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CORRELATION OF COTYLENOL WITH THE AGLYCONE OF FUSICOCCIN*

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Key Word Index—Ascomycetes; diterpenes; fusicoccins; cotylenins; cotylenol; structural correlation.

Abstract—The stereostructure of cotylenol, the aglycone of the cotylenins, has been confirmed by chemical correlation with the aglycone of fusicoccin A.

INTRODUCTION

Fusicoccins and cotylenins are fungal metabolites which share a large number of activities with higher plants[1]. The structures proposed for the two types of compounds are very similar, but while those of the fusicoccins have been confirmed by X-ray investigations[2–6], those of the cotylenins have been deduced from chemical and spectroscopic evidence only[7–10]. Therefore, it was felt to be desirable to confirm the stereostructure assigned to cotylenol (**1**), the aglycone moiety common to all cotylenins, through a direct correlation with the aglycone of fusicoccin A (**2**). Such a correlation became feasible when it was observed[11] that permanganate oxidation of some fusicoccins yields with high stereo- and regio-specificity the corresponding 3α-hydroxy derivatives; of particular relevance for the present work is the conversion of the *O*, *O'*-isopropylidene derivative of fusicoccin A aglycone (**3**) into **4**.

RESULTS AND DISCUSSION

Attempts to convert by permanganate oxidation the *O*, *O'*-isopropylidene derivative of the 12,19-deoxy-aglycone of fusicoccin (**5**), prepared from **3** in three steps[18], to *O*, *O'*-isopropylidenecotylenol (**6**) consistently failed. This failure was attributed to the absence of a hydroxyl group on C-12 of the substrate, since all positive results previously obtained by this oxidative reaction involved the use of fusicoccin derivatives having hydroxyl groups either on both C-12 and C-19, or on C-12 only[11]. The significance of a hydroxyl group already present in the substrate to the course of the oxidation had been noted for some aliphatic and monoterpene compounds[12]. Therefore, an alternative approach was tried. Compound **4** was reacted with mesyl choride to afford the 12,19-dimesylderivative (**7**), which was treated with potassium *t*-butoxide to give the tetraene (**8**). The tetraene was then converted by catalytic hydrogenation to a product identical to a sample of *O*, *O'*-isopropylidenecotylenol (**6**) which had been prepared by reacting cotylenol (**1**) with 2,2-dimethoxypropane and a trace of *p*-toluenesulphonic acid in *N*,*N*-dimethylformamide. All attempts to convert **6** to **1** by acid hydrolysis of the isopropylidene group failed on account of the lability of the hydroxyl group on C-3[9]. While the assignment of the α-orientation to the C-3 hydroxyl group of **6** relies on the same evidence as that reported in previous papers [11, 13–15], the chirality of carbon atoms 6, 7, 8, 9 and 11 is obviously the same as in fusicoccin A aglycone (**2**). Thus the stereochemistry attributed by Sassa *et al.*[9] to **1** is confirmed by the present investigation, and in consequence the interpretation of the results obtained with several cotylenins in studies concerning structure–activity relationships of fusicoccins [1, 16, 17] is correct.

EXPERIMENTAL

General methods. Mps are uncorr; ^{1}H NMR: 270 MHz, $CDCl_3$, TMS as int. standard; MS: 70 eV; TLC spots were visualized by spraying with 10% H_2SO_4 in MeOH and then heating at 105°.

