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STRUCTURE DETERMINATION OF SIX TRYPTOQUIVALINE-RELATED METABOLITES FROM ASPERGILLUS FUMIGATUS

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Eight indole-containing metabolites (tentatively named FTA-H) have been isolated from Aspergillus fumigatus and the structures of two among them, fumitremorgins A and B(FTA and B) being strongly tremorgenic, have already been elucidated by us.[1] The remaining six(FTC-H) have different chemical and spectral properties from that of FTA or B and no detectable tremorgenic effect to the experimental animals.

FTC(I), mp.215-217°(decomp), $[\alpha]_D^{28}$+168°(c=0.23, $CHCl_3$), $C_{29}H_{30}N_4O_7$(M^+, m/e 546) exhibits the absorption maxima at 228(39800), 233(38000), 255(21100), 280(14200), 307(4200) and 320 (2700) nm(ε) in the uv spectrum. From the ir spectrum, the presence of hydroxyl, γ-lactone, ester and amide groups in the structure is expected. The pmr spectral data on FTC are summarized in Table together with those of the other metabolites and an acetate. During our study on FTC structure is under way, Clardy et al. have reported the result of X-ray analysis on tryptoquivaline structure,[2] and the properties reported therein on that fungal metabolite suggest the close similarity of that to our FTC although two are not entirely identical. A direct comparison of FTC-acetate (II) with acetate of tryptoquivaline has shown their complete identity as a result. This indicates that FTC is an isomer of tryptoquivaline regarding the position of acetyl group. By treatment with alkali, I receives epimerization possibly at C-12 and the epimer further affords acetate(III), amorph., $[\alpha]_D^{24.5}$-199°, $C_{31}H_{32}N_4O_8$, with Ac_2O/pyridine, which seems to be identical with the epimer-acetate from tryptoquivaline.[2]

FTD(IV), mp.224-225°(decomp), $[\alpha]_D^{28}$+115°(c=0.23, $CHCl_3$), $C_{28}H_{28}N_4O_7$(M^+, m/e 532) exhibits quite similar uv and ir spectra to those of I. Very equivalent signals are also observed in the pmr spectrum of IV comparing with those of I, although a doublet methyl(1.56ppm) appears instead of two singlet methyls(1.48ppm and 1.50ppm) in the spectrum of I. Both I and IV are oxidized with CrO_3/90% AcOH and afford the same product, compound A, mp.154.5-157°, $[\alpha]_D^{28}$+228°, $C_{25}H_{23}N_3O_6$(M^+, m/e 461.1583). The structure of compound A has been determined by the chemical and spectral studies as V. The fact suggests that I and IV may have the similar structures

Table PMR Data of FTC (I), D (IV), E (VIII), F-Ac (XI), G (XII), and H (XIV) (δ(ppm) from TMS)

