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PHOTOSENSITIZED OXYGENATION OF INDOLE DERIVATIVES

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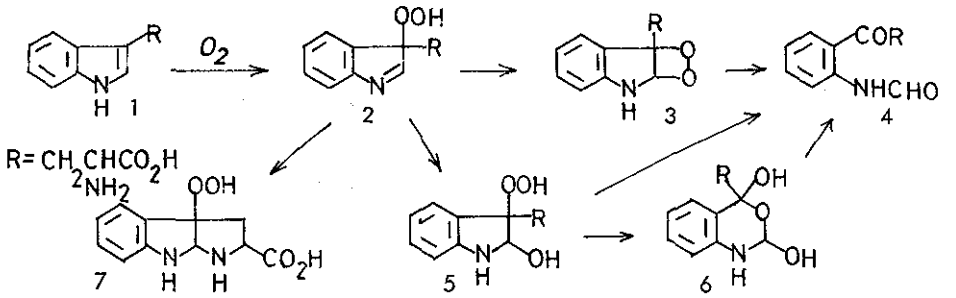
Since the early 1950s, when the first reports on methylene blue sensitized photooxygenation of tryptophan appeared[1], this field of study has been developed as a tool for the elucidation of the active site in enzymes, and as a model reaction for the dioxygenase catalyzed reaction of tryptophan to formylkynurenine[2,3]. There is, however, considerable variation in the earlier results and the structural assignments of the photoproducts rest mainly on UV spectrum, paper chromatography, and / or electrophoresis. Moreover, dye-sensitized oxygenation of tryptophan derivatives in an organic solvent has not been investigated. Prior to our preliminary publication of this work, the only detailed study of the photosensitized oxygenation of tryptophan in non-aqueous solvent had been that of Scoffone and coworkers[4], who showed that proflavine-sensitized photooxygenation of tryptophan derivatives in an acidic solvent results in high yields of the corresponding kynurenine derivatives.

(1) L. Weil, W.G. Gorden and A.R. Buchert, Arch.Biochem.Biophys., 33, 90 (1951).
(2) A. Fontana and C. Toniolo, "Progress in the Chemistry of Organic Natural Products" Vol 33, W. Herz, H. Grisebach, and G.W.Kirby Ed., Spring-Verlag, New York, N.Y., 1976, p 309 and references cited therein.
(3) M. Nakagawa and T. Hino, J.Syn.Org.Chem., 35, 42 (1977) and references cited therein.
(4) C.A. Benassi, E. Scoffone, G. Galiazzo, and G. Iori, Photochem.Photobiol., 6, 857 (1967).

In these investigations, very little attention has been given for the reaction mechanism and the reaction was presumed to proceed via the dioxetane intermediate 3 derived from the *hydroperoxyindolenine* 2, by *analogy* with the autoxidation of 2,3-disubstituted indoles[2,3]. However, there appears to be no unambiguous evidence for the intermediacy of 2 and 3. More recently Hamilton[5] proposed a new pathway involving addition of water to 2 followed by Baeyer-Villiger type rearrangement for the enzyme catalyzed oxidation of tryptophan to formylkynurenine in place of the well accepted dioxetane pathway[6,7].

