Tetrahedron Letters No. 42, pp 3827 - 3830, 1976. Pergamon Press. Printed in Great Britain.

STRUCTURE OF ILICICOLIN H, AN ANTIFUNGAL ANTIBIOTIC

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(Received in Japan 20 August 1976; received in UK for publication 6 September 1976)

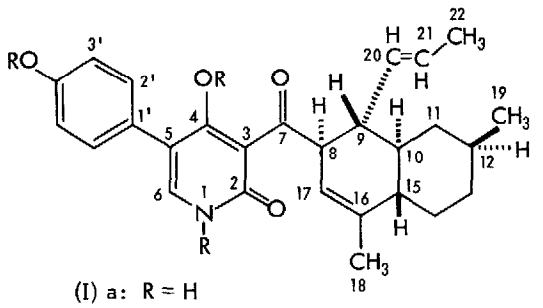
We have isolated ilicicolin H[1] (Ia), an antifungal antibiotic from the mycelium of an imperfect fungus, Cylindrocladium ilicicola.

Ilicicolin H (Ia), $C_{27}H_{31}NO_4$ [m.p. 144-150 , $[\alpha]_D^{23}$ -17.4°, M^+ 433, λ_{max}^{EtOH} 248 nm (ε 23,200), 349 (5,300)], has hydroxy groups and a lactam ring (ν_{max} 3590-3400, 1653 cm^{-1}). On treatment with dimethylsulfate, it gave a trimethyl derivative (Ib) [δ 3.90 and 3.60 ($2OCH_3$), δ 3.48 (NCH_3), ν_{max} 1694 (C=C·CO), 1646 cm^{-1}]. In its ^1H n.m.r. spectrum, Ia exhibited a methyl at δ 0.88 (d), two vinyl methyls at δ 1.55 (d) and 1.59 (s), three vinyl protons at δ 5.34, 5.27, and 5.17, a singlet vinyl proton at δ 7.31, four vinyl protons at δ 7.07 (AA'BB' type, $\Delta\nu_{AB}$ 45.0 Hz, J_{AB} 8.4 Hz: 1,4-subst. Ar.), and one proton[2] exchanged with D_2O at δ 16.55 (-C(OH)=C·CO).

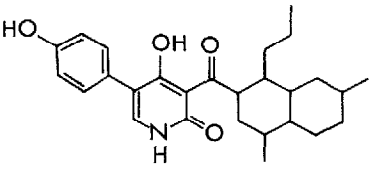
Ilicicolin H (Ia) gave p-hydroxybenzoic acid on alkaline peroxide oxidation, indicating that it has a p-hydroxyphenyl substituent. On hydrogenation with 10% Pd-C in ethanol, Ia afforded a tetrahydro derivative (II) with the only significant difference being the disappearance of the absorption of the E-ethylenic double bond in the i.r. With PtO_2 in acetic acid, it absorbed more than five moles of hydrogen to give three products (III, IV, and V), which had almost the same i.r. and u.v. spectra [235 nm (ε 9,000), 280 (5,000), and 340 (8,000)] and no longer showed signals due to the p-hydroxyphenyl group in the ^1H n.m.r.

On heating under reflux in hydrochloric acid and acetic acid, III ($C_{27}H_{41}NO_3$) gave a lactam (VI), $C_{11}H_{15}NO_2$, and a carboxylic acid (VII), $C_{16}H_{28}O_2$. The lactam (VI) was assumed to be a 4-hydroxy-pyridone-2 derivative[3-5] from spectral data [ν_{max} 3500-2300 and 1644 cm^{-1}, λ_{max} 285 nm (ε 3,700), δ 5.83 (s, vinyl H) and 7.10 (s, vinyl H)]. The combined results suggest that III has a β-diketone system and is a 3-acyl-4-hydroxy-pyridone-2 derivative. In the ^1H n.m.r. spectrum, the broad singlet-like signal of the vinyl proton in III or VI at δ 7.10 ($W\frac{1}{2}$ 4 Hz) became a sharp singlet by exchange of the active proton with deuterium by addition of D_2O. This fact indicates that the vinyl proton is coupled with the proton of the NH group and is at the C-6 position of the 2-pyridone ring. These results lead to the conclusion that ilicicolin H has a conjugated system represented by the formula Ia, which is the same as that of tenellin,[2] a metabolite of Beauveria sp.

