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DYE-SENSITIZED PHOTOOXIDATION OF 1-METHYLINDOLYL-3-ACETIC ACID

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Abstract: The structure of the products constituting the complex mixture afforded by the entitled reaction is similar to that proceeding from the N-unmethylated acid and supports the presumed mechanistic analogy with the enzymatic oxidation.

The enzyme catalyzed[1] and photosensitized[2] oxidations of the plant growth hormone indolyl-3-acetic acid, 1b, have been the subject of substantial attention. The photosensitized oxidation of this acid in aqueous solution is rather unusual, as the major ultimate product is 3-methyleneoxindole, which does not correspond to the normal mode of oxidative cleavage of the 2,3 double bond of the indole ring.[3] The same oxindole is obtained in the enzymatic process. Interest on this compound arises from its potential biological activity, a controversial subject not yet totally elucidated.[4] A thorough qualitative and quantitative analysis of the products obtained in the photosensitized oxidation of 1b and its methyl ester 1c, led us[5] to formulate the hypothesis that Type I and Type II mechanisms were competing in those cases, the relative weight of each one being mainly pH dependent.

Continuing that work, we report here on the photosensitized oxidation of 1-methylindolyl-3-acetic acid, 1a, carried out under the formerly employed experimental conditions.[6] Nine products, which are summarized in the Table, could be separated by chromatographic methods and identified. Although the

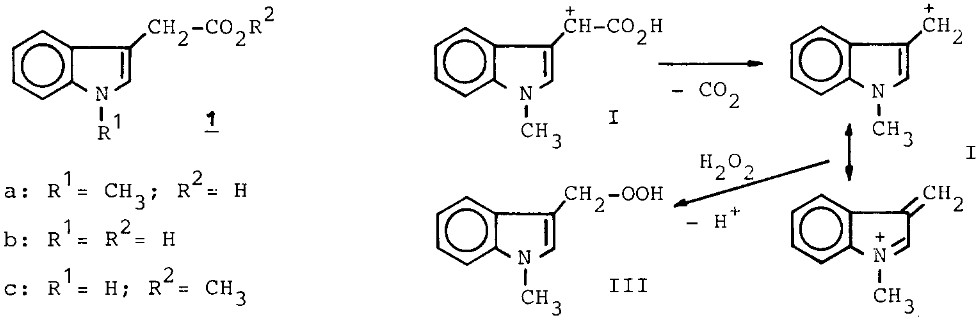
TABLE

compound [a]		2	3	4	6	7	8	9	10	11
% [b]	pH 5	23	–	–	9	7	22	10	5	–
	pH 8	11	7	7	12	26	4	–	–	8
m.p. °C		112–113	128–129	168–170	67–68	110–111	124–125	185–186	undefined	liquid
Rf [c]		0.21	0.69	0[d]	0.56	0.94[e]	0.79	0.54	0.81	0.44
MS m/z (%)		117 (31) 159 (15) 147(100)	161 (90) 133 (43) 104(100)	205 (28) 159(100)	159 (74) 158(100) 130 (15)	274(100) 259 (6) 144 (28)	290 (8) 144(100)	332(100) 287 (72) 273 (92)	433 (7) 287(100) 271 (7)	177 (8) 149 (37) 134(100)

a) Spectroscopic data (UV, IR, ^{1}H-NMR) are in accordance with the assigned structures. In the cases of 4, 6, 7, 8 and 11, additional evidence was achieved by comparison with authentic samples; b) approximate yields determined by tlc separation and gravimetric or spectrophotometric evaluation (% refers to the weight of applied sample); c.a. 15 % of polymeric material is always obtained; c) Rf on silicagel precoated (0.2 mm) aluminium sheets, $CHCl_3$-EtOAc 4:1; d) Rf=0.33, $CHCl_3$-HOAc 95:5; e) Rf=0.64, $CHCl_3$-hexane 1:2.

