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PHOTOSENSITIZED OXYGENATIONS OF TRYPTOPHAN DERIVATIVES: EVIDENCE FOR INVOLVEMENT OF SINGLET OXYGEN[1]

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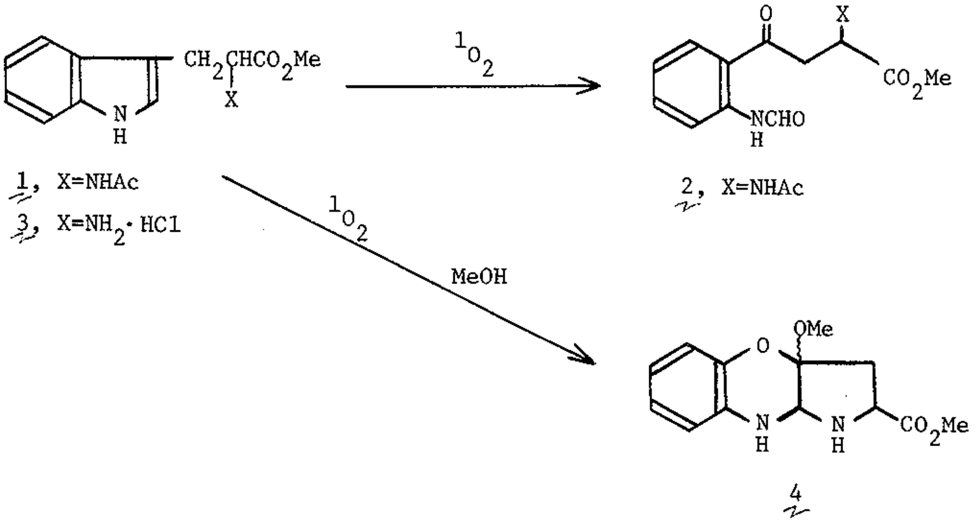
Photosensitized oxygenations and microwave discharge-generated singlet-oxygen reactions of tryptophan derivatives were investigated.

Photosensitized oxygenation of tryptophan has drawn much attention in connection with the photodynamic degradation of the tryptophan residue in proteins[2] and with the mechanisms for the biological oxygenation of tryptophan catalyzed by dioxygenases.[3,4] A large number of reports have appeared on the photoproducts as well as the mechanisms for the primary step, of the photosensitized oxygenations.[5,6] Most of the photoproducts are considered to derive from the secondary reactions of an initially formed hydroperoxide and of N-formylkynurenine, a primary photoproduct, both of which are suggested to be formed by Type I mechanism involving sensitizer triplet[7] or by singlet-oxygen process.[8] We now report that singlet oxygen generated by microwave discharge method is capable of oxidizing Nb-acetyltryptophan methyl ester in solid phase to give a formylkynurenine type product. In addition, we show that photooxygenation of tryptophan derivatives under acidic conditions produces 2,3-dihydro-1,4-benzoxazine derivatives. Previously, we[9] and Nakagawa *et al.*,[10] reported that photooxygenation of 3-substituted indoles such as tryptophol or tryptamine derivatives gave 3-hydroperoxyindolines as primary intermediates which underwent a new type of rearrangement to 1,4-benzoxazines under acidic conditions. Related photooxygenations of indoles are also described.

Rose bengal-sensitized photooxygenation[11] of Nb-acetyl-L-tryptophan methyl ester (1) (5 mM) in methanol at room temperature gave a formylkynurenine type product 2[12] (90 %).[13] Oxidation using microwave discharge-generated singlet oxygen were carried out by adsorbing 1 (3 % by weight) on silica gel in the dark. The experimental setup is essentially the same as that of Scheffer.[15] A small mercury reservoir is placed before the discharge so that it can be warmed briefly to remove oxygen atoms and ozone formed in the electric discharge. After the electric discharge was continued for *ca.* 40 hr (oxygen pressure, *ca.* 0.5 torr), the products were eluted with acetone. From the complex mixture of products, 2 was isolated in 9 % yield by preparative tlc. The result indicates that pure singlet-oxygen reaction with 1 in the absence of solvent can also produce the formylkynurenine type product.

Photosensitized oxygenation of L-tryptophan methyl ester hydrochloride (3), on the other hand, proceeded more slowly but gave a different type of product. When 3 (5 mM) was photooxygenated in methanol in the presence of methylene blue followed by work-up with aqueous bicarbonate, 2,3-dihydro-1,4-benzoxazine 4 (60 %) was obtained as an inseparable mixture of *cis*- and *trans* isomers. The structire of 4 was assigned on the basis of spectral data (Table). Heating of 4 in methanol and 2N H_2SO_4 (2 : 1) at reflux gave



o-aminophenol (32 %).