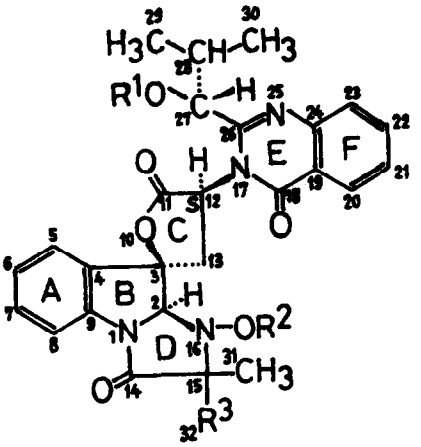
	-CH$_3$			-CH$_2$-		-CH-			aromatic =CH-				C-OH	N-OH
	29 or 30	31 or 32	Ac	13	13	28	15	2	27	12	5,6,7,8, 21,22,23	20	26	27	16
a) in $CDCl_3$															
FTC	1.04 (d.,6) 1.14 (d.,6)	1.48 (s.) 1.50 (s.)	2.17 (s.)	3.03 (d.d.,14,10)	3.20	2.67 (m.)		4.99 (s.)	5.59 (d.,9)	5.67 (t.,10)	7.33 - 7.93 (7H,m.)	8.22 (1H.d.,8)		7.08 (s.)	
FTD	0.97 (d.,7) 1.09 (d.,7)	1.56 (d.,7)	2.14 (s.)	2.93 (d.d.,14, 9)	3.19	2.57 (m.)	4.32 (q.,7)	5.10 (s.)	5.61 (d.,8)	5.74 (t.,9)	7.11 - 7.99 (7H,m.)	8.24 (1H,d.,8)		7.26 (s.)	
FTF-Ac		1.68 (d.,7)	2.15 (s.)	3.16 (d.d.,13, 9)	3.33		4.44 (q.,7)	5.65 (s.)		5.40 (t.,9)	7.48 - 8.11 (7H,m.)	8.41 (1H,d.,7)	8.04 (1H,s.)		
b) in Pyridine-d_5															
FTE		1.63 (d.,7)		3.38 (d.d.,13,10)	3.56		4.26 (q.,7)	5.42 (s.)		6.48 (t.,10)	6.83 - 7.80 (7H,m.)	8.17 (1H,d.,8)	8.59 or 8.66 *) (1H,s.)		10.42 (br.s.)
FTG		1.50 (s.) 1.62 (s.)		3.43 (d.d.,14,10)	3.64			5.30 (s.)		6.56 (t.,10)	6.96 - 7.96 (7H,m.)	8.23 (1H,d.,8)	8.66 (1H,s.)		10.64 (br.s.)
FTH		1.45 (d.,8)		2.96 (d.d.,13,10)	3.60		3.98 (q.,8)	5.25 (s.)		5.76 (t.,10)	6.68 - 7.88 (7H,m.)	8.11 (1H,d.,8)	8.38 or 8.41 *) (1H,s.)		10.60 (br.s.)
c) in Dimethylsulfoxide-d_6															
FTE		1.43 (d.,7)		unassignable **)			4.01 (q.,7)	5.38 (s.)		6.20 (t.,10)	7.17 - 8.10 (7H,m.)	8.22 (1H,d.,8)	8.57 (1H,s.)		8.52 (br.s.)
FTG		1.30 (s.) 1.35 (s.)		unassignable **)				5.16 (s.)		6.16 (t.,10)	7.16 - 8.04 (7H,m.)	8.20 (1H,d.,7)	8.52 (1H,s.)		8.41 (br.s.)
FTH		1.48 (d.,6)		unassignable **)			un-assign-able **)	5.46 (s.)		5.62 (t.,10)	7.16 - 8.08 (7H,m.)	8.22 (1H,d.,6)	8.49 (1H,s.)		8.75 (s.)

Coupling pattern and/or coupling constant(Hz) of signals are shown in parentheses.

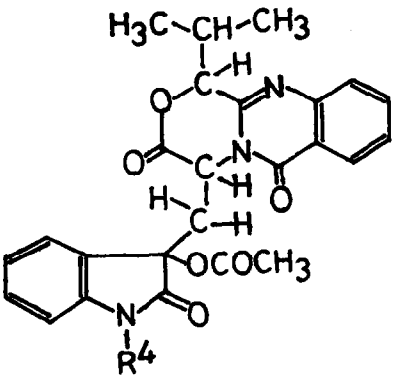
s.: singlet, d.: doublet, t.: triplet, q.: quartet, m.: multiplet, br.: broad.

*) Either one of the two is expected of the signal from the solvent.

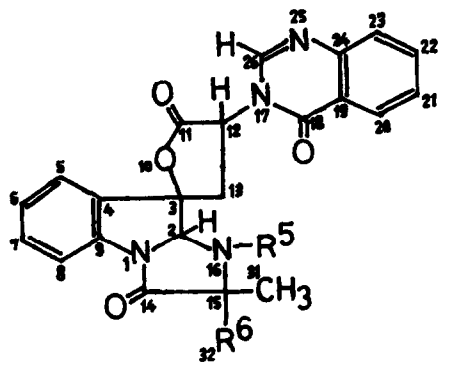
**) Overlapped with the signal of water in the solvent.