12,19 - *Deoxy* - O,O'-*isopropylideneaglycone of fusicoccin* (**5**). The tetraene (**9**) [18] (132 mg) was added to a suspension of 10% Pd–$BaSO_4$ (263 mg) in THF (190 ml); hydrogenation was carried out overnight at room temp. with stirring. After filtration the solvent was evapd and the residue was purified by CC (Si gel). Elution with $CHCl_3$ gave a homogeneous substance which crystallized from MeOH at −20° yielding white needles of **5** (118 mg); mp 87–88°; $[\alpha]_D^{25}$ −10.1 (*c* 2.12, $CHCl_3$); UV $\lambda_{max}^{CHCl_3}$ nm: <220; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1370–1380 (Me–CH–Me); ^{1}H NMR: δ 0.92 (3H, *d*, *J* = 7 Hz, 17-Me), 0.98 and 1.01 (3H each, *d*, *J* = 7 Hz, 19 and 20-Me), 1.09 (3H, *s*, 18-Me), 1.27 and 1.52 (3H each, *s*, two Me of isopropylidene group), 3.26 (3H, *s*, 21-Me), 3.32 (1H, *m*, H-15; 2H, *m*, H_2-16; by ^{1}H NMDR), 3.94 (1H, *dd*, *J* = 10 and *J* = 5 Hz, H-8), 4.16 (1H, *d*, *J* = 10 Hz, H-9) and 5.52 (1H, *t*,

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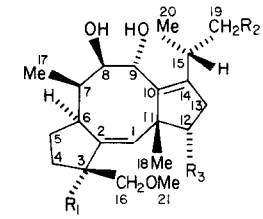
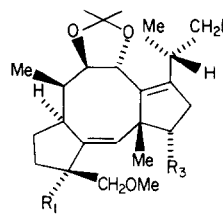
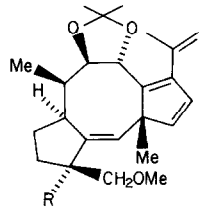


1 R_1 = OH; R_2 = R_3 = H (cotylenol)
2 R_1 = H; R_2 = R_3 = OH (fusicoccin aglycone)



3 R_1 = H; R_2 = R_3 = OH
4 R_1 = R_2 = R_3 = OH
5 R_1 = R_2 = R_3 = H
6 R_1 = OH; R_2 = R_3 = H
7 R_1 = OH; R_2 = R_3 = OSO_2Me



8 R = OH
9 R = H

J = 1.5 Hz, H-1); MS *m/z* (rel. int.): 374 $[M]^+$ (86), 359 (54), 301 (100).

3α-Hydroxy-12, 19-dimesyl-O,O'-isopropylideneaglycone of fusicoccin (**7**). To a soln of 3α-hydroxy-*O,O'*-isopropyldeneaglycone of fusicoccin (550 mg) (**4**) [11] in dry pyridine (3.4 ml), CH_3SO_2Cl (0.40 ml) was slowly added at 0°. After standing 2 hr at room temp. the mixture was poured onto ice and then extracted with Et_2O. The extracts were evapd to leave a residue (616 mg) (**7**) which crystallized from Et_2O; mp 153–155°; $[\alpha]_D^{25}$ +15.6 (*c* 1.25, $CHCl_3$); UV λ_{max}^{MeOH} nm: <220; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530 (OH); ^1H NMR: δ0.98 (3H, *d*, J = 7 Hz, 17-Me), 1.18 (3H, *d*, J = 7 Hz, 20-Me), 1.28 (3H, *s*, 18-Me), 1.38 and 1.52 (3H each, *s*, two Me of isopropylidene group), 2.65 (1H, *d*, J_{AB} = 18 Hz, H-13), 2.82 (1H, *dd*, J_{AB} = 18 Hz, J_{AX} = 4.5 Hz, H-13), 3.09 and 3.06 (3H each, *s*, two Me of mesyl groups), 3.42 (1H, *d*, J_{AB} = 9 Hz, H-16), 3.46 (3H, *s*, 21-Me), 3.56 (1H, *d*, J_{AB} = 9 Hz, H-16), 4.02 (2H, *m*, H_2-19), 4.76 (1H, *d*, J = 4.5 Hz, H-12), 5.58 (1H, *d*, J = 0.5 Hz, H-1); MS *m/z* (rel. int.): 560 $[M-H_2O]^+$ (16), 533 (96), 502 (24), 482 (100).

