PHOTOOXYGENATION OF 9-KETO-7-METHOXY-6-METHYL-9H-PYRROLO[1,2-a]INDOLE AS A SYNTHETIC APPROACH TO THE MITOMYCINS

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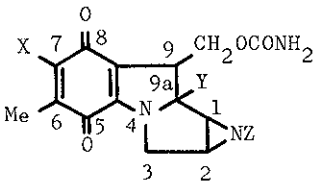
Sensitized photooxidation in methanol of 9-keto-7-methoxy-6-methyl-9H-pyrrolo[1,2-a]indole (9), prepared from 2-bromo-5-methoxy-4-methylbenzaldehyde (5) via 2-(2-bromo-5-methoxy-4-methylbenzoyl)pyrrole (8), afforded 9,9a-dihydro-3-hydroperoxy-9-keto-7,9a-dimethoxy-6-methyl-3H-pyrrolo[1,2-a]indole (11) and the 3-hydroxy compound (12), the latter of which is considered as a potential precursor of the mitomycins.

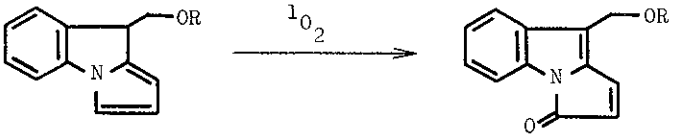
The mitomycins (1), a group of antibiotics with antitumor and antibacterial activity, possess an acid labile hydroxyl or methoxyl group at the C-9a position. In spite of tremendous efforts by many investigators,[1-8] the synthesis of the mitomycins has not yet been achieved. As a matter of fact, no report for building up the oxo-substituent at the C-9a position in the tricyclic pyrrolo[1,2-a]indole ring system has appeared. While Franck and co-workers[6,7] tried the photooxidation of the 9H-pyrrolo[1,2-a]indoles (2) but only the dehydrated products (3) were obtained. Furthermore, 9-keto-9H-pyrrolo[1,2-a]indole (4) did not react with singlet oxygen.[6] In contrast, we considered that the presence of electron-donating groups on ring A would activate the

Scheme 1



(1)

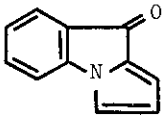
	X	Y	Z
mitomycin A	MeO	MeO	H
mitomycin B	MeO	HO	Me
mitomycin C	NH_2	MeO	H
porfiromycin	NH_2	MeO	Me



(2)

(R=Me, CH_2Ph)

(3)



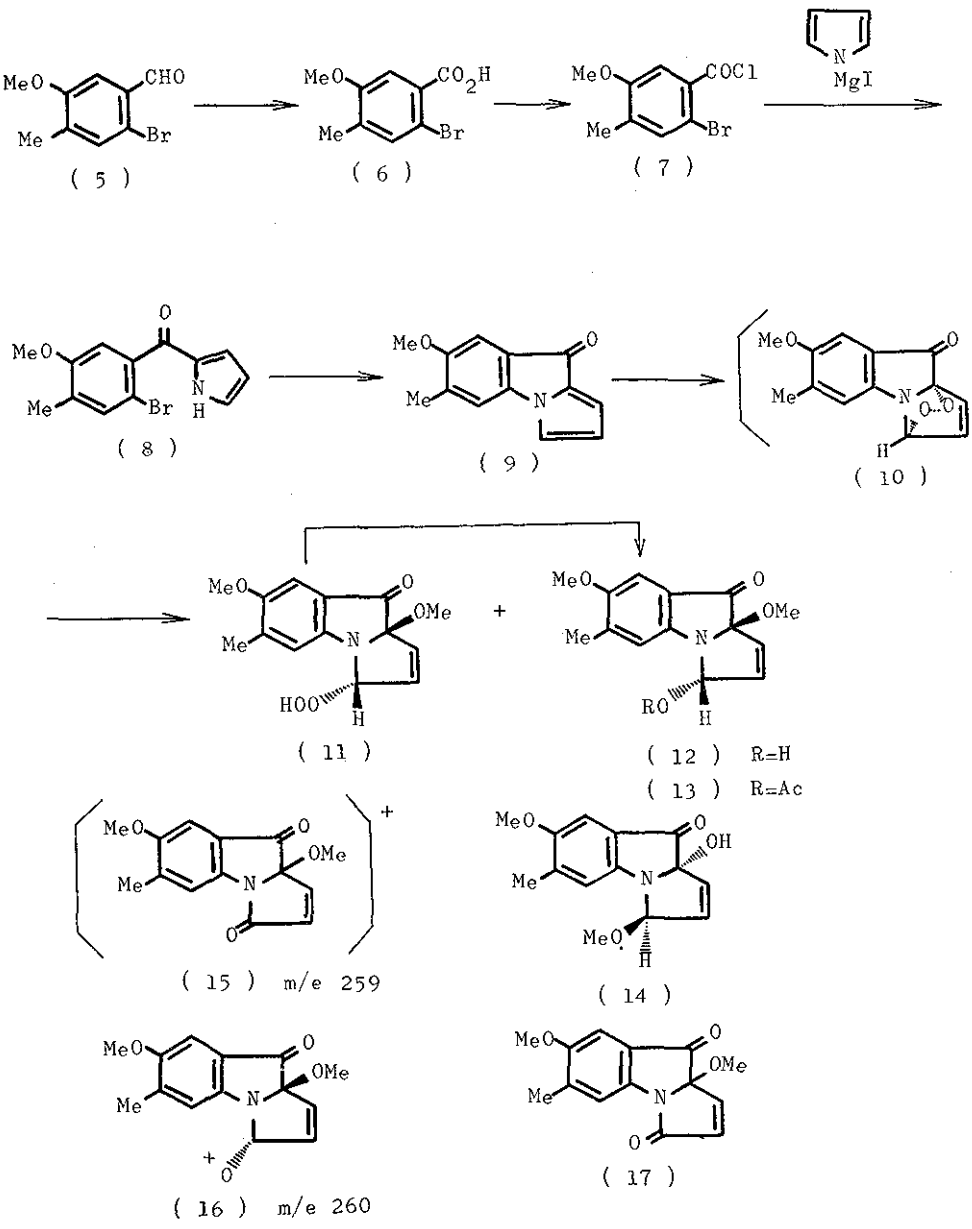
(4)

