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STRUCTURE OF PATULOLIDE A, A NEW MACROLIDE FROM PENICILLIUM URTICAE MUTANTS

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Abstract: A new macrolide named patulolide A was isolated from the culture broth of Penicillium urticae mutants. The structure and absolute configuration of it was determined.

In the course of isolating secondary metabolites from the patulin-minus mutants, Penicillium urticae S11(ATCC 48165)[1,2] and P. urticae S11R59 we have isolated a new compoud which we named patulolide A(1). The strain S11R59 was grown in glucose-yeast extract medium[1] at 28°C for 72 h and the culture filtrate was extracted with $CHCl_3$. The extract was developed on a preparative TLC with C_6H_6-petroleum ether-$CHCl_3$-EtOAc(6:4:1:1). The band of patulolide A was located on TLC by UV light. This compound was also detected as bright yellow spot on TLC plate with 3-methyl-2-benzothiazolinonehydrazone monohydrate[1]. Patulolide A was crystallized from n-hexane at 4°C(mp 83-84°C, 18 mg from 1 l culture).

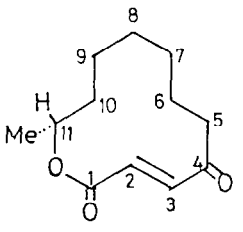
Patulolide A was characterized by the following physicochemical properties. Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%. Found : C, 67.84; H, 8.63%. LRMS m/z: 210(M^+), 142, 114, 97, 96, 83, 82, 81, 69, 55. $[\alpha]_D^{25}$=+30.1° (c=0.95, in EtOH). UV λ_{max}($CHCl_3$): 240 nm (ε 3620). IR(KBr) ν_{max} cm^{-1}: 3390(s), 3320(s), 3070(s), 3030(s), 2935, 2860, 1700, 1680, 1620, 1465, 1340, 1310, 1260, 1200, 980.
^1H nmr (100 MHz, CCl_4, TMS) δ : 7.25(1H, d, J=16.0 Hz, olefinic proton), 6.45 (1H, d, 16.0 Hz, olefinic proton), 4.91(1H, m, H-C-O), 2.44(2H, t, J=6 Hz, CH_2CO), 1.8-1.2(10H, m), 1.35(3H, d, J=6 Hz, C-CH_3). ^{13}C nmr(60 MHz, $CDCl_3$) δ : 20.1(q, CH_3), 22.4, 24.5, 25.8, 25.9, 34.9(CH_2), 39.2(t, $\underline{C}H_2CO$), 74.9(d, CH-O), 147.7(d, =CH), 129.8(d, =CH), 166.6(s, COO-), 202.4(s, C=O). NMDR shows the coupling between the protons at δ 1.35 and 4.91. These fact

indicated presence of CH_3-CH-O partial structure. On the basis of these NMR and spectroscopic data, the structure of patulolide A was assinged as **1**.

In order to determine the absolute configuration at C-11, patulolide A was converted to the ester **4** as following steps. Patilolide A was hydrogenated (Pd-C MeOH) to dihydropatulolide A(3) in 78% yield[6]. The lactone **3** was hydrolyzed with KOH in MeOH-H_2O at R. T. for 12 h to give 4-oxo-11-hydroxydodecanoic acid. mp 57-58°C. IR(Nujol)ν_{max}: 1700 cm^1. ^1H nmr($CDCl_3$)δ:3.9(1H, m, CH-O), 2.8-2.5(4H, broad, CH_2CO), 2.4(2H, t, CH_2CO), 1.2(3H, d, J=6Hz CH_3). Methyl ester(**4**): $[\alpha]_D^{23}$=-5.64°(c=1.16,MeOH). ^1H nmr($CDCl_3$) :3.65(3H,s,OCH_3).

The ester **4**(21.6 mg) was treated with 2-phenylbutanoic anhydride(54.8 mg, 2 equiv) in pyridine according to Horeau's procedure[3] to yield the corresponding ester in 96% yield. The specific rotation of recovered 2-phenylbutanoic acid was $[\alpha]_D^{23}$=+ 5.75°(c=2.3, in C_6H_6) which established R configuration at C-11. This absolute configuration is same with that of R-(-)-pyrenophorin[4,5] which has same functional groups and the similar skeleton as patulolide A.

Patulolide A has a weak antibiotic activity and as the structurally similar compound, cladosplide A(**2**) isolated from a fungus Cladosporium fulvum FI-113 is a phytotoxin[7], it is interested in investigating effects of patulolide A on plants.



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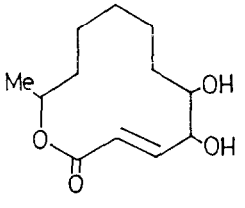

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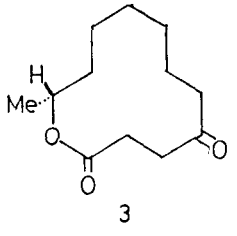

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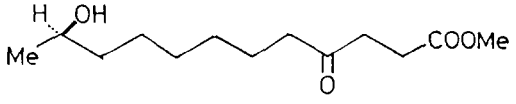

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6) IR(film) ν_{max} cm^{-1}: 1730, 1720. ^1H nmr($CDCl_3$)δ :4.90(1H, m, CH-O), 3.2-2.1 (6H, m, CH_2CO9, 1.18(3H, d, J=6 Hz, CH_3). Mass m/z: 212(M^+).

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