HETEROCYCLES, Vol. 4, No. 7, 1976

PHOTOSENSITIZED OXYGENATION OF 2,3-DIPHENYLINDOLE DERIVATIVES

Masako Nakagawa*, Noriko Ohyoshi, and Tohru Hino

Faculty of Pharmaceutical Sciences, Chiba University, Chiba, Japan

Photosensitized oxygenation of 2,3-diphenylindole (1a) gave 3-hydroxyindolenine (5) as a major product. N-Acetyl-2,3-diphenylindole (1b) yielded 2,3-dihydroxy derivative (10a) whereas N-methylderivative (1c) gave 2,3-bond cleavage product (8c) and 2,3-dihydro-1,4-benzoxazine (11).

It has been reported[1] that singlet oxygen reacts with a tertiary enamine to give a dioxetane as 1,2-cycloaddition product which readily decomposes to carbonyl fragments, while with enamines having an NH hydrogen the ene reaction takes place to give hydroperoxides ($RN=\overset{|}{C}-\overset{|}{C}-OOH$). Available experimental evidences[1c, 2] and recent theoretical investigation[3] have been suggested these reactions procced in steps via a zwitter ionic intermediate rather than a concerted process.

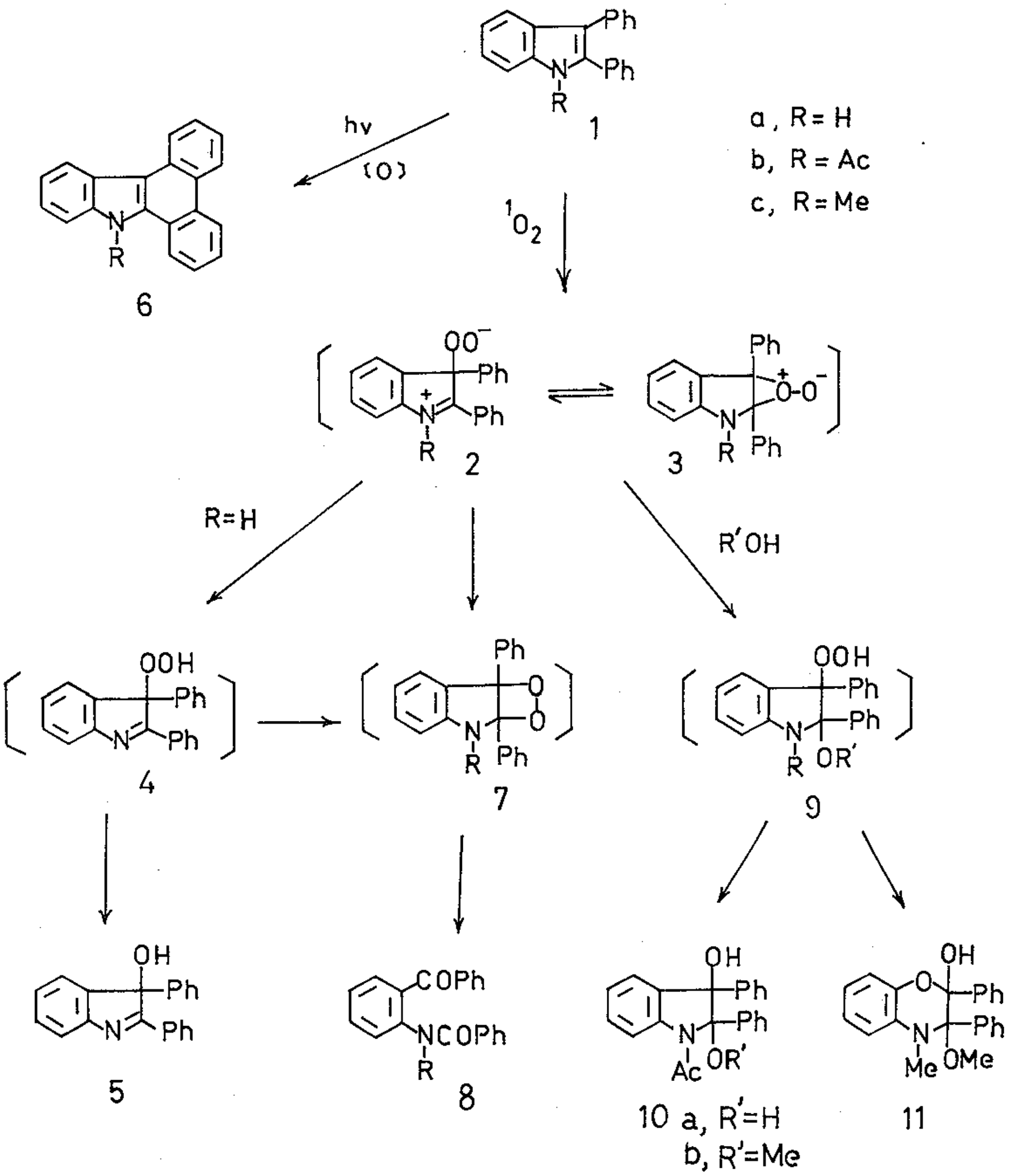
In our recent studies[4], we have shown that tryptophan and tryptamine derivatives react with singlet oxygen to give 3a-hydroperoxypyrroloindole as the primary product which was transformed into final products including formylkynurenine derivative. On the other hand, Saito and Matsuura have reported the photosensitized oxygenation of