Tryptoquivaline[2],
(R^1: $COCH_3$, R^2: H, R^3: CH_3).
FTC (Isotryptoquivaline) (I),
(R^1: H, R^2: $COCH_3$, R^3: CH_3).
FTC acetate (II) = Tryptoquivaline acetate[2],
($R^1 = R^2$: $COCH_3$, R^3: CH_3).
12-epi-FTC acetate (III) = 12-epi-Tryptoquivaline acetate[2],
($R^1 = R^2$: $COCH_3$, R^3: CH_3, C-12: R-configuration).
FTD (Norisotryptoquivaline) (IV),
(R^1: H, R^2: $COCH_3$, R^3: H).
FTD acetate (VII),
($R^1 = R^2$: $COCH_3$, R^3: H).



Compound A (V), (R^4: H).
λ_{max}^{MeOH} nm(ε),225.5(44000),260(10700),268(11000),280(8400),307(4500),318(3400).
$\nu_{max}^{CHCl_3}$ cm^{-1},3425,1800,1755,1745,1685.
δ(ppm) from TMS in $CDCl_3$,1.07(3H,d.,J=7Hz), 1.19(3H,d.,7),2.15(3H,s.),2.52(1H,m.),2.67(1H,d.d.,14,9),3.51(1H,d.d.,14,9),5.56(1H,d.,9),5.79(1H,t.,9),7.04-7.80(7H,m.),8.32(1H,br.d.,8),9.07(1H,br.s.,>NH).
Compound A acetate (VI), (R^4: $COCH_3$).
mp. 134-137°, $C_{27}H_{25}N_3O_7$(M^+,m/e503).
δ(ppm) from TMS in $CDCl_3$,2.07(3H,s.),2.68(3H,s.),no NH.



FTE (VIII), (R^5: OH, R^6: H).
FTE acetate (IX), (R^5: $OCOCH_3$, R^6: H).
FTF (X), (R^5: H, R^6: H).
FTF acetate (XI), (R^5: $COCH_3$, R^6: H).
FTG (XII), (R^5: OH, R^6: CH_3)
FTG acetate (XIII), (R^5: $OCOCH_3$, R^6: CH_3).
FTH (XIV, epimer of FTE), (R^5: OH, R^6: H).
FTH acetate (XV), (R^5: $OCOCH_3$, R^6: H).

including stereochemistry except their D rings which are decomposed during the oxidation reaction. The configuration at C-15 in IV would be estimated as S if this part is supposed to be derived biogenetically from L-alanine which has S configuration at the assymmetric carbon.

The uv spectra of FTE, F, G and H are also quite similar to that of I or IV and all of these compounds are expected to have OH or NH and carbonyl groups from their ir spectral data. A detailed comparison of the pmr spectra of these compounds with I or IV(Table) easily shows that these compounds have very many features in common and have close similarity to that of I or IV. The physico chemical properties of these compounds are shown as follows: FTE(VIII), mp.~240°(decomp), $[\alpha]_D^{11.5}$ +257°(c=0.009, $CHCl_3$), $C_{22}H_{18}N_4O_5$(M^+, m/e 418). FTF(X), mp.~283°(decomp), $[\alpha]_D^{15.5}$ -109° (c=0.006, $CHCl_3$), $C_{22}H_{18}N_4O_4$(M^+, m/e 402.128). FTG(XII), mp.240-241.5°(decomp), $[\alpha]_D^{11}$ +215° (c=0.011, acetone), $C_{23}H_{20}N_4O_5$(M^+, m/e 432.139). FTH(XIV), mp.239-241°(decomp). $[\alpha]_D^{11}$ -155° (c=0.021, acetone), $C_{22}H_{18}N_4O_5$(M^+, m/e 418.127).

Among them, XIV gives the similar mass spectral pattern but the opposite optical rotation comparing with VIII. In the pmr spectrum, the signal pattern of XIV regarding to the $-CH_2CH<$ system in the ring C resembles to that of III nevertheless that of VIII resembles to that of I. Accordingly XIV could be estimated as being 12-epimer of VIII and a possible artefact from VIII. X has also minus optical rotation but it is obscure whether this is an artefact or not.

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References

1) M. Yamazaki, H. Fujimoto, T. Kawasaki, Tetrahedron Letters, 1975, 1241, and references cited therein.

2) J. Clardy, J. P. Springer, G. Büchi, K. Matsuo, R. Wightman, J. Am. Chem. Soc, 97, 663 (1975).