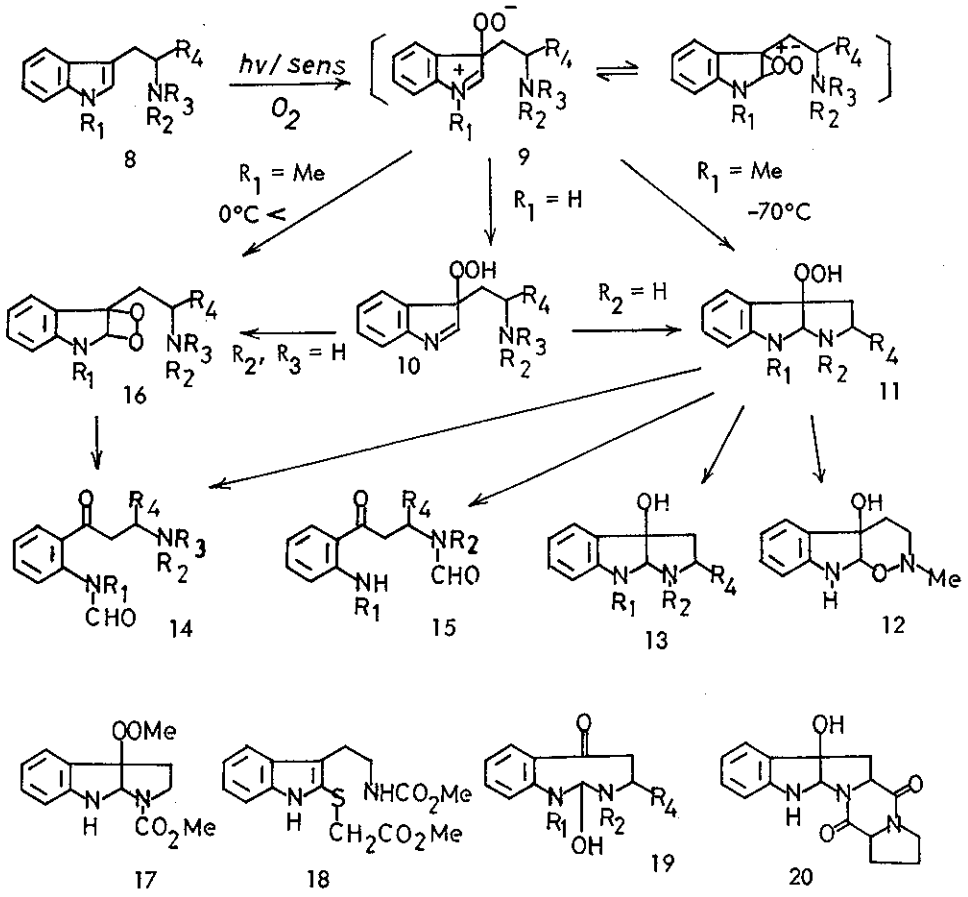


Considering the reactivity of the indolenine 2, there may be another reaction path in which the ethylamino side chain participates, leading to the formation of 3a-hydroperoxypyrroloindole 7. The isolation of 7 would provide not only an evidence for the intermediacy of 2 in dye-sensitized oxidation of 1 but also a suggestion of the biosynthesis of 3a-hydroxypyrroloindole ring system found in sporidesmins, brevianamide E, and hunteracine chloride. In this paper we present our results on the isolation, the nature, and the reactivity of the initially formed hydroperoxide intermediates in dye-sensitized oxygenation of the tryptopans and tryptamines.

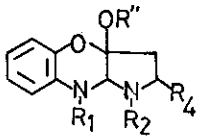
(5) G.A. Hamilton, Advan.Enzymol., 32, 55 (1969).
(6) A.Ek.H. Kissman, J.B. Patrick, and B. Witkop, Experientia, 8, 36 (1952).
(7) R.J. Sundberg, "Chemistry of Indoles", Academic Press, New York, 1970 p 282.