addition of singlet oxygen to the pyrrole ring C in 9-keto-9H-pyrrolo-[1,2-a]indoles. Based on this premise, 9-keto-7-methoxy-6-methyl-9H-pyrrolo[1,2-a]indole (9) which has suitable substituents on ring A for the synthesis of the mitomycins was prepared and subjected to photooxidation. We now wish to report some interesting results on photooxygenation of 9.

Potassium permanganate oxidation[9] of 2-bromo-5-methoxy-4-methyl-benzaldehyde (5)[8] in aqueous acetone gave the carboxylic acid (6), m.p. 187 ∿ 188°, in 55 % yield. The acid was converted, by treatment with thionyl chloride in the usual manner, to the acid chloride (7), which was condensed with pyrrylmagnesium iodide[10,11] at room temperature in ether to afford 2-(2-bromo-5-methoxy-4-methylbenzoyl)pyrrole (8), m.p. 145.5 ∿ 146° in 47 % overall yield from 6. The i.r. spectrum ($CHCl_3$) showed absorptions due to the NH group at 3460 and a carbonyl group at 1620 cm^{-1}, while the u.v. spectrum (MeOH) exhibited the absorptions at 227 and 302 nm (log ε 3.82 and 3.94). Singlet signals due to C-methyl group at 2.22 and the O-methyl group at 3.73 were observed in the n.m.r. spectrum ($CDCl_3$) along with three protons on the pyrrole ring as multiplets at 6.22, 6.58, and 7.10 and two aromatic protons as singlets at 6.87 and 7.30 p.p.m.

By a route involving intramolecular nucleophilic aromatic substitution, 8 was cyclized in the presence of sodium hydride and cuprous bromide in dimethylformamide at room temperature[8] to provide 9, m.p. 178 ∿ 179°, in 53 % yield. The structure of 9 was consistent with the following sepctral data [u.v. λ_{max}(MeOH) 258, 290^{sh} and 335 nm (log ε) 4.18, 3.94 and 3.78); i.r. ν_{max}($CHCl_3$) 1690 cm^{-1} (C=O); n.m.r. δ 2.27 (3H, s, 6-Me), 3.83 (3H, s, OMe), 6.17 (1H, dd, J 3 and 4 Hz, 2-H),

Scheme 2


MeO
CHO
Me
Br
(5)
CO2H
(6)
COCl
(7)
N
MgI
O
H
(8)
(9)
(10)
OMe
HOO
(11)
RO
(12) R=H
(13) R=Ac
(15) m/e 259
OH
(14)
(16) m/e 260
(17)

6.68 (1H, d, J 4 Hz, 3-H), 6.85 (1H, s, 5-H), 6.92 (1H, d, J 3 Hz, 1-H) and 7.00 (1H, s, 8-H); m/e 213 (M^+)].