N-substituted 1,2,3,4-tetrahydrocarbazoles[1c]. These results led us to study the effect of N-substituent on the photooxygenation of simple indole.

We wish to report here the photosensitized oxygenation of 2,3-diphenylindole and its N-derivatives. Photooxygenation of 2,3-diphenylindole (1a) [5] in benzene, at 0°, sensitized by Rose Bengal (dissolved in a small amounts of methanol) with 250 W halogen lamp was carried out under a stream of oxygen for 9.5 hr. Evaporation of the solvent and subsequent chromatographic separation gave *2,3-diphenyl-3-hydroxyindolenine (5)* [6], mp 190.5-192.5°, 40%, as the main product, together with 2-benzamidobenzophenone (8a) [6,7], 11%, 9H-dibenzo[a, c]carbazole (6a) [7], mp 191.5-193°, 4.5% and recovered (1a), 23%. The same reaction in methanol gave a better result giving 5, 58% and 8a, 37% after 4.5 hr. Of some interest is that there is virtually no other precedent for direct formation of 3-hydroxyindolenine as a major product by the reaction of singlet oxygen with indole derivatives[8].

With regard to the mechanism of formation of 5, the first step presumably involves the formation of the 3-hydroperoxyindolenine (4) via the well-known ene reaction, followed by O-O bond fission during the reaction[9]. On the other hand, the competing cyclic process of 4 leading to the dioxetane (7) has been occured to give 8a [10]. The transformation of 1a to 6a might be analogous to the reaction involves photochemical dehydrocyclization[7].

The irradiation of the N-acetyl derivative (1b) in methanol under the similar conditions was carried out for 7 hr and the diol (10a), mp 206-208.5° [11], was obtained in 54% yield along with a small amount of 8a, 2%, which probably formed by hydrolysis of 8b during isolation, whereas in benzene, the reaction afforded only a trace of 10b[13], mp 194-196°, and 8a, and 81% of the starting material was recovered after 7 hr. The reaction of singlet oxygen with 9-acetyl-tetrahydrocarbazole has been reported to give the similar


1
a, R = H
b, R = Ac
c, R = Me
hν
(O)
6
$^1O_2$
2
3
R=H
R'OH
4
7
9
5
8
10 a, R'=H
b, R'=Me
11

results[1c]. The isolated product (10) suggest an intermediacy of the zwitter ion (2) or the peroxirane (3) followed by addition of the solvent or water and subsequent reduction to give 10.

A similar reaction of N-methyl derivative (1c) in methanol, however, produced 2,3-bond cleavage product (8c), mp 111-113° [7], 59%, as a major product, 2,3-dihydro-1,3-benzoxazine (11), mp 177-179° [13,14], 15%, and dibezocarbazole (6c)[7], mp 142-143°, 4%. 11: λ_{max}(95% EtOH) 249 (ϵ 10800), 298 nm (5500) ; ν_{max} (KBr) 3550 cm^{-1} (OH) ; δ ($CDCl_3$) 2.81 (s, N-Me), 3.15 (s, O-Me), 3.62 (s, OH, exchangeable), 6.60-7.40 (m, aromatic H) ; m/e 347. Acid hydrolysis of 11 yielded o-methylaminophenol and benzil quantitatively. Formation of 8c seems to involve the dioxetane intermediate (7c) produced from 2. On the other hand, nucleophilic addition of methanol to 2 or 3 to give 9 followed by the Baeyer-Villiger type rearrangement [2e,4c] is a likely mechanism for formation of 11. The reason for this pronounced substituent effect on the photooxygenation of 2,3-diphenylindole, viz., exclusive formation of 10a from 1b rather than the ketoamide 8b or 1,4-benzoxazine derivative in contrast with 1c, is not apparent. Extension of present observation is now in progrss.