On the other hand, the carboxylic acid (VII) gave an alcohol (VIII), $C_{15}H_{28}O$, m.p. 100-102°, and its epimer (IX), m.p. 75-77°, by m-chloroperbenzoic acid oxidation of the acid chloride (VII + $SOCl_2$),



(I) a: R = H
b: R = CH_3



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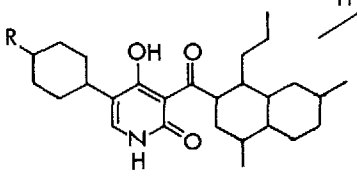
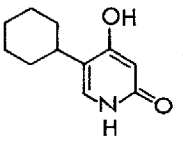
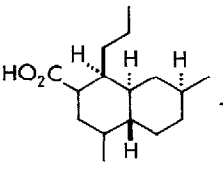


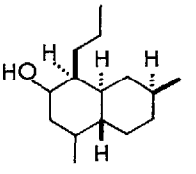
(III) R: H
(IV) and (V) R = OH



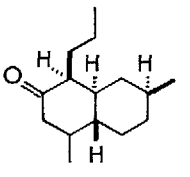
(VI)



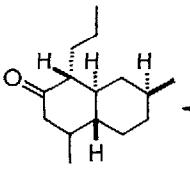
(VII)



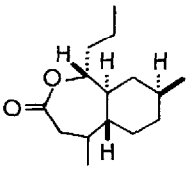
(VIII) and (IX)



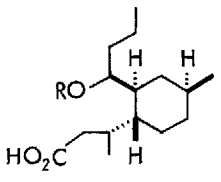
(X)



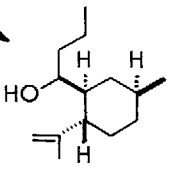
(XI)



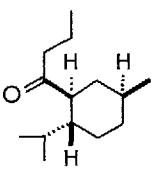
(XII)



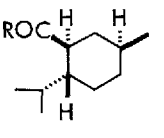
(XIII) a: R = H
b: R = Ac



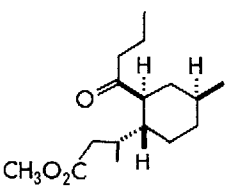
(XIV)



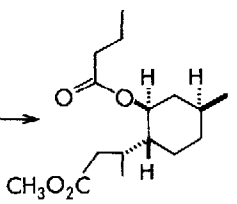
(XV)



(XVI) R = OH
(XVII) R = NH



(XVIII)



(XIX)

$CH_3CH_2CH_2COOH$

H2

i) SOCl2
ii) O

O

H+

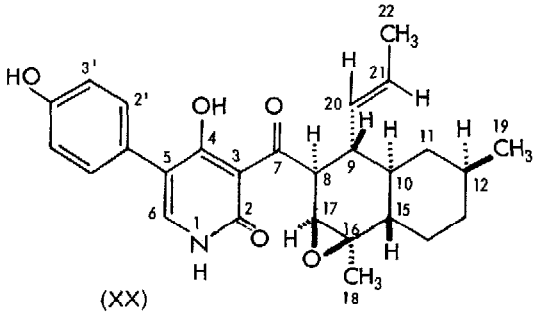
i) OH⁻
ii) Ac2O

i) Pb(OAc)4
ii) OH⁻

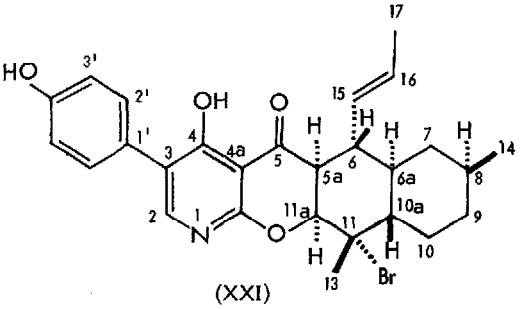
i) H2
ii) O

i) CH2N2
ii) O

OH⁻



(XX)



(XXI)

Table 1. Chemical Shifts (δ) in $CDCl_3$

	Ia	XX	XXI
6-H (2-H)	7.31 (s)	7.33 (s)	8.25 (s)
8-H (5a-H)	4.95 (dd)	4.75 (dd)	3.26 (dd)
9-H (6-H)	2.54 (ddd)	2.47 (m)	~2.01 (m)
17-H (11a-H)	5.27 (d)	3.30 (d)	4.68 (d)
18-H (13-H)	1.59 (s)	1.27 (s)	2.03 (s)
19-H (14-H)	0.88 (d)	0.88 (d)	0.86 (d)
20-H (15-H)	5.17 (ddq)	5.04 (ddq)	~5.15 (m)
21-H (16-H)	5.34 (dq)	5.40 (dq)	~5.15 (m)
22-H (17-H)	1.55 (d)	1.55 (d)	1.64 (d)
2'-H	6.89 (m)	6.90 (m)	6.95 (m)
3'-H	7.24 (m)	7.25 (m)	7.42 (m)

Proton numbers for formula XXI are given in the parentheses.