3α-Hydroxy-tetraene (**8**). To a stirred soln of **7** (472 mg) in dry DMSO (37.7 ml) at 85°, freshly sublimated *tert*-BuOK (1.41 g) was added in one portion. After 15 min the reaction was stopped with H_2O (60 ml) and the aq. phase extracted with Et_2O. The extracts were washed with 10% H_2SO_4, H_2O, $NaHCO_3$ (satd soln) and H_2O to neutrality and evapd to give a residue which was purified first on TLC (Si gel: $CHCl_3$-*iso* PrOH, 99:1) and then on a column of neutral Al_2O_3 grade III (Et_2O as solvent). The residue of **8** crystallized from Et_2O (187 mg); mp 135–137°; $[\alpha]_D^{25}$ +7.3 (*c* 3.22, $CHCl_3$); UV λ_{max}^{hexane} nm: 275 (ε 2200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH); ^1H NMR: δ 0.92 (3H, *d*, J = 7 Hz, 17-Me), 1.29 (3H, *s*, 18-Me), 1.33 and 1.40 (3H each, *s*, two Me of isopropylidene group), 1.87 (3H, *s*, 20-Me), 2.71 (1H, *m*, H-6), 2.93 (1H, *d*, J_{AB} = 9 Hz, H-16), 3.12 (1H, *d*, J_{AB} = 9 Hz, H-16), 3.31 (3H, *s*, 21-Me), 4.02 (1H, *dd*, J = 9 and J = 4.5 Hz, H-8), 4.35 (1H, *d*, J = 9 Hz, H-9), 4.97 (2H, *m*, H-19), 5.64 (1H, *d*, J = 1.5 Hz, H-1), 6.06 (1H, *d*, J_{AB} = 6 Hz, H-13), 6.22 (1H, *d*, J_{AB} = 6 Hz, H-12); MS *m/z* (rel. int.): 386 $[M]^+$ (33), 341 (76.6), 283 (100).

O,O'-Isopropylidenecotylenol (**6**). (A) Pure **8** (87.3 mg) was added to a suspension of 10% Pd–$BaSO_4$ (500 mg) in THF (270 ml); hydrogenation was carried out overnight at room temp. with stirring. The catalyst was removed by filtration, the solvent evapd and the residue purified by TLC on 5% $AgNO_3$–Si gel ($CHCl_3$-*iso*-PrOH, 99:1) and then by CC on Si gel (hexane–EtOAc, 7:3). The residue crystallized for hexane–EtOAc (7:3) as needles (**6**) (30 mg); mp 104–106°; $[\alpha]_D^{25}$ −28.4 (c 0.5, $CHCl_3$); UV λ_{max}^{MeOH} nm: <220; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH), 1370–1380 (Me–CH–Me); ^1H NMR: δ 1.30 and 1.46 (3H each, *s*, two Me of isopropylidene group), 2.86 (1H, *m*, H-6), 3.16 (1H, *d*, J_{AB} = 9 Hz, H-16), 3.34 (1H, *d*, J_{AB} = 9 Hz, H-16; 1H, *m*, H-15; 3H, *s*, 21-Me; by ^1H NMDR), 3.90 (1H, *dd*, J = 12 and J = 4.5 Hz, H-8), 4.05 (1H, *d*, J = 12 Hz, H-9), 5.58 (1H, *d*, J = 1.5 Hz, H-1); MS *m/z* (rel. int.): 390 $[M]^+$ (25), 345 (100), 287 (85).

(B). Cotylenol (**1**) (30 mg) dissolved in DMF (0.9 ml) and 2,2-dimethoxypropane (0.9 ml), was treated with a trace of *p*-toluenesulphonic acid. After 30 min at room temp. the mixture was treated with $NaHCO_3$ (5%) and then extracted with EtOAc. The organic phase was washed with H_2O and evapd. The residue was crystallized from hexane–EtOAc (7:3) to yield a product identical in all respects [$[\alpha]_D^{25}$ −29.1 (*c* 0.5 $CHCl_3$), R_f in $CHCl_3$-*iso*-PrOH (19:1), hexane–EtOAc (7:3) and C_6H_6–Me_2CO (3:2), UV, IR, ^1H NMR and MS] to **6** prepared by route (A).

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