yields included have only an approximative value, they clearly show the scarce importance of the cleavage process, acetophenone 11 being the unique representative of this reaction. This result is in contrast with those[5] proceeding from the N-unmethylated derivatives 1b and 1c, which showed a greater proportion of cleavage products, even under neutral or acidic conditions. The formation of the majority of the identified compounds can be conveniently rationalized by assuming the existence of the key intermediates II and III (Scheme 1). Current work in our laboratory indicates that the primary photochemical species is likely the carbocation I, which would rapidly decarboxylate to II. The process generating I might be an acid-mediated two-electron transfer to the excited sensitizer. Under aerobic conditions, the oxygen would react with the reduced sensitizer to form hydrogen peroxide that is inmediately trapped by the decarboxylated carbocation to form the hydroperoxide III. Both types of intermediates, II and III, have already been proposed[1b,1d] in the enzymatic oxidation of the acid 1b, but decarboxylation was regarded as an essential step to assist the intermediate-forming process. The above mention study on the methyl ester 1c[5] showed that this step is not critical in the photosensitized oxidation.

Three possible reaction routes to 2, 4 and 6 are denoted in Scheme 2. The oxindole 2 dehydrates to a product with UV absorption in accordance with the

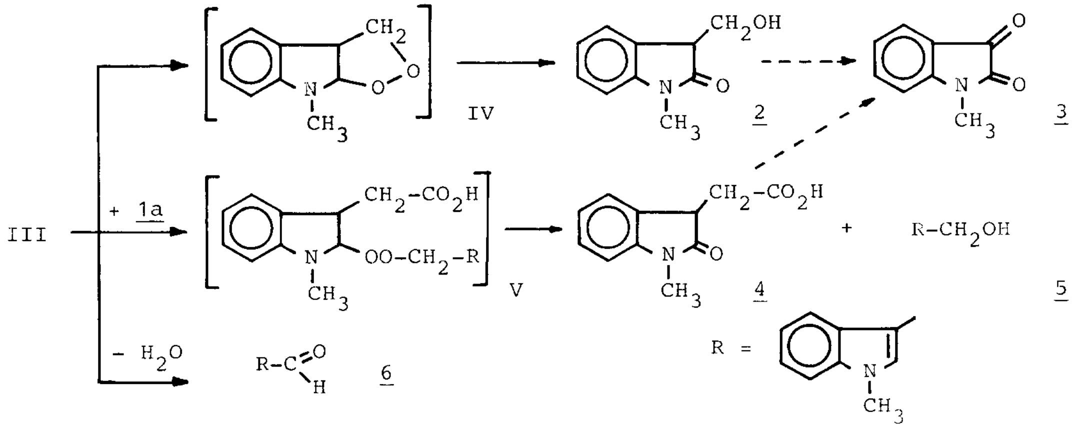


a: $R^1 = CH_3$; $R^2 = H$

b: $R^1 = R^2 = H$

c: $R^1 = H$; $R^2 = CH_3$

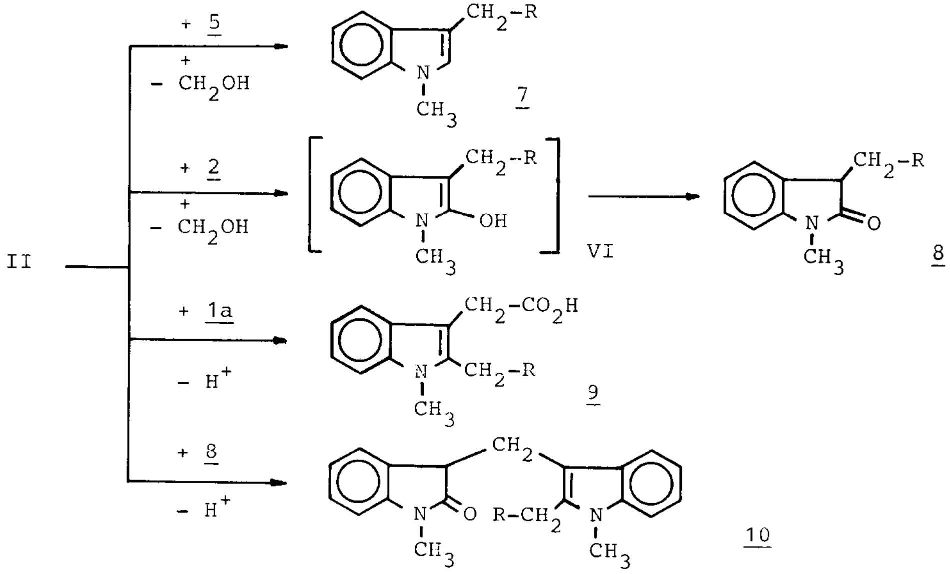
Scheme 1



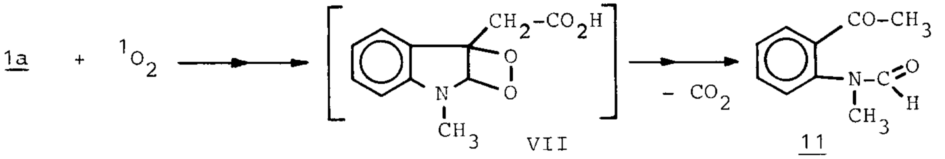
Scheme 2

expected 1-methyl-3-methyleneoxindole, which could not be isolated due to its lack of stability. The 1,2-dioxolane IV would arise from an intramolecular addition, whereas a similar intermolecular process involving the starting acid would afford the adduct V. Rearrangement of both intermediates would lead to the observed products. In fact, carbinol 5 was not found out among the reaction products, but as indicated below, it probably disappears by a secondary pathway giving 7. 1-Methylisatine, 3, may represent a second stage of a ground-state, or photochemical, oxidation of either 2 or 4. Finally, III can be converted directly into aldehyde 6.

A second group of compounds, all of them of a dimeric or trimeric character, could result from the electrophilic attack of carbocation II on the positions 2 and 3 of the indoles present in the reaction medium. In Scheme 3 the reaction routes leading to 7, 8, 9 and 10 are indicated. The intermediacy of a protonated alkylideneindolenine is accepted[7] to justify the acid catalyzed 3,3'-condensation of 3-hydroxymethylindoles into 3,3'-diindolylmethane derivatives. Thus, formation of 7 following this pathway seems not only