

OXIDATIVE DIMERIZATION OF  $N_b$ -METHOXYCARBONYLTRYPTAMINES BY DYE-SENSITIZED  
PHOTOXYGENATION IN FORMIC ACID. SYNTHESIS OF ( $\pm$ )-FOLICANTHINE AND  
( $\pm$ )-CHIMONANTHINE

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Dye-sensitized photooxygenation of  $N_b$ -methoxycarbonyltryptamines and tryptophan methyl ester in methanol at 0° has been disclosed to give 3a-hydroperoxy-pyrroloindoles (1) which were stable enough to be isolated and transformed into the hydroxy derivative (2), the ketoamide (3), and the  $N_b$ -formyl derivative (4) in various conditions such as silica-gel/methylene chloride, heat, or light.<sup>1</sup> Under similar conditions an aqueous solution of tryptophan afforded a tricyclic hydroperoxide (1) which gave the hydroxy derivative (2) in excellent yield on reduction and rearranged to formylkynurenine (3) on heating at 100°.<sup>2</sup>

On the other hand, proflavine-sensitized photooxygenation of tryptophan and  $N_b$ -benzyloxycarbonyltryptophan in formic acid has been reported to give kynurenine-type compounds in good yields.<sup>3</sup> As the tricyclic hydroperoxide (1) rearranges to 1,4-benzoxazine derivative (5) in methanol-HCl at room temperature,<sup>1</sup> we reexamined proflavine-sensitized photooxygenation of tryptophan and  $N_b$ -benzyloxycarbonyltryptophan in formic acid, but neither kynurenine-type compound nor 1,4-benzoxazine derivative was obtained, and polymeric compounds were isolated. Proflavine-sensitized photooxygenation of  $N_b$ -methoxycarbonyltryptamine in formic acid, however, was found to give dimeric products which have not previously been obtained in the sensitized photooxygenation of indole derivatives and were converted to folicanthine and chimonanthine.

When  $N_b$ -methoxycarbonyltryptamine (6) was irradiated in thoroughly O<sub>2</sub>-saturated formic acid at 10-15° with a 500W halogen lamp for 1 hr in the presence of proflavine hemisulfate (1/100 molar equivalent),  $N_a$ -formyl-3a-hydroxypyrroloindole (7, 13-28%), mp 139-140°, and dimeric pyrroloindoles (8, 16-27%) as a mixture of two isomers were obtained.<sup>4</sup> However, the 2,3-bond

cleaved products were not isolated from this reaction. The structure of 7 was confirmed by the direct comparison with a sample obtained by the  $N_a$ -formylation of 2 ( $R_1 = CO_2Me$ ,  $R_2 = H$ ) and by the hydrolysis to 2 with  $MeOH-NaOH$  at room temperature. The dimeric compounds (8) could be separated by careful chromatography on silica-gel and recrystallization to 8a (racemic), mp 255-256°, and 8b (meso), mp 282-284°. 8a:  $\lambda_{max}^{EtOH}$  nm( $\epsilon$ ); 247(21000), 276<sup>sh</sup>(4300), 286(3400). Mass  $\underline{m/e}$ (%); 490( $M^+$ , 3), 462( $M-CO$ , 7), 217( $(M-2CO)/2$ , 100). NMR( $DMSO-d_6$ )  $\delta$ ; 3.64(s, OMe), 6.06(s, NCHN), 8.88(s, CHO). 8b:  $\lambda_{max}^{EtOH}$  nm( $\epsilon$ ); 249.5(20200), 276.5<sup>sh</sup>(4300), 286.5(3200). Mass  $\underline{m/e}$ (%); 490( $M^+$ , 16), 462(43), 217(100). NMR( $DMSO-d_6$ )  $\delta$ ; 3.34(s, OMe), 5.93(s, NCHN), 8.54(br.s, CHO).

