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THE STRUCTURE OF A TREMORGENIC METABOLITE FROM ASPERGILLUS FUMIGATUS FRES., FUMITREMORGIN A.

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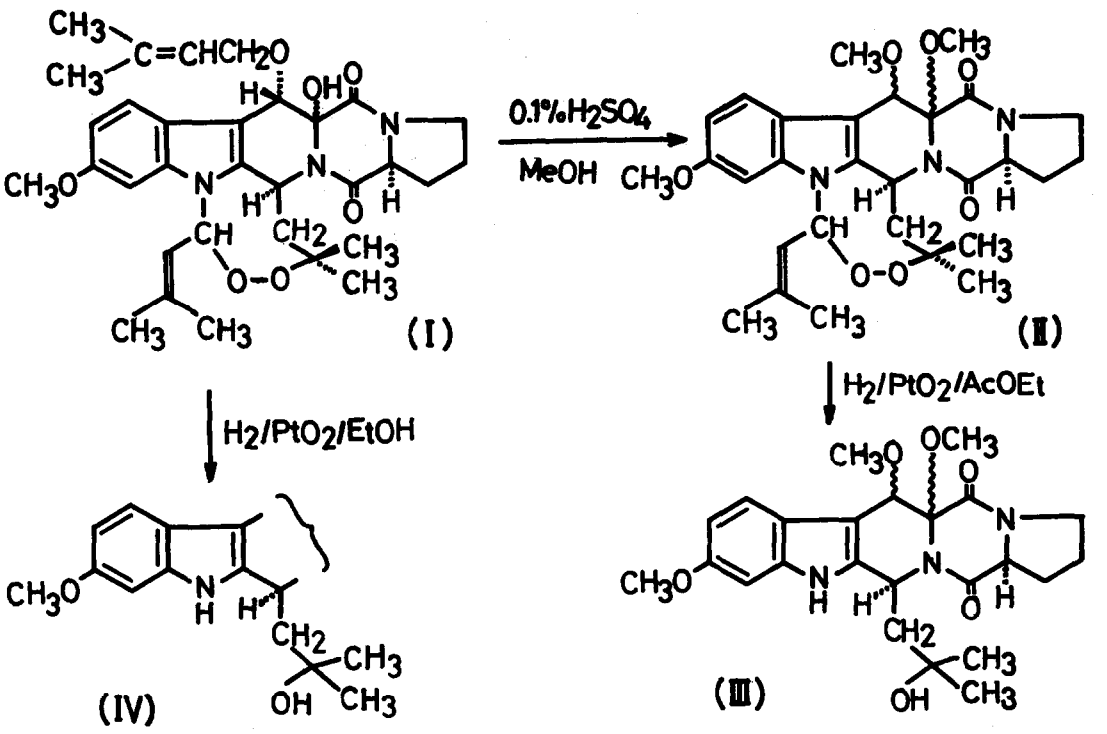
Fumitremorgin A (FTA), one of two potent tremorgenic toxins isolated from a strain of Aspergillus fumigatus Fres.[1], $C_{32}H_{41}O_7N_3$ (M^+ 579), mp 206-209°, $[\alpha]_D^{10}$ +61° (acetone), showed the similar UV and IR spectra to those of fumitremorgin B (FTB),[1,2] $C_{27}H_{33}O_5N_3$ on which structure[2] and absolute configuration[3] we have already reported. From the PMR data, it was expected that only one hydroxyl group was present in FTA but two (one of two was secondary) in FTB. (Table I)
FTA as well as FTB afforded proline by acid hydrolysis with 6N-HCl. In isotope feeding experiment, tryptophan-3-^{14}C, proline-U-^{14}C and mevalonic acid-2-^{14}C were well incorporated into FTA as well as into FTB. The difference between the formulae of FTA and B was C_5H_8 and O_2.

By refluxing with 0.1% H_2SO_4 in methanol, FTA gave a degradation product (II) $C_{29}H_{37}O_7N_3$ (M^+ 539), mp 222-224° (decomp.). The UV and IR spectra of II were very similar to those of FTA except no OH absorption bands were observed in the IR of II. In the PMR spectrum of II, two signals of CH_3-O at 3.16 and 3.38ppm newly appeared whereas the signals, 1.71 and 1.81ppm ($\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!=$), 5.60ppm (triplet,-CH=) and 4.71ppm (quartet,-CH_2-O-) which were originally present in that of FTA disappeared. This indicated the elimination of isopentenyl ether from FTA and the new formation of two methoxyl groups in II by the acid treatment of FTA.

On hydrogenation of II over Adams catalyst in ethyl acetate, a product (III) $C_{24}H_{31}O_6N_3$ (M^+ 457), mp 218-219°(decomp.) was obtained. The UV spectrum of III, λ_{max}(ε) 223(41,000), 265(4,600), 296(6,200), 302(sh.5,200), was slightly different from those of FTA, B and also II, but very similar to that of a model



compound,7-methoxytetrahydrocarbazol, indicating that III contained the 6-methoxyindole ring which had no substituent on N_1. In the IR spectrum, absorption bands of OH or NH at ~3370cm^{-1}, amide at 1665 and 1655cm^{-1} and aliphatic ether at 1096 cm^{-1} were observed. The presence of OH and NH in III was also suggested from the PMR analysis of III in which the signals of tertiary OH at 2.50ppm (br.singlet) and NH of the indole at 10.00ppm (both disappeared by D_2O treatment) were observed. While the signals of two olefinic methyls, an olefinic proton and a proton of C-CH-N disappeared in the spectrum of III. It was presumably considered that the isopentenyl group attached to N_1 of the indole ring might be removed by the catalytic hydrogenation. Attempt to hydrogenate FTA itself provided the similar result as a new appearance of OH and NH and simultaneous disappearance of the isopentenyl signals were observed in the PMR spectrum of the hydrogenated product (IV).

