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RING CLEAVAGE AND RING EXPANSION OF INDOLES BY SUPEROXIDE ION

É.Balogh-Hergovich and G.Speier

Research Group for Petrochemistry of the Hungarian Academy of Sciences and
Department of Organic Chemistry, Veszprém University of Chemical Engineering
8201 Veszprém, Hungary

Summary: The reaction of indoles (**1**) with superoxide ion resulted in ring cleavage to give *o*-formyl and *o*-acylaminoketones (**6**) or N-acylanthranilic acid (**8**) and ring expansion yielding 2-quinolones (**7**). All reactions are chemiluminescent except that of 2-methylindole (**1h**), which gave a coupled product (**9**).

There is now considerable interest in the role of superoxide ion in chemical and biochemical oxidation reactions[1]. The enzyme tryptophan-2,3-dioxygenase is believed to require O_2^- as a substrate[2]. Since superoxide ion can be easily generated in aprotic solvents under phase transfer conditions using either crown ethers or quaternary ammonium salts[3] we decided to investigate its reactions with a number of indoles.

In less polar solvents, such as benzene, no reaction occured, in agreement with the work of Yoshida et al.[4] In tetrahydrofuran, however, indoles did react with O_2^- using 18-crown-6 or triethyl(benzyl)ammonium chloride in an argon atmosphere under the reaction conditions listed in the Table. The reaction mixture so obtained, was then poured into water (20-40 ml), acidified slightly with diluted hydrochloric acid and extracted with ether. After evaporation of the solvent the oily residues were solidified by treatment with hexane and recrystallized from methanol to give the compounds in the Table in moderate to good yields.

Depending on the substituents of the indoles three types of products have been isolated. When R^2=H or Ph *o*-formyl or *o*-acylaminoketones (**6**) were formed, where R^2=Me 2-quinolones (**7**) were found. In some cases N-acetylanthranilic acid (**8c**) was formed. All reactions were found to be chemiluminescent where ring splitting occured for which the singlet triplet transition of (**6**) is presumably responsible.[5] Chemiluminescence did not occur with 2-methylindole (**1h**), instead it was coupled to 2-methyl-2-(2-methyl-3-indolyl)indoxyl (**9**).

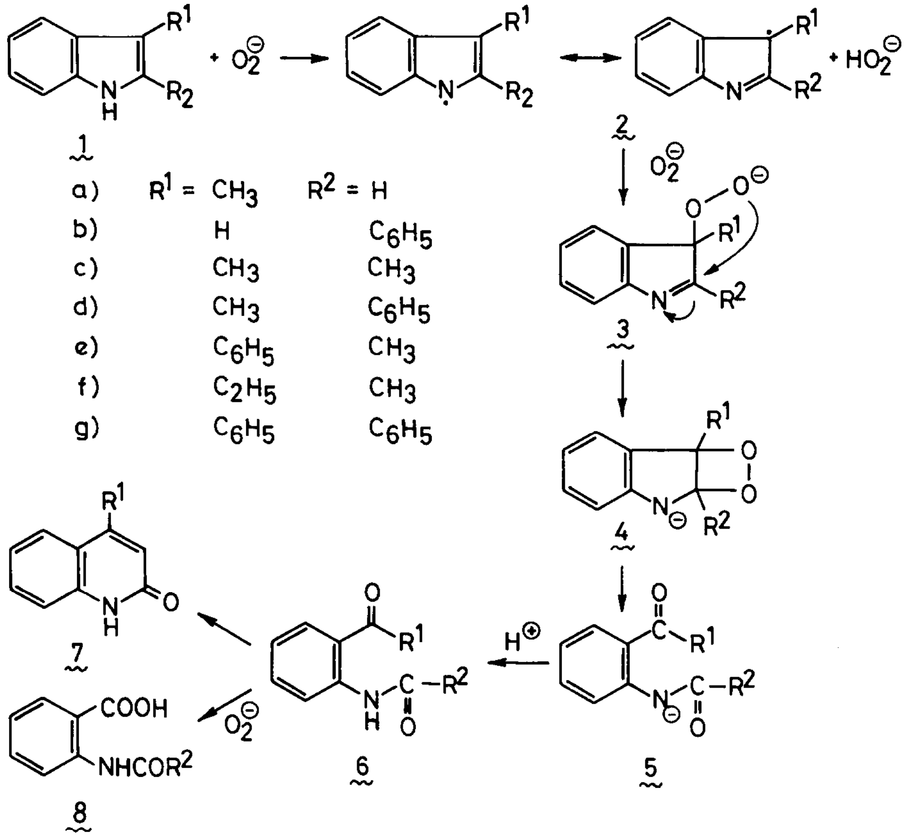
Table The Reaction of Indoles with Superoxide Ion

