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SENSITIZED PHOTOOXYGENATION OF MELATONIN AND RELATED COMPOUNDS

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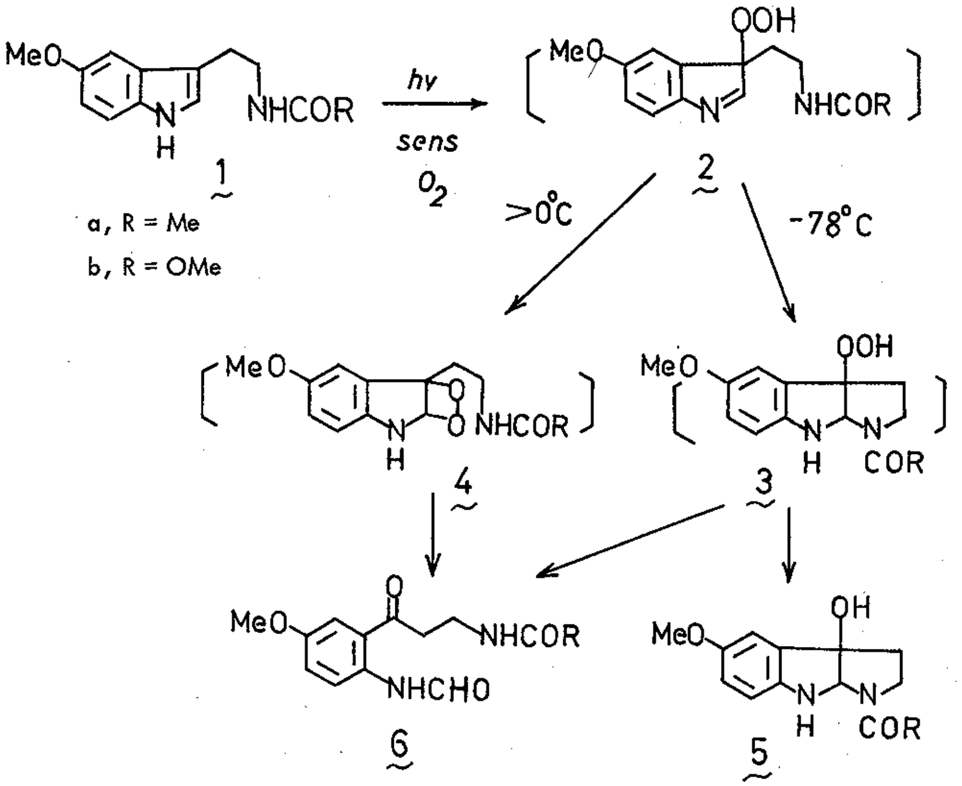
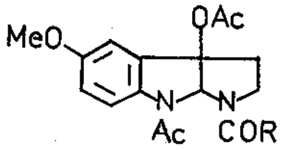
Photosensitized oxygenation of melatonin (1a) and 1b at 0°C has been found to give the corresponding 6, whereas low temperature oxygenation of 1 provided exclusively 3 which rearranged to 6 at room temperature.

The classical tryptophan 2,3-dioxygenase has been known to convert L-tryptophan to L-formylkynurenine[1], whereas indoleamine 2,3-dioxygenase isolated more recently was found to catalyze the 2,3-bond cleavage reaction of not only the D- and L-tryptophan and 5-hydroxytryptophan but also tryptamine and its derivatives such as serotonin and melatonin[2]. Although the photosensitized oxygenation of tryptophan and related compounds has been extensively studied[3], sensitized photooxygenation of melatonin has not been investigated. Besides mechanistic interest, our studies are also considered to eventually contribute to the extended preparative usefulness of sensitized photooxygenation in obtaining not easily accessible compounds such as 5.

