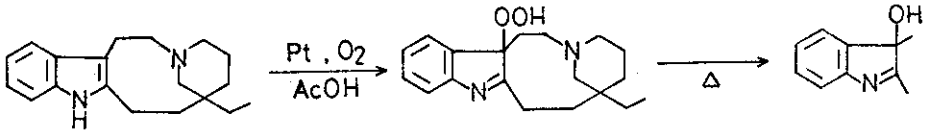
Ibogamine gave the similar results. Tabernanthine was oxidized to the hydroxyindolenine on catalytic oxygenation and reduction.

Voacangine was reported to give the hydroxyindolenine on exposure of its $CHCl_3$ solution to air[72]. However, a lactam was obtained by catalytic oxygenation of voacangine.



Reaction of the Grignard reagent derived from voacangine with O_2 also gave the hydroxyindolenine[66]. Voacangine and voacristine gave the corresponding 3-hydroxyindolenine on exposure of their benzene solution to O_2 and UV light[72].

Quebrachamine is reported to give 3-hydroperoxyindolenine on catalytic oxygenation in AcOH, but not in AcOEt, which is a popular solvent for these catalytic oxygenation[73].



Quebrachamine

X Conclusion

The most of the indoles having a hydrogen at the 1-position have been oxidized by triplet oxygen in neutral or basic media or in the presence of metal complex. Although a variety of oxidation products have been obtained depending upon the structures and reaction conditions, the first intermediate is assumed to be 3-hydroperoxyindolenines some of which are actually isolated as stable crystalline compounds. On the other hand, 1-substituted indoles are stable towards triplet oxygen in most cases.

Dye-sensitized oxygenation of indole derivatives which is effective to both 1-unsubstituted and 1-substituted indoles, has been extensively studied in recent years[74,75], but it beyonds the scope of this review.

REFERENCES

1 O.Baudisch and A.B.Hoschek, Ber., 49, 2579(1916).

2 B.Oddo, Gass.chim.ital., 46, 323(1916)(Chem.Abst.,11, 1143) ; ibid., 50, 268(1920) (Chem.Abst.,15, 2272).

3 C.Toffoli, Atti. X congr. intern. chim., 3, 369(1939)(Chem.Abst., 33, 9321) ; Rend ist sanita. publ., 2, 565(1939)(Chem.Abst., 34, 4733).

4 B.Witkop and J.B.Patrick, J.Am.Chem.Soc.,73, 713 (1951).

5 G.Plancher and U.Colacicchi, Atti.accad. Lincei, 20,1,453(1911)(C.A. 5, 3403)

6 I.Saito,M.Imuta, and T.Matsuura, Chem. Letters, 1972, 1173.

7 R.J.S.Beer,L.McGrath,A.Robertson, and A.B.Woodier, Nature, 164, 362(1949); R.J.S.Beer,L.McGrath, and A.Robertson, J.Chem.Soc., 1950, 2118, 3283; ibid., 1952, 4351.