Table 2. Coupling Constants (J = Hz)

	Ia	XX	XXI
$J_{8,9}$ ($J_{5a,6}$)	10.4	11.1	11.8
$J_{9,10}$ ($J_{6,6a}$)	~10	~10	...
$J_{8,17}$ ($J_{5a,11a}$)	~3	2.0	2.3
$J_{9,20}$ ($J_{6,15}$)	~9	9.0	...
$J_{20,21}$ ($J_{15,16}$)	~15	15.2	15.2
$J_{21,22}$ ($J_{16,17}$)	~6	6.0	...

Proton numbers for formula XXI are given in the parentheses.

followed by hydrolysis with an alkali. When the alcohol (VIII or IX) was oxidized with Jones' reagent, it gave an unstable ketone (X), which was easily isomerized to a stable ketone (XI) against an acid or an alkali. On Baeyer-Villiger reaction with m-chloroperbenzoic acid, the ketone (XI) gave a lactone (XII), $C_{15}H_{26}O_2$.

When a carboxylic acid (XIIIb), obtained from hydrolysis of XII followed by acetylation, was treated with lead tetraacetate and cupric acetate in benzene and then hydrolyzed with an alkali, it gave an unsaturated alcohol (XIV), $C_{14}H_{26}O$ [δ 0.93 (doublet CH_3 and triplet CH_3), δ 1.69 (vinyl CH_3), δ 4.73 (2H, vinyl H)]. The alcohol (XIV) afforded a ketone (XV), $C_{14}H_{26}O$, by hydrogenation with 10% Pd-C followed by Jones' oxidation.

The Baeyer-Villiger reaction of XV with m-chloroperbenzoic acid or trifluoroperacetic acid was unsuccessful. Moreover, although the reaction of a keto ester (XVIII) derived from the methyl ester of the acid (XIIIa) afforded an ester (XIX), the yield was very poor; this oxidation reaction was abandoned. However, hydrolysis of the ester (XIX) gave n-butyric acid. This showed that the ketone (XV or XIX) has the n-butyroyl function.

On air oxidation with potassium t-butoxide in dimethylformamide, the ketone (XV) gave a carboxylic acid (XVI), which was converted into its acid anilide (XVII), $C_{17}H_{25}NO$, m.p. 151-152°, $[\alpha]_D^{22}$ +58.7°. Although the anilide was identified with an authentic sample of (-)-menthanecarboxylic acid anilide[6] by comparison of the i.r. and the mass spectra and t.l.c. values, it possesses an opposite rotatory power.

Therefore, the acid was confirmed to be (+)-menthanecarboxylic acid (XVI), and the absolute configuration of carboxylic acid VII was represented by the formula VII except for the configuration of the carboxyl group.

The absolute configuration of ilicicolin H (Ia) was clarified by further detailed double- and triple-resonance experiments of *ilicicolin H and its derivatives (XX and XXI) in 100-MHz* ^{1}H n.m.r. *Ilicicolin H* afforded a monoepoxide (XX), $C_{27}H_{31}NO_5$, by peracid oxidation; its structure was elucidated as 16,17-epoxy-ilicicolin H by n.m.r. study. Moreover, bromination of Ia with phenyltrimethylammonium perbromide gave a monobromide (XXI), the spectral data of which indicate that it is a brominated cyclization product represented by the formula XXI. ^{1}H n.m.r. data of Ia, XX, and XXI are shown in Tables 1 and 2.

As shown in Table 2, $J_{8,9}$ was 10.4 and 11.1 Hz in Ia and XX, respectively, and $J_{9,10}$ was ~10 Hz in both compounds. Therefore, 8- and 9-H and 9- and 10-H are both in transdiaxial relationship.* $J_{20,21}$ in Ia, XX, and XXI indicates that the double bond is an E-ethylenic one. Thus, the absolute configuration of ilicicolin H is structure Ia.

The authors are very much indebted to Dr. K. Tori and Dr. M. Ueyama for conducting the double- and triple-resonance experiments in ^{1}H n.m.r. *and their helpful advice.*

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* Assuming that III was derived from double bond migration of Ia followed by hydrogenation, it is reasonable that the configuration of the propyl group in the acid (VII) is reversed.