reasonable but also capable of explaining our failure to find out the carbinol 5. Of course, a previous blank test had demonstrated that under the smooth experimental conditions and relatively short irradiation times employed, the "in dark" self-condensation of 5 did not take place, showing that the condensation must be photochemically initiated. A similar electrophilic attack on the hydroxymethyloxindole 2 serves to explain the formation of 8. An unstable 2-hydroxyl tautomeric form, VI, is shown to bring out the similarity of both reactions. The pathways leading to 9 and 10 involve coupling at position 2, which is not an odd process when electrophilic attack is carried out on 3-substituted indoles. Results obtained in our laboratory directed to study this kind of indole condensation will add support to these proposals.[8]



Scheme 3



Scheme 4

The presence of 11 requires no special commentary. Obviously, it comes from a Type II photooxidation mechanism in which the singlet oxygen is the reactive species (Scheme 4). The intermediate dioxetane VII decomposes to give an acetophenone that afterwards is decarboxylated to 11. The CO_2 elimination can occur during the irradiation or during the work-up of the reaction mixture. This result contrasts with those corresponding to the N-unmethylated derivatives,[5] where the great part of the acetophenones were recovered without having been decarboxylated. On the other hand, it is particular relevant to remark that similar condensation products to these described here have been isolated and identified[1d] in the peroxidase catalyzed oxidation of 1b, a result that stresses the resemblance existing between both the enzymatic and the photosensitized oxidations. It is also worth noticing that this type of dimeric adducts were detected also by us, although total identification was then not possible.[9]

Further studies including direct and sensitized anaerobic irradiations are in progress.

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6. Buffered aqueous solutions (300 ml) of 1a (250 mg), contining 5 % methanol to dissolve completely the substrate, were externally irradiated with incandescent lamps, while a stream of filtered air was bubbled into the solution. The temperature of the reaction mixture was maintained at 20° by a water jacket surrounding the vessel. Riboflavin (in some occasion, rose bengal) was employed as sensitizer in a molar proportion of 1:100 with respect to the substrate.
7. R.J. Sundberg, "The Chemistry of Indoles", Academic Press, New York (1970), p. 39.
8. To be published.
9. Correct structures of compounds Ik and Im in ref.[5] correspond to 2-(indolyl-3'-methyl)indolyl-3-acetic acid and 2-(indolyl-3'-methyl)-3-methylindole, respectively. Therefore, they constitute other examples of a 2,3-condensation.

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