We now wish to report the results of some preliminary experiments on the rose bengal sensitized photooxygenation of melatonin and related compounds. Photooxygenation of melatonin 1a in 5% pyridine-MeOH at 0°C, sensitized by rose bengal with a 200 W halogen lamp under an oxygen atmosphere for 1.5 hr followed by column chromatography(Al_2O_3) gave the 2,3-bond cleavage compound 6a,[11] mp 144.5-145.5° in 59% yield as the sole product, while the reaction carried out at -78°C for 9 hr (hν > 480 nm)[4] gave excusively 3a[5] which without isolation was reduced by Me_2S to give 3a-hydroxypyrroloindole 5a as the sole product in 66% yield, based on consumed 1a(64%). 5a : chromatographically homogeneous oil ; λmax (EtOH) nm 242.5, 314 ; νmax ($CHCl_3$) cm^{-1} 3640, 3350(OH, NH), 1630(C=O) ; ν max (KBr) 3300(OH, NH), 1620(C=O) ; δ ($CDCl_3$) 1.94(s, 3H, NAc), 2.20-2.60(m, 2H, CH_2), 3.10-3.80(m, 2H, CH_2N), 3.73(s, 3H, OMe), 4.30(broad s, 2H, OH and NH, exchangeable), 5.24(s, 1H, NCHN), 6.48(d, 1H, J= 8 Hz, C_7-H), 6.68(dd, 1H, J = 8 Hz and 3 Hz, C_6-H), 6.84(d, 1H, J = 3 Hz, C_4-H) ; m/e (relative intensity) 248(100) M^+, 233(13), 230(2), 178(23), 177(16), 176(18), 78(64), 63(89). Acetylation of 5a with Ac_2O-pyridine gave the diacetate 7a : mp 156-158°[6] (EtOH) ; λmax (EtOH) nm (ε) 251(14040), 299(2990) ; ν max (KBr) cm^{-1} 1752, 1680, 1668 (C=O), 1255, 1245, 1055(C-O) ; δ ($CDCl_3$) 2.00(s, 3H, OAc or NAc), 2.06(s, 3H, OAc or NAc), 2.55(s, 3H, NaAc), 2.00-3.25, 3.60-3.90(m, 4H, CH_2), 3.78(s, 3H, OMe), 6.30(s, 1H, NCHN), 6.88(dd, 1H, J = 8 Hz and 3 Hz, C_6-H), 7.04(d, 1H, J = 3 Hz, C_4-H), 7.96(d, 1H, J = 8 Hz, C_7-H) ; m/e 332(52) M^+, 290(100), 230(85), 188(63), 176(17), 160(17).

On the other hand, when the reaction mixture obtained by low temperature (-78°C) oxygenation of 1a was concentrated in vacuo below 30°C and the residue[7] was chromatographed on alumina column, 6a was the only product isolated in 32% yield besides the recovered 1a(42%). In addition, when the same reaction mixture was left for 48 hr at room temperature (22°C) in the dark and under daylight followed by dimethyl sulfide reduction[8], 6a(38%) and 5a(7%) were obtained with the recovered 1a(30%), showing





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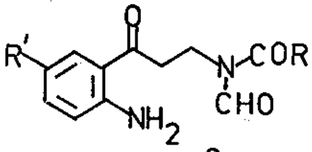

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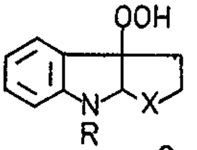

9 a, R = H, X = NCO_2Me
b, R = Me, X = NCO_2Me
c, R = Me, X = O

that in contrast to 9b[9] and 9c[10], 3a rearranged to Na-formylkynurenamine 6a. Unlike 9a[9], however, neither 3a nor 9b rearranged to the corresponding Nb-formyl derivatives 8.