Rose bengal sensitized photooxygenation of N^b-methyltryptamine 1a in benzene-MeOH at room temperature gave the unexpected compound 12 as the major product together with 13, whereas in MeOH at 0°C followed by rapid work-up, gave 3a-hydroperoxypyrroloindole 11a which was converted to 12 on standing in organic solvents[8,9]. The formylkynurenine type compound 14 which has been widely known as the normal product of photooxygenation of tryptophan and indoles[3], however, was not isolated from 1a. On the other hand, photooxygenation of N^b-acyltryptamines and -tryptophans was found to give the hydroperoxides 11(b-e)[10]. Methylation of 11b with CH_2N_2 gave 17, mp 91-91.5°[11]. When treated with silica gel in CH_2Cl_2, 11(b-e) rearranged to formylkynurenine type 14(b-e) and N^b-formylkynurenine type 15(b-e) compounds, accompanied with 13(b-e). The transformation of 11b to 13b, 14b, and 15b was catalyzed by heat, light, and metal ions (Fe^{++}, Fe^{+++}), whereas the reaction of 11b with Ac_2O-pyridine gave only 15b and its acetylated derivative[12]. The mechanistic aspects of these transformations are intriguing, although not yet clearly defined. An intramolecular process of 11 leading to a common intermediate 19 could conceivably occur from which 14 and 15 could be formed. An alternate explanation for the rearrangement of 11 to 14 via crucial cyclization of 10 formed by the reversed ring opening of 11 to 16 could not be excluded. When 13a and methyl thioglycolate in CH_2Cl_2 was stirred for 24 hr in the presence of SiO_2 at room temperature, 18 has, in fact, been isolated in 15% yield[11].

(8) M. Nakagawa, T. Kaneko, K. Yoshikawa, and T. Hino, J.Am.Chem.Soc., 96, 624 (1974).
(9) M. Nakagawa, K. Yoshikawa, and T. Hino, J.Am.Chem.Soc., 97, 6496 (1975).
(10) M. Nakagawa, H. Okajima, and T. Hino, J.Am.Chem.Soc., 98, 635 (1976).
(11) M. Nakagawa, H. Watanabe, and T. Hino, Unpublished observations.
(12) I. Saito, T. Matsuura, M. Nakagawa, and T. Hino, AccountsChem.Res., in press.



a, $R_1 = R_2 = R_4 = H$, $R_3 = Me$
b, $R_1 = R_2 = R_4 = H$, $R_3 = CO_2Me$
c, $R_1 = R_2 = R_4 = H$, $R_3 = Ac$
d, $R_1 = R_2 = H$, $R_3 = R_4 = CO_2Me$
e, $R_1 = R_2 = H$, $R_3 = R_4 = Ac$
f, $R_1 = R_2 = R_3 = H$, $R_4 = CO_2H$
g, $R_1 = Me$, $R_2 = R_4 = H$, $R_3 = CO_2Me$ h, $R_1 = R_4 = H$, $R_2 = Me$, $R_3 = CO_2Me$



In addition, the oxygenation of 8b in both MeOH and MeOH-H_2O followed by Me_2S reduction gave the similar results (13b, major and 14b, minor), eliminating the possibility for formation of 14 via 5 type intermediate. Photosensitized oxygenation of tryptophan itself in an aqueous solution followed by Me_2S reduction provided the two isomers of 13f. Similar reaction of cyclo-L-tryptophyl-L-proline also gave the two isomers of 20.

Photooxygenation of 8h at 0°C, however, proceeded exclusively to give 14h, showing that the direct formation of 14 occurs in the absence of the ethylamino side chain participation probably via 16. On the other hand, when the similar oxygenation of 8g was carried out at -70°C followed by treatment with Me_2S, 13g was obtained as a sole product whereas at 0°C 14g was obtained as the major product along with 13g and 11g[13]. However, neither 14g nor 15g was formed from 11g.

All the hydroperoxides 11 isolated undergo acid-catalyzed rearrangement to 1,4-benzoxazine derivatives 21[10].

Conclusions

From the foregoing results, it becomes apparent that photooxygenation of tryptamine and tryptophan related compounds gives the 3-hydroperoxyindolenines 10 as the primary intermediates, which then cyclize to the corresponding tricyclic hydroperoxides 11 by the side chain participation besides competing cyclization to dioxetanes 16. One of the most important reactions of 11 is their facile transformation into the 14 and 15, providing a new pathway for tryptophan oxidation to kynurenine other than the widely accepted dioxetane pathway. This work provides considerable implication on understanding of the nature and mechanism of enzyme catalyzed oxidation of tryptophan to kynurenine.

(13) M. Nakagawa, H. Okajima, and T. Hino, J.Am.Chem.Soc., 99, in press.