Indole (mmol)	THF (ml)	Temp. (°C)	Reaction time,(h)	KO_2 (mmol)	18-crown-6 (mmol)	TEBA[a] (mmol)	Products[b] (yield %)
1a (5)	20	25	10	10	1	-	-
1a (2.5)	20	25	60	10	2.5	-	6a (~10)
1a (5)	40	25	60	20	-	0.2	6a (~10)
1b (2.5)	20	25	15	10	2.5	-	6b (in traces)
1b (5)	40	25	24	20	-	0.1	6b (48)
1b (5)	50	50	20	20	-	0.1	6b (42), 8b (in traces)
1c 2.5	20	25	24	5	0.5	-	7c (18)
1c (2.5)	20	25	15	10	2.5	-	8c (12)
1c (5)	20	25	24	10	-	0.1	7c (46)
1d (2.5)	20	25	15	10	2.5	-	6d (72)
1d (2.5)	20	25	10	10	-	0.1	6d (34)
1e (2.5)	20	25	15	10	2.5	-	7e (96), 6e (in traces)
1e (5)	40	25	24	20	-	0.2	7e (69)
1f (5)	40	25	24	20	5	-	8f (42)
1f (5)	20	25	40	10	-	0.1	7f (2-3)
1g (2.5)	20	25	20	10	2.5	-	6g (28)
1g (2.5)	20	25	24	10	-	0.1	6g (21)
1h (5)	20	25	10	10	1	-	9 (52)
1h (10)	40	25	20	20	-	0.2	9 (19)

[a] Triethyl(benzyl)ammonium chloride; [b] isolated yields; the compounds were characterized by m.p., IR, ^{1}H-NMR and microanalytical data

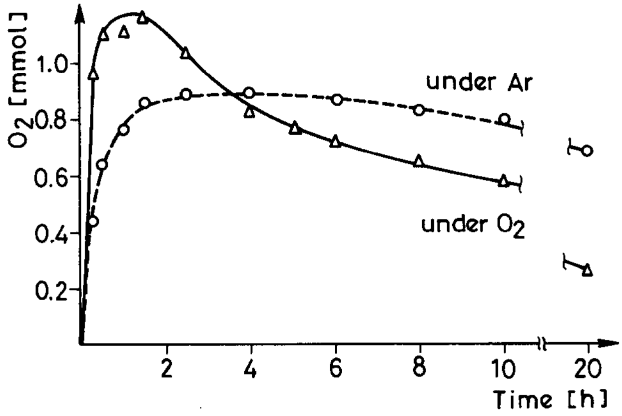
The products formed can be rationalized by the mechanism shown in the Scheme. Superoxide ion generates by hydrogen abstraction indolyl radicals (2) which react further with O_2^- to give the indoxyl hydroperoxides (3). This follows an intramolecular nucleophilic addition to the dioxetanes (4), which break down *via* (5) to the *o*-formyl or *o*-acylaminoketones (6). In some cases (1c, 1f) the *o*-acylaminoketones are further oxidized by O_2^- to N-acetylanthranilic acid (8c) and in others (1c, 1e, 1f) with R^2=Me 2-quinolones (7) are formed through intramolecular condensation.

Scheme



When the indoles were mixed with KO$_2$, in a reaction vessel connected to a gas buret, dioxygen was evolved and later partially consumed by the deprotonated indole. Fig.1 shows that in the case of 2-methyl-3-phenylindole (2.5 mmol) in a dioxygen atmosphere more dioxygen (0.9 mmol) was consumed than under argon (0.2 mmol). From these experiments it seems that a smaller part of the indoles was autoxidized to (6) and/or (7) according to the well established and accepted mechanism, which is a minor competitive pathway to that outlined in the Scheme.

Figure 1. The Evolution and Consumption of O_2 in the Reaction of 2-Methyl-3-phenylindole with O_2^- [a]



[a] 2-Methyl-3-phenylindole (2.5 mmol); KO_2 (10 mmol); 18-crown-6 (1 mmol); THF (20 ml); yield of 4-phenylquinolone-2 96%; remaining KO_2 under Ar 4.3 mmol and under O_2 6.0 mmol (measured by hydrolysis with H_2O)

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