8 B.Witkop, J.Am.Chem.Soc., 72, 1428(1950) ; B.Witkop and J.B.Patrick, ibid., 73, 2188, 2196(1951).

9 F.McCapra, Y.C.Chang, and A.Burford, J.C.S.Chem.Comm., 1976, 608.

10 R.J.S.Beer,T.Broadhurst, and A.Robertson, J.Chem.Soc., 1953, 2440.

11 C.S.Barnes,K.H.Pausacker,W.E.Badcock, J.Chem.Soc., 1951, 730.

12 R.J.S.Beer,T.Broadhurst, and A.Robertson, J.Chem.Soc., 1952, 4946.

13 B.Witkop,J.B.Patrick and M.Roenbium, J.Am.Chem.Soc., 73, 2641(1951).

14 T.Hino and M.Nakagawa, Unpublished results.

15 B.Witkop and J.B.Patrick, J.Am.Chem.Soc.,74, 3855(1952).

16 R.J.S.Beer,T.Donavanik, and A.Robertson, J.Chem.Soc., 1954, 4139.

17 E.Leete, J.Am.Chem.Soc.,83, 3645 (1961).

18 W.I.Taylor, Proc.Chem.Soc., 1962, 247.

19 F.Y-H.Chen and E.Leete, Tetrahedron Letters, 1963, 2013.

20 H.H.Wasserman and M.B.Floyd, ibid., 1963, 2009.

21 A.Z.Britten and G.F.Smith, J.Chem.Soc. Perkin I,1972, 418.

22 J.W.Kershaw and A.Taylor, J.Chem.Soc., 1964, 4320.

23 K.M.Biswas and A.H.Jackson, Tetrahedron, 24, 1145(1968).

24 S.Ghosal and S.K.Dutta, Ind.J.Chem., 7, 139(1969).

25 G.Berti, A.Da Settimo, G.Di Colo, and E.Nannipieri, J.Chem.Soc.(C), 1969,2703.

26 S.McLean, E.K.Strom-Gundersen,K.S.Dichmann, J.K.Fawcett, and S.C.Nyburg, Tetrahedron Letters, 1970, 2645.

27 V.Dave and E.W.Warnhoff, Chem.Comm., 1970, 919.

28 V.Dave and E.W.Warnhoff, Can.J.Chem.,49, 1911, 1921 (1971).

29 S.McLean and G.I.Dmitrienko, Can.J.Chem., 49, 3642(1971).

30 V.Dave and E.W.Warnhoff, Can.J.Chem., 54, 1015(1976).

31 H.I.Kesswani, Can.J.Chem., 48, 689 (1970).

32 T.Matsuura,'Sanso Sanka Hanno(Oxygenation Reactions)' Maruzen, Tokyo, 1977.

33 J.Kebrle and K.Hoffmann, Helv., 39, 116(1956).

34 T.Hino,M.Nakagawa,K.Ogawa,T.Wakatsuki,and S.Yamada, Tetrahedron, 23, 1441 (1967).

35 T.Hino, M.Nakagawa,T.Hashizume,N.Yamaji, and Y.Miwa, Tetrahedron Letters, 1970, 2205; T.Hino,M.Nakagawa,T.Hashizume,N.Yamaji,Y.Miwa,K.Tsuneoka,and S.Akaboshi, Tetrahedron, 27, 775(1971).

36 J.B.Hester, J.Org.Chem., 35, 875(1970).

37 Yu.N.Portnov,G.A.Golubena, and A.N.Kost, Khim.Geterotsikl.Soedin.,1972, 61(Chem.Abst., 77, 48377v); G.A.Golubena,Yu.N.Portnov, and A.N.Kost, ibid., 1973, 511(Chem.Abst., 79, 31782s) ; A.N.Kost, G.A.Golubena, and V.G.Zabrodynaya, ibid., 1975, 1632 (Chem.Abst., 84, 105529s).

38 M.Nakagawa, H.Yamaguchi, and T.Hino, Tetrahedron Letters, 1970, 4035.

39 C.W.Bird, J.Chem.Soc., 1965, 3490.

40 J.B.Hester, J.Org.Chem., 32, 3804(1967).

41 T.Hino,M.Nakagawa, and S.Akaboshi, Chem.Comm., 1967, 656 ; M.Nakagawa, and T.Hino, Tetrahedron, 26, 4491 (1970).

42 H.Pleninger and H.Bauer, Angew.Chem., 73, 433(1961) ; H.Plieninger,U.Lerch and D.Wild, Angew.Chem., 77, 505 (1965); H.Plieninger and D.Wild, Chem.Ber., 99, 3063 (1966).

43 J.Harley-Mason and T.J.Leeney, Proc.Chem.Soc., 1964, 368.

44 H.Plieninger, H.Bauer,W.Buhler, J.Kurze, and U.Lerch, Ann., 680, 69(1964).

45 T.Hino and M.Nakagawa, J.Am.Chem.Soc., 91, 4598 (1969).

46 T.Hino,H.Yamaguchi, and M.Nakagawa, Chem.Comm.,1972, 473 ; T.Hino, H. Yamaguchi,M.Endo, and M.Nakagawa, J.C.S.Perkin I, 1976, 745.