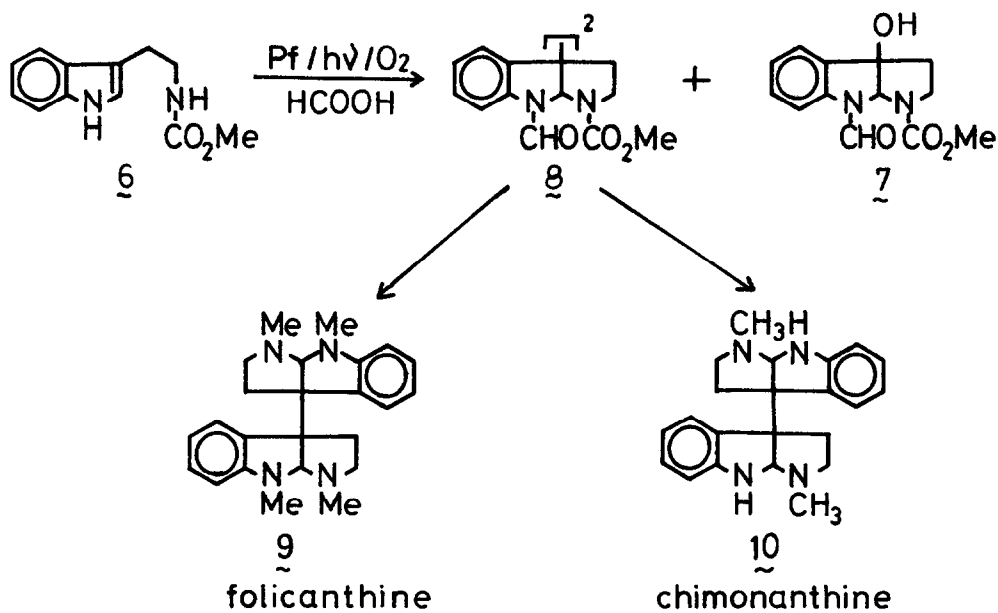
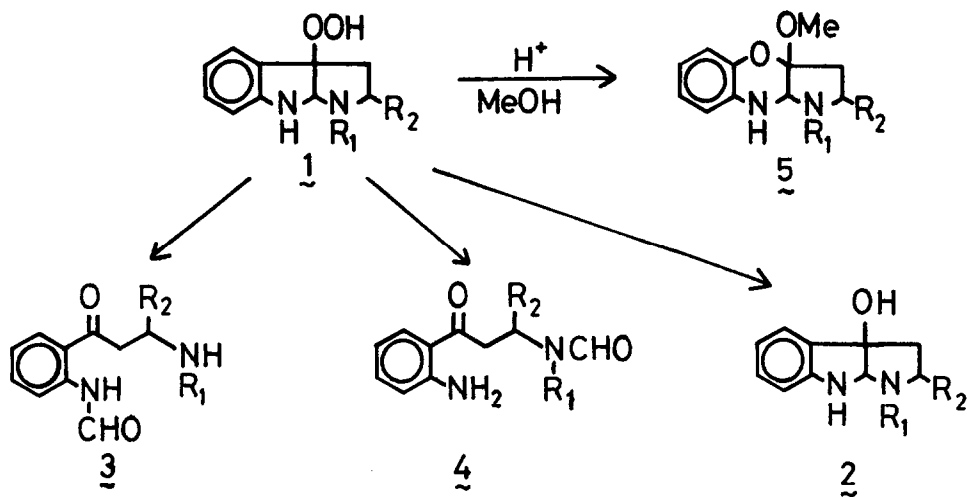
The dimers (8) were not formed when the reaction was carried out under  $N_2$ -atmosphere or in acetic acid. The stereochemistry of 8 has been unequivocally established by  $LiAlH_4$  reduction to chimonanthine and folicanthine which have been isolated from Calycanthaceae plants. Chimonanthine has been synthesized by Hendrickson<sup>5</sup> and Scott<sup>6</sup>, while we have reported a synthesis of folicanthine.<sup>7</sup> Scott and coworkers succeeded in the oxidative dimerization of  $N_b$ -methyltryptamine by ferric chloride oxidation of the indole Grignard reagent, but failed in ferricyanide oxidation of tryptamine derivatives.

$LiAlH_4$  reduction of a mixture of 8a and 8b in boiling ether for 20 hr afforded ( $\pm$ )-folicanthine, mp 167.5-168.5°, in 29% yield, which was identified with a sample obtained by our previous synthesis(mmp and IR). Its NMR spectrum in  $CDCl_3$  was superimposable with that of natural folicanthine. On the other hand,  $LiAlH_4$  reduction of 8b in boiling dioxane gave meso-folicanthine, mp 174-175°, hitherto not reported compound, in 60% yield. The UV and mass spectra of meso-folicanthine were very close to those of rac-folicanthine, but differences were observed in their NMR spectra as shown in Table.

Table The NMR spectra of folicanthenes in  $CDCl_3$

	$C_2, C_3-H$	$N_b-Me$	$N_a-Me$	NCHN	arom. H
racemic	1.6-2.8 <sup>m</sup>	2.40 <sup>s</sup>	3.00 <sup>s</sup>	4.36 <sup>s</sup>	6.1-7.1 <sup>m</sup>
meso	1.8-3.0 <sup>m</sup>	2.40 <sup>s</sup>		3.6-4.6 <sup>br</sup>	6.2-7.2 <sup>m</sup>

Furthermore, hydrolysis of 8a with  $MeOH-10\%NaOH$  to remove  $N_a$ -formyl group followed by  $LiAlH_4$  reduction in boiling tetrahydrofuran provided ( $\pm$ )-chimonanthine, mp 184-186°, in 29% yield. Under similar conditions a mixture of 8a and 8b gave meso-chimonanthine, mp 198-203°, and ( $\pm$ )-chimonanthine. Spectral data(UV, mass, and NMR) and mp of these compounds agreed with those<sup>6</sup> reported. Furthermore, ( $\pm$ )-chimonanthine was converted to ( $\pm$ )-calycanthine



in boiling acetic acid as reported.<sup>6</sup> Accordingly, 8a has racemic structure and 8b is meso isomer.

Similar results were obtained by the oxygenation of N<sub>a</sub>-methyl-N<sub>b</sub>-methoxycarbonyltryptamine and N<sub>b</sub>-benzyloxycarbonyltryptamine. Both compounds gave the corresponding dimeric products which were converted to folicanthines. The mechanism of the oxidative dimerization by the sensitized photooxygenation is not clear at present, but simple hydrogen abstraction from N<sub>a</sub>-H can be excluded due to the fact that the N<sub>a</sub>-methyl derivative also provides dimeric products.

Although oxidative dimerization by dye-sensitized photooxygenation is restricted to N<sub>b</sub>-acyltryptamines at present, it may represent an example for wider application of dye-sensitized photooxygenation in the biomimetic synthesis of natural products.

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#### References and notes

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