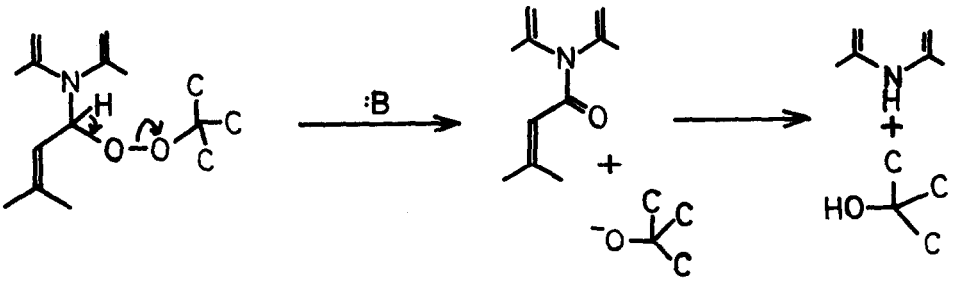
It is known that a secondary-tertiary dialkyl peroxide gives a ketone and a tertiary alcohol by treatment with Lewis base or electron donors.[4] Accordingly, it was assumed that the two extra oxygen atoms in FTA were those of the secondary-tertiary dialkyl peroxide and formed ketone (subsequently removed) and tertiary alcohol by the catalytic hydrogenation.

Table I.

P.M.R. data of I, II, III and IV (δ (ppm) from TMS in $CDCl_3$)

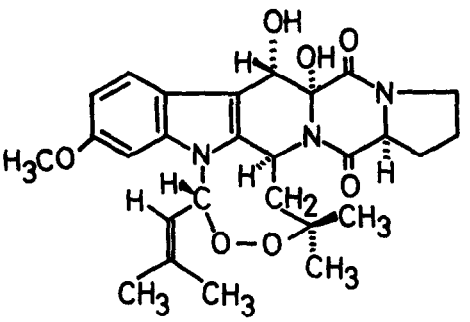
Compound	I	II	III	IV
$\underline{CH_3}$-CH=C<	——	——	——	0.77 (3H, d.) 0.83 (3H, d.)
$\underline{CH_3}$-C(=O)-C	0.99 (3H, s.) 2.00 (3H, s.)	1.14 (3H, s.) 2.00 (3H, s.)	1.42 (3H, s.) 1.71 (3H, s.)	1.28 (3H, s.) 1.48 (3H, s.)
$\underline{CH_3}$-C=C	1.71 (6H, s.) 1.81 (6H, s.)	1.68 (3H, s.) 1.76 (3H, s.)	——	——
$\underline{CH_3}$-O-C	3.84 (3H, s.)	3.16 (3H, s.) 3.38 (3H, s.) 3.85 (3H, s.)	3.22 (3H, s.) 3.42 (3H, s.) 3.86 (3H, s.)	3.80 (3H, s.)
C-$\underline{CH_2}$-C C-$\underline{CH}$=C	1.60-2.20(4H, m.) 2.40 (2H, m.)	1.60-2.30(4H, m.) 2.50 (2H, m.)	1.60-2.30(4H, m.) 2.44 (2H, m.)	1.20-2.30(7H, m.) 2.44 (2H, m.)
C-$\underline{CH_2}$-N	3.63 (2H, m.)	3.78 (2H, m.)	3.80 (2H, m.)	3.60 (2H, m.)
C-$\underline{CH_2}$-O	4.71 (2H, br. q.)	——	——	3.60 (2H, m.)
C-$\underline{CH}$=C	5.02 (H, br. d.) 5.60 (H, br. t.)	4.74 (H, br. d.)	——	——
C-$\underline{CH}$-N	5.06 (H, t.) 6.13 (H, br. d.)	4.26 (H, q.) 6.61 (H, d.)	4.28 (H, q.) 6.00 (H, br. d.)	4.30 (H, m.) 6.04 (H, br. q.)
C-$\underline{CH}$-O	5.50 (H, s.)	5.00 (H, s.)	5.03 (H, s.)	4.77 (H, s.)
C-$\underline{CH}$-O	6.62 (H, d.)	6.74 (H, d.)	——	——
$\underline{H}$-O-C	4.48 (H, s.)	——	2.50 (H, br. s.)	2.94 (H, br. s.) 4.64 (H, br. s.)
aromatic H	6.59 (H, d.) 6.82 (H, q.) 7.68 (H, d.)	6.68 (H, d.) 6.86 (H, q.) 7.50 (H, d.)	6.79 (H, q.) 6.84 (H, d.) 7.44 (H, d.)	6.76 (H, q.) 6.85 (H, d.) 7.38 (H, d.)
$\underline{H}$-N-C	——	——	10.00 (H, br. s.)	9.72 (H, br. s.)

s. : singlet, d. : doublet, t. : triplet, q. : quartet,
m. : multiplet, br. : broad.



Conclusively, the structure of FTA was shown as I. The difference between the chemical shifts of two methyls, 0.99 and 2.00ppm, in the PMR of FTA could be explained consistently by postulating the presence of 8-membered ring which included peroxide -O-O- in FTA. The two methyls direct upward (internal) and downward (outside) of the ring, respectively.

The spectrum of CMR of FTA was also observed as being quite consistent with the structure as shown as I. Quite recently, the structure of verruculogen isolated from Penicillium verruculosum has been deduced from a X-ray diffraction experiment, which showed very close similarity to that we proposed for FTA.[5] The stereostructure of FTA should be identical to that of verruculogen since they have close similarity of the structure and the biological activity.



verruculogen

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