47 T.Hino,T.Suzuki, and M.Nakagawa, Chem.Pharm.Bull., 22, 1053(1974).

48 T.Wieland,O.Weiberger, and W.Dilger, Ann., 592, 69 (1955).

49 T.Hino,T.Suzuki, and M.Nakagawa, Unpublished observations.

50 G.A.Russel and G.Kaupp, J.Am.Chem.Soc., 91, 3851 (1969).

51 B.Robinson and M.Zubair, J.Chem.Soc.(C), 1971, 976.

52 B.Robinson and M.Zubair, Tetrahedron, 29, 1429 (1973).

53 B.Robinson, Chem. & Ind., 1962, 1291 ; J.Chem.Soc., 1963, 586.

54 D.Swern (editor), Organic Peroxides, Vol 2, Wiley-Interscience, New York, 1971.

55 M.Nakagawa,T.Suzuki,T.Kawashima, and T.Hino, Chem.Pharm.Bull., 20,2413(1972).

56 M.Nakagawa,K. Yoshikawa, and T.Hino, J.Am.Chem.Soc., 97, 6496(1975).

57 G.Sosnovsky and E.H.Zare, 'Base-catalyzed Autoxidation' in D.Swern(ed), Organic Peroxides, Vol 1, Wiley-Interscience, New York, 1970; J.A.Howard, 'Homogenous Liquid-phase Autoxidation' in J.K.Kochi (ed), Free Radicals, Vol II, John Wiley, New York, 1973; J.O.Howthorne,K.A.Schowalter,A.W.Simon,M.H.Wilt, and M.S. Morgan, Oxidation of Organic Compounds, I (Advances in Chemistry No 75), 203(1968); G.A.Russel,A.G.Bemis, E.J.Geels,E.G.Janzen,and A.J.Moye, Oxidation of Organic Compounds, I, 174 (1968).

58 G.E.Philbrook,J.B.Ayers,F.J.Garst and J.R.Totter, Photochem. Photobiol., 4, 869(1965).

59 M.F.McCapra,D.G.Richardson, and Y.C.Chang, Photochem. Photobiol., 4, 1111 (1965).

60 A.W.Berger,J.N.Driscoll and J.A.Pirog, Photochem. Photobiol., 4, 1123(1965).

61 N.Sugiyama,M.Akutagawa,T.Gosha,Y.Saiga, and H.Yamamoto, Bull.Chem.Soc. Japan, 40, 347 (1967).

62 F.McCapra and Y.C.Young, Chem.Comm., 1966, 522.

63 See Y.Omote, J.Synth.Org.Chem.Japan, 26, 464(1968) ; T.Goto and Y.Kishi, Angew.Chem.Intern.Ed. 7, 407(1968) ; F.McCapra, Accounts Chem.Res., 9, 201(1976).

64 E.Winterfeldt, Ann., 745, 23(1971);E.Winterfeldt and H.Radunz, JCS Chem.Comm., 1971, 374; J.Warneke and E.Winterfeldt, Chem.Ber., 105,2120 (1972); E.Winterfeldt,

T.Korth,D.Pike, and M.Boch, Angew.Chem. Intern.Ed., 11, 289(1972), Chem.Ber., 105, 2126 (1972).

65 T.Hino,M.Hirose,Y.Kuroki, and M.Nakagawa, Unpublished observations. cf Abstracts of Annual Meeting of Pharmaceutical Society of Japan, 1976.

66 G.B.Guise,E.Ritchie, and W.C.Taylor, Aust.J.Chem., 18, 1278(1965).

67 G.A.Russel, J.Am.Chem.Soc., 76, 1595(1954).

68 A.Nishinaga, Chem.Letters, 1975, 273.

69 M.N.Dufour-Ricroch and A.Gaudenmer, Tetrahedron Letters, 1976, 4079.

70 M.Goutarel,M.M.Janot,F.Mathys, and V.Prelog, Helv., 39, 742 (1956).

71 M.F.Bartlett,D.F.Dickel, and WI.Taylor, J.Am.Chem.Soc.,80, 126 (1958).

72 D.N.Thomas and K.Biemann, Tetrahedron, 24, 4223(1968); cf. B.Hwang,J.A. Weisbach,B.Douglas, and R.Raffauf, J.Org.Chem., 34, 412(1969).

73 S.Markey,K.Biemann, and B.Witkop, Tetrahedron Letters, 1967, 157; cf. B.Witkop, J.Am.Chem.Soc., 79, 3193(1957).

74 T.Matsuura and I.Saito, Photochemistry of Heterocyclic Compounds (edited by O.Buchardt), pp 456, Wiley, 1976.

75 M.Nakagawa and T.Hino, J.Synth.Org.Chem.Japan, 35, 42(1977).

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