Irradiation of 9 in methanol under an oxygen atmosphere in the presence of Rose Bengal as sensitizer with a 200 W tungsten lamp for 72 h gave two products along with starting material which were separated by preparative t.l.c. on silica gel. The structure of the faster running product, obtained as an unstable solid in 21 % yield, was assigned as the hydroperoxide (11), while that of the slower running compound, isolated as pale yellowish needles, m.p. 158 ∿ 159° (decomp.) in 21 % yield, as 9,9a-dihydro-3-hydroxy-9-keto-7,9a-dimethoxy-6-methyl-3H-pyrrolo[1,2 -a]indole (12) on the basis of the following evidence. The i.r. spectrum ($CHCl_3$) of the latter (12) showed carbonyl absorption at 1708 cm^{-1}, and the u.v. spectrum [λ_{max} (MeOH) 235, 269^{sh} and 337 nm (log ε 4.13, 3.74 and 3.18)] is similar to that of a 2,2-disubstituted 5-methoxy-3-oxoindole derivative.[12] The n.m.r. spectrum ($CDCl_3$) gave signals due to a C-methyl group at 2.30 as a singlet, two O-methyl groups at 3.35 and 3.80 as singlets, one methine proton at 5.30 as a broad singlet and two olefinic protons at 6.70 as a broad singlet in addition to two aromatic protons at 6.97 and 7.05 p.p.m. as singlets. Furthermore, a molecular ion peak was observed at m/e 261 in the mass spectrum. These spectral data indicated two possible structures 12 and 14. On acetylation with acetic anhydride in pyridine, the hydroxide (12) gave the acetate (13), whose n.m.r. spectrum ($CDCl_3$) showed a methine proton at 6.39 as a doublet with J 2 Hz, two olefinic protons at 6.06 as a double doublet with J 2 and 5 Hz and 6.20 as a doublet with J 5 Hz and two aromatic protons at 7.00 and 7.48 as singlets along with a methyl signal due to the acetyl group at 2.22, a 6-methyl

group at 2.30 and two O-methyl groups at 3.40 and 3.88 p.p.m. as singlets. Such a big deshielding of the methine proton by acetylation suggested that the hydroxyl group was at the C-3 position.

The other product from the above photooxidation was the hydroperoxide (11) [i.r. ($CHCl_3$) 1708 cm^{-1} (C=O); n.m.r. ($CDCl_3$) 2.32 (3H, s, 6-Me), 3.36 (3H, s, 9a-OMe), 3.82 (3H, s, 7-OMe), 5.57 (1H, d, J 2 Hz, 3-H), 5.97 (1H, dd, J 2 and 5 Hz, 2-H), 6.22 (1H, d, J 5 Hz, 1-H), 7.00 (1H, s, 5-H), and 7.15 p.p.m. (1H, s, 8-H)] which showed a molecular ion peak at m/e 277 in addition to the fragment ion peaks at m/e 259 (15) and 260 (16) in the mass spectrum (chamber volt, 30eV) and also gave a positive starch-iodide test. Treatment with dimethyl sulfide transformed the hydroperoxide (11) to 12. On further irradiation in methanol under the same conditions as above, the hydroperoxide (11) was also converted to 12. It is thus considered that cyclic addition of singlet oxygen to the 9-keto-9H-pyrrolo[1,2-a]indole (9) formed the endo-peroxide (10) which was attacked by methoxide ion at the C-9a position to yield the hydroperoxide (11). Reductive cleavage of the hydroperoxyl group also afforded 12, which is consistent with literature of photoreduction in alcoholic solution.[13] Based on the above mechanism, the methoxyl group at C-9a is trans to the hydroperoxyl or the hydroxyl group at the C-3 position.

It is interesting that the reaction of the 9-keto-9H-pyrrolo[1,2-a]-indole (9) with singlet oxygen in methanol did not form the product (17) which was expected from photooxygenation behavior of pyrrole derivatives in methanol,[14] but gave instead the hydroperoxide (11) and the hydroxide (12).

The potential utility of the acetate (13) as an intermediate in the

synthesis of the mitomycins is at present under investigation.

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