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AUTOXIDATION OF INDOLES HAVING A HETERO-ATOM AT 2-POSITION.

DECOMPOSITION OF THE INTERMEDIATE 3-HYDROPEROXIDE.

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Autoxidation of 3-alkylindoles 1(a,b,c) having a hetero-atom at 2-position was previously described[1]. Direct hydroxylation at 3-position of 1a and 1b by molecular oxygen took place spontaneously to give 2a and 2b, respectively, whereas 1c produced the sulfoxide 3 besides 2c in 1:1 ratio in quantitative yield. On the other hand, N-methylated compounds 4(a,b) were quite stable toward air oxidation. Therefore, we proposed a free radical oxidation sequence in which a hydroperoxide or a peroxy radical is involved[2].

We have now obtained further evidence to support the mechanism in which the hydroperoxide is the precursor to the 3-hydroxylated product as outlined in the chart. The general feature of the autoxidation products of 2,3-dialkyl or arylindoles[3] has been known to be a 3-hydroperoxide or its rearranged products and 3-hydroxylated compound has not been obtained. It was interested in the mechanism of autoxidation of 2-aminoindoles. We have measured the O_2 consumption in various conditions in order to obtain information about the possible sequence of 2 from 1. The reaction of 1 with oxygen may be considered to require 0.5 mole of O_2 to form 2. However, the rapid reaction of the free bases 1(a,b) with O_2, which generated in situ upon basification of the corresponding salts with 2 moles of NaOMe in EtOH, took place and 1 mole of O_2 was absorbed, unexpectedly. Similar results were obtained by the in situ basification with 4 moles of NaOMe. The same stoichiometry was also obtained when the corresponding salts were freed with excess of Et_3N in $ClCH_2CH_2Cl$ or with 10% NaOH in EtOH. A quantitative yield of 2(a,b) was obtained in all experiments after 1 mole O_2absorption had ceased. These observations exclude the formation of the RO•radical 8 via ROOR or ROOOOR[4] since this path way should requires 0.5 mole of O_2. The stoichiometry of the oxidation appears to require the formation of the hydroperoxide as intermediate, which then convert to the alcohol 2 without the evolution of oxygen. Although the intermediate 7 has not been isolated, decomposition of 7 to the alcohol 2 will result in liberation of oxidizing species [OH]. In order to trap this oxidizing species, the reaction of 1a with O_2 was carried out in i-PrOH instead of EtOH and acetone was isolated as 2,4-dinitrophenylhydrazone in 9% yield. Better result was obtained when HBr salt of 1a was liberated by addition of NaOMe in the presence of Hantzsch ester 9. A 94 % yield of 10 was isolated after 1 mole O_2-uptake. Blank experiments demonstrated that the treatment of Hantzsch ester in the reaction condition without 1a did not yield significant amount of 10 and 9 was recovered quantitatively.*

Secondly the effect of hetero-atoms at 2-position upon the stability of the intermediate hydroperoxide was demonstrated by the action of Et_3N upon 3-hydroperoxy-3-methyl-2-phenylindolenine 11[5], which is a stable crystalline compound and recovered mostly unchanged after 3 days stirring in CH_2Cl_2. However, addition of Et_3N into the CH_2Cl_2 solution of 11 resulted in formation of 12 in 70% yield within 4 to 5 hrs. This offers a support that the catalytic effect of 2-heteroatoms such as N and O may be attributed to their ability to induce intramolecular homolytic fission of a hydroperoxide to produce the corresponding alcohol. In the course of oxidation of 1c, 7c would be able to oxidize the thioether moiety of 1c to produce the sulfoxide 3. Consequently the O_2-uptake must approach to 0.5 mole. The absorption of O_2 proceeded in cyclohexane to give 2c and 3 in 1:1 ratio in quantitative