On the other hand, the similar oxygenation of 1b carried out with a 200 W halogen lamp at 0°C in both benzene and MeOH gave 6b as the sole product in 32% and 39% yields, respectively. 6b : mp 153.5-154° (MeOH) ; λmax (EtOH) nm (ϵ) 237(24900), 266.5 (9550), 350(4470) ; ν max (KBr) cm^{-1} 3290(NH), 1732, 1684, 1658(C=O), 1542(CONH), 1260, 1200, 1050 ; δ ($CDCl_3$) 3.24(t, 2H, CH_2), 3.55(t, 2H, CH_2N), 3.65(s, 3H, CO_2Me), 3.84(s, 3H, OMe), 5.20(broad s, 1H, exchangeable), 7.12(dd, 1H, J = 8 Hz and 3 Hz, C_4-H), 7.38(d, 1H, J = 3 Hz, C_6-H), 8.43(s, 1H, CHO), 8.64(d, 1H, J = 8 Hz, C_3-H), 11.10(broad s, 1H, NHCHO, exchangeable) ; m/e 280(40) M^+, 252(15), 205(25), 177(85), 176(100), 162(23), 150(75), 122(35). Furthermore, irradiation of 1b in MeOH with 500 W halogen lamp (480 nm < hν) at 0°C under O_2 atmosphere followed by Me_2S reduction generated 6b(24%) and 5b(17%), whereas at -78°C for 7.5 hr led to the formation of 5b(81%), based on consumed 1b(41%). On the other hand, irradiation of 5b under the reaction conditions with a 200 W halogen lamp at 0°C resulted in the decomposition of 5b, demonstrating that 5b was sensitive to the reaction conditions (especially to the light λ < 480 nm) at higher temperature (0°C). 5b : chromatographically homogeneous oil ; λmax (EtOH) nm 241, 315 ; ν max (KBr) cm^{-1} 3350(NH, OH), 1710, 1690(C=O), 1200, 1040 ; δ ($CDCl_3$) 2.32(m, 2H, CH_2), 2.90-4.00(m, 2H, CH_2N), 3.65, 3.72(s, 6H, OAc, OMe), 5.10(s, 1H, NCHN), 6.48(d, 1H, J = 8 Hz, C_7-H), 6.70(dd, 1H, J = 8 Hz and 3 Hz, C_6-H), 6.83(d, 1H, J = 3 Hz, C_4-H) ; m/e 264(100) M^+, 249(9), 246(5), 176(66), 162(21), 149(18). Diacetate 7b : mp 135.5-136.5° (EtOH) ; λmax (EtOH) nm (ϵ) 251(14510), 299(2920) ; ν max (KBr) cm^{-1} 1754, 1715, 1670 (C=O), 1248, 1062 ; δ ($CDCl_3$) 2.00(s, 3H, OAc), 2.48(s, 3H, NAc), 2.10-3.10(m, 2H, CH_2), 3.60-4.05(m, 2H, CH_2N), 3.72(s, 3H,

NCO_2Me or OMe), 3.76(s, 3H, NCO_2Me or OMe), 6.16(s, 1H, NCHN), 6.86(dd, 1H, J = 8 Hz and 3 Hz, C_6-H), 7.01(d, 1H, J = 3 Hz, C_4-H), 7.94(d, 1H, J = 8 Hz, C_7-H) ; m/e 348(33) M^+, 306(64), 246(100), 176(18), 160(12).

The results indicate the effect of temperture on the product composition. At low temperature, the participation of the aminoethyl group in 2 leading to the formation of 3 prevails. At higher temperatures, the reaction favorably proceed to form 6 probably via a dioxetane 4. Although details of the mechanism for the transformation of 3 to 6 remain obscure at present, it could be explained analogously to that proposed previously[3b].

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4. Irradiation was carried out with a tungsten-iodine lamp through an aqueous $CuCl_2$-$CaCl_2$ filter soluition (cut off $\lambda < 480$ nm).

5. Isolation of pure **3** was failed due to its instability to alumina as well as silica gel.

6. The new compounds given with reported melting point analyzed correctly for C,H, and N.

7. The TLC showed it contained **3a** and **6a**. It gave a positive starch-KI test.

8. The reaction mixture still contained **3a** after 48 hr, detected by TLC as well as starch-KI test.

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