ACKNOWLEDGEMENT We thank the Foundation for the Promotion of Research on Medicinal Resources (Japan) for financial support.

REFERENCES

1 a) C.S.Foote and J.W.Lin, Tetrahedron Lett., 3267 (1968) ; J.E.Huber, ibid., 3271 (1968) ; c) I.Saito, M.Imuta, and T.Matsuura, Chem.Lett., 1173, 1197 (1972) ; d) W.E.Savige, Aust.J.Chem., 24, 1285 (1971) ; e) C.S.Foote, A.A.Dzakpasu, and

J.W-P.Lin, Tetrahedron Lett., 1247 (1975) ; f) H.H.Wasserman and S.Terao, ibid., 1735 (1975) ; g) W.Ando, T.Saiki, and T.Migita, J.Am.Chem.Soc., 97, 5028 (1975) ; h) R.W. Denny and A.Nickon, “Organic Reactions” Vol 20, ed. by W.G.Dauben, John Wiley & Sons, New York, 1973, p 133 and references cited therein.

2 a) H.H.Wasserman, K.Stiller, and M.B.Floyd, Tetrahedron Lett., 3277 (1968) ; b) T.Matsuura and I.Saito, Tetrahedron, 25, 549 (1969) ; c) H.H.Wasserman, J.R.Scheffer, and J.L.Cooper, J.Am.Chem.Soc., 94, 4991 (1972) ; d) H.H.Wasserman and I.Saito, ibid., 97, 905 (1975) ; e) I.Saito, M.Imuta, S.Matsugo, and T.Matsuura, ibid., 97, 7191 (1975).

3. M.J.S.Dewar and W.Thiel, J.Am.Chem.Soc., 97, 3978 (1975).

4 a) M.Nakagawa, T.Kaneko, K.Yoshikawa, and T.Hino, J.Am.Chem.Soc., 96, 624 (1974) ; b) M.Nakagawa, K.Yoshikawa, and T.Hino, ibid., 97, 6496 (1975) ; c) M. Nakagawa, H.Okajima, and T.Hino, ibid., 98, 632 (1976).

5 2,3-Diphenylindole has been reported to resist to air oxidation. cf. R.J.S.Beer, T. Donavanik, and A.Robertson, J.Chem.Soc., 4139 (1954).

6 L.J.Dolby and R.M.Rodia, J.Org.Chem., 35, 1493 (1970).

7 C.A.Mudry and A.R.Frasca, Tetrahedron, 30, 2983 (1974).

8 G.B.Guise, E.Ritchie, and W.C.Taylor, Aust.J.Chem., 18, 1279 (1965).

9 The reaction which involves a loss of OH group, is less clear. However, some indication that 4 would be able to oxidize the solvent or the another molecule of 1a, is provided by our previous experiment. a) M.Nakagawa, H.Yamaguchi, and T.Hino, Tetrahedron Lett., 4035 (1970) ; b) M.Nakagawa, T.Suzuki, T.Kawashima, and T.Hino, Chem.Pharm.Bull., 20, 2413 (1972).

10 Addition of 1% AcOH to the same reaction in methanol gave 5, 24%, and increased the yield of 8a up to 43%. However, 1,4-benzoxazine derivative was not obtained, indicating the protonation has been occured exclusively on the imino nitrogen rather than on the OOH group.

11 The melting point of 10a is identical with that of the diol obtained by OsO_4 oxidation of 1b[12].

12 D.W.Ockenden, K.Schofield, J.Chem.Soc., 612 (1953).

13 The possibility of the reversed position for the hydroxy and the methoxy groups can not be excluded.

14 The compound (11) analyzed correctly for C.H.N.

Received, 12th May, 1976