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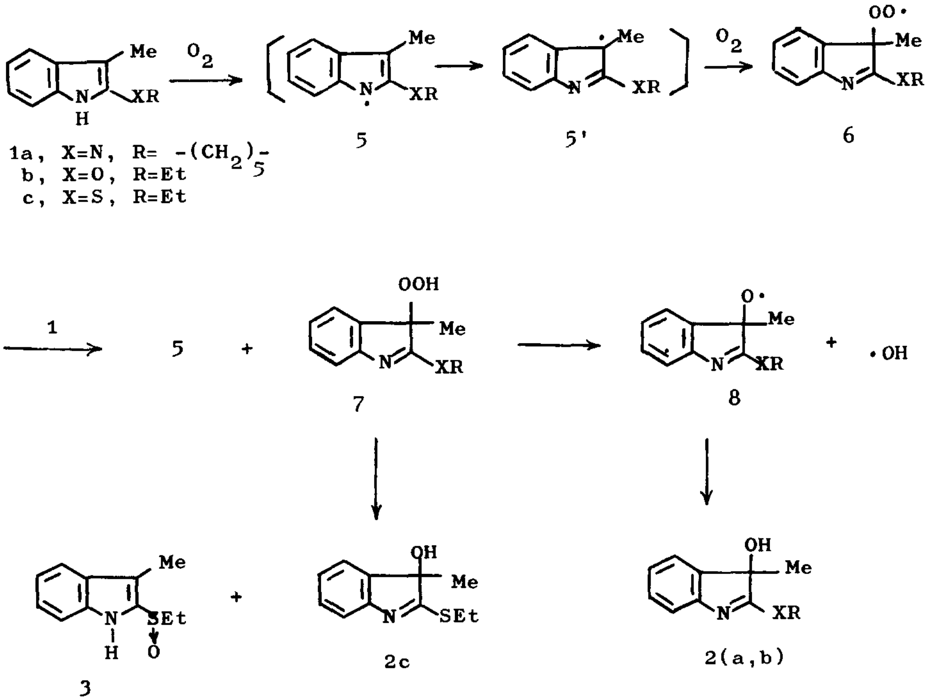
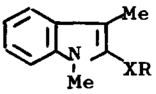
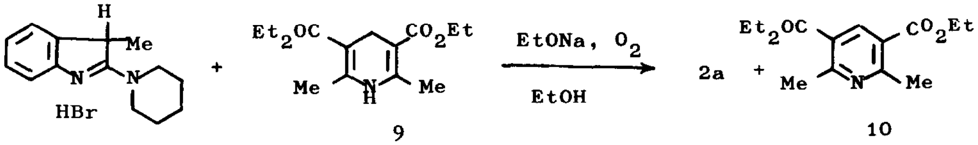
* It is interesting to note that 2-aminoindoles is capable of catalyzing the autoxidation of Hantzsch ester, which has been considered as one of the model compounds of NADH.


Me
O_2
XR
N
H
1a, X=N, R= $-(CH_2)_5-$
b, X=O, R=Et
c, X=S, R=Et
5
5'
O_2
OO•
6
1
5
+
OOH
7
O•
8
+
•OH
SEt
O
3
+
OH
2c
2(a,b)



4


H
Me
N
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Et_2OC
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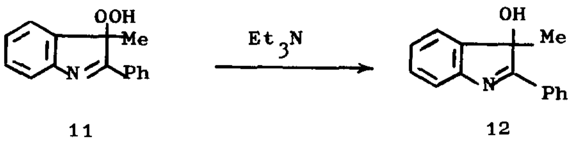
N
H
9
EtONa, O_2
EtOH
2a
+
10


OOH
Me
Ph
11
Et_3N
OH
12

yield. In most experiments the volume absorbed was 0.69± 0.2 mole/mole 1c. In order to obtain further evidence, the cross oxidation between 7a and 1c was carried out in EtOH, in which solvent 1c alone do not autoxidize. The product obtained was not only the expected sulfoxide 3 but always accompanied by 2c: presumably a free radical reaction induced by addition of 7a competed. However, in contrast to the case of the autoxidation of 1c in cyclohexane, the yield of 3 is predominating over that of 2c, indicating some part of 3 obtained are formed by the reaction of 1c with 7a. Furtheremore, the oxidation of 1c in cyclohexane in presence of a small amounts of a base such as KOH and NaOMe gave 2c as a sole product and 3 was not obtained, suggesting that 7c has been decomposed by the base to 2c before it oxidize 1c to give 3. The formation of 2c and 3 in a 1:1 ratio appears to be a characteristic feature of autoxidation of 2-ethylthio-3-alkylindoles in comparison with the oxidation with H_2O_2[6].

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