OXIDATION OF INDOLO-QUINOLINE STRUCTURES

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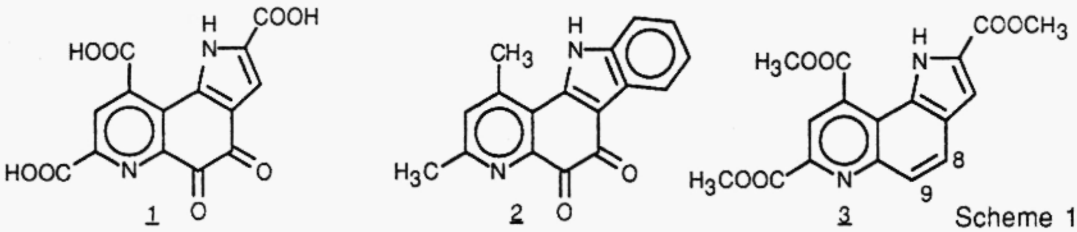
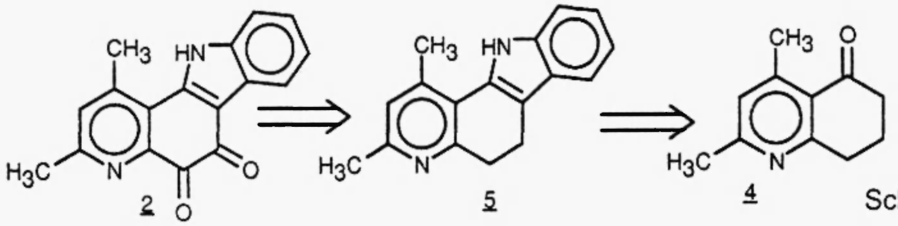
Abstract : Oxidation of new indolo-quinoline structures was studied. Herein, the use of a new oxidizing reagent, *eg* sodium perxenate, and other reagents (PIFA, tBuOCl) which lead to indolenin 8-10 from indolic compound 5 is described.

The copper amine oxydases constitute an important class of mammalian enzymes involved in endo- and xenobiotic metabolism. Some of them utilize an ortho-quinone cofactor to achieve transamination of primary alcohol to aldehyde.(1) This cofactor of the copper amine oxidases, a pyrroloquinoline quinone 1 (methoxatine, PQQ), was isolated from bacteria(2) and some analogous compounds were described. (3)



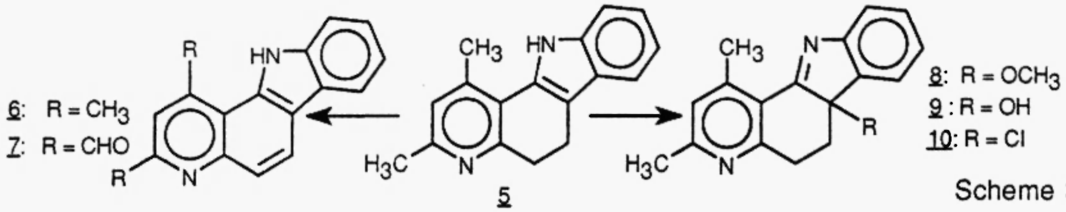
Scheme 1

In this preliminary work, we planned to study the oxidation of compound 5 in the aim to synthesize an indolic analogue 2 of methoxatine 1. The synthesis of this compound was based on the following retro-synthetic scheme:



Scheme 2

The first step was an indolisation by the Fischer reaction from 4 (4) and phenylhydrazine, involving 5 (10,11-dihydro-2,4-dimethylpyrido[3,2,*a*]carbazole) in medium yield (45%). Oxidation of 5 by using Yonemitsu's conditions (DDQ-THF-H_2O) (5) did not give the 10-keto compound or the corresponding phenol, but 6 which was isolated in 55 % (scheme 3). The same product was obtained by several reagents (Pd-C, xylene, reflux temperature : 30%; Pd-C, decaline, reflux temperature : 26%; MnO_2, xylene, room temperature : 52%). An unusual reagent, *eg* sodium perxenate (Na_4XeO_6, $6H_2O$) (6) in methanol-H_2O (4:1) (1.5 equivalent, reflux temperature, 5h) oxidized 5 into 8 (42%); the high resolution mass spectroscopy gave a molecular formula corresponding to $C_{18}H_{18}N_2O$ and the mass spectroscopy revealed a loss of m/z 31 ($M^{+\cdot}$ - MeO) (hrms : $C_{17}H_{15}N_2$). The ^{1}H-NMR exhibited a singlet (δ = 2.82 ppm) and the ^{13}C-NMR gave a signal at δ 52.6 ppm. These data suggested the presence of a methoxy group; this compound is the 10*a*-methoxy-indolenin 8. The oxidation with PIFA (bis(trifluoroacetoxy)-iodobenzene) in CH_3CN-H_2O (7) lead to the product 6 (40%) and a by-product 9 (20%). The ^{1}H-NMR of 9 exhibited a broad signal (δ 3.8 ppm) and the ir spectroscopy showed an absorbtion between 3050 and 3200 cm^{-1}, characteristic of a hydroxylic group. The mass spectroscopy gave a molecular mass at m/z 364. This product is the 10*a*-hydroxy-indolenin 9. The reaction with *t*-butyl hypochlorite (*t*-BuOCl) (8) lead to 10 : the mass spectroscopy gave a molecular mass at m/z 282. The ^{1}H-NMR spectrum was very closed of those of 8 and 9. All the spectroscopic data (ms, hrms, ^{1}H-, ^{13}C-NMR) suggest the chloro-indolenin structure 10.



Scheme 3

In 1982, Hendrickson and de Vries observed that it is impossible to oxidize the central ring of 3 into *ortho*-quinone system : the double bond C8-C9 shows no olefinic character toward oxidants (9). The classical oxidizing reagents (Fremy salt, iodosylbenzene, iodylbenzene ($PhIO_2$), SeO_2(10), PIFA(6)) to oxidize 6 gave only tars. In 1991 Yusybod described oxidation of styrene into benzil by using DMSO-I_2 at reflux temperature (11). In our hands, in these conditions methyl groups of 6 were oxidized into aldehyde functions to give 7 (60%) but no ortho-quinone structure was obtained.

In conclusion, this work shows the surprising stability of 6 during the oxidation and confirms the previous observation of Hendrickson (9). Moreover, a new oxidizing indole reagent, *eg* Na_4XeO_6 is proposed for the preparation of indolenin structures.

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