Rose bengal-sensitized photooxygenation of cyclic tryptophan derivative, pyrrolo[2,3-b]indole 5[16] (7.5 mM), which is readily available from the reaction of 1 with NBS, in methanol gave a eight-membered ring product 6 (46 %). Likeweise, rose bengal-sensitized photooxygenation of 7 (6 mM)[17] in methanol followed by silica gel chromatography produced a ten-membered ring lactum 8 (50 %) along with 1,4-benzoxazine 9 (25 %). Thus the photooxygenations provide a convenient and simple synthetic route to medium-sized ring compounds from corresponding indole derivatives.

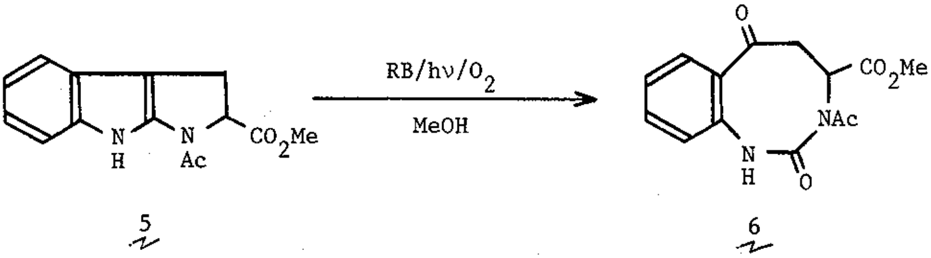
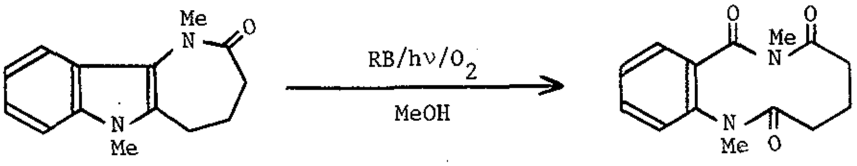


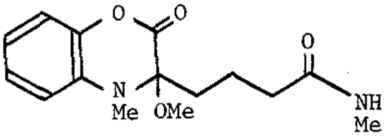
Table. Spectral Data[a]

Compounds	^{1}H-NMR (CDCl$_3$) δ (ppm)	IR cm^{-1} (CHCl$_3$)	UV(EtOH) nm(log ε)	MS (m/e)
4 (oil)	2.10-2.84 (m, 2 H), 3.35 (br s, 2 H, NH), 3.39 (s, 3 H), 3.50-4.10 (m, 1 H), 3.75 (s, 3 H), 4.63 (s, 1 H), 6.60-6.90 (m, 4 H)	3020 1740 1205	239 (3.64) 289 (3.27)	264 (M$^+$) 249 219 205
	2.10-2.84 (m, 2 H), 3.35 (br s, 2 H, NH), 3.37 (s, 3 H), 3.50-4.10 (m, 1 H), 3.73 (s, 3 H), 4.45 (s, 1 H), 6.60-6.90 (m, 4 H)			
6 (mp.51 -52°)	2.05 (s, 3 H), 3.35 (q, A of ABX, J=8, 11), 3.75 (q, B of ABX, J=8, 3.5), 3.73 (s, 3 H), 5.16 (q, X of ABX, J=3.5, 11), 6.50-7.80 (m, 4 H), 8.40 (br s, NH)	3400 1735 1680 1660 1640	226 (4.18) 244 (4.00) 319 (3.16)	290 (M$^+$) 275 247
8 (mp.213 -215°)	1.60-1.98 (m, 2 H), 2.03-2.80 (m, 4 H), 3.03 (s, 3 H), 3.45 (s, 3 H), 6.98-7.90 (m, 4 H)	1715 1650 1605	224 (4.35) 282 (3.38)	260 (M$^+$) 232 191 105
9 (oil)	1.95-2.70 (m, 6 H), 2.97 (d, 3 H, J=5 Hz, singlet on addition of D$_2$O), 3.23 (s, 3 H), 3.60 (s, 3 H), 6.60 (m, NH), 7.05-7.83 (m, 4 H)	3440 1733 1645 1300	206 (4.24) 271 (3.37)	292 (M$^+$) 274 261 234 215

[a] Satisfactory elemental analyses were obtained for all new compounds.



7 **8**



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