Communication to the editor

POLYENE ANTIBIOTICS. VI THE STRUCTURES OF DERMOSTATINS A AND B[1]

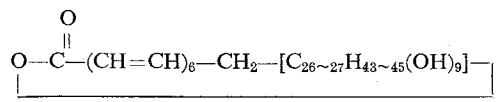
Sir:

Polyene antibiotics have assumed increasing importance in very recent years, with the reports of their activities in reducing benign prostatic hyperplasia[2] and in lowering blood cholesterol level[3]. Structures of heptaenes, pentaenes, and tetraenes are thus far recorded[4]. We assign in the present report structures **1A** and **1B** to dermostatins A and B, the two components of the hexaene[5] antibiotic dermostatin (viridofulvin), which has been shown to be active against fungi[6a] and useful in the treatment of fungal infections[6b].

The mass spectrum of dermostatin acetate [mp 146~147°C, $[\alpha]_D^{23}$ −59.8° (*c* 1.37, $CHCl_3$), no OH absorption in ir spectrum] shows it to be a mixture of two homologs, **2A** and **2B**, with molecular ions at *m/e* 1098.5378 ($C_{58}H_{82}O_{20}$, Calcd. 1098.5399) and *m/e* 1112.5576 ($C_{59}H_{84}O_{20}$, Calcd. 1112.5555),* corresponding to nona-acetates (**2A**, **2B**) of dermostatins A and B ($C_{40}H_{64}O_{11}$ and $C_{41}H_{66}O_{11}$), respectively. Formulation as a nona-acetate is based on the nmr spectrum of dermostatin acetate (mixture of two homologs), which showed singlet peaks corresponding to nine acetyl groups at δ 2.00 (6H), 2.04 (9H), 2.06 (9H), and 2.12 (3H). Thus, nine of the oxygen atoms in dermostatin are present in hydroxyl groups. Since dermostatin does not react rapidly with periodate, no hydroxyl groups are in *vicinal* glycol pairs.

The remaining two oxygen atoms are in a conjugated ester group absorbing in the infrared at 1700 cm^{-1} but shifting to 1740 cm^{-1} on hydrogenation of **1** to tetradecahydrodermostatin [$C_{40}H_{78}O_{11}$ and $C_{41}H_{80}O_{11}$, mp 100~102°C, $[\alpha]_D^{23}$ +5.8° (*c* 1.87, MeOH),* characterized as tetradecahydrodermostatin nona-acetate $[\alpha]_D^{23}$ +16.6° (*c* 1.94, $CHCl_3$), $M^{+\cdot}$ 1112 and 1126; and nona-O-methyltetradecahydrodermostatin, $M^{+\cdot}$ 860 and 874]. The ester function must, moreover, be a lactone since dermostatin is converted by exhaustive (modified COPE) reduction[4a,8] to a saturated hydrocarbon ($C_{40}H_{82}$, $C_{41}H_{84}$; $M^{+\cdot}$ 562, 576 by gc-ms) with the same number of carbon atoms as **1** and by CEDER reduction[4a,8] to an acid [$C_{40}H_{80}O_2$ and $C_{41}H_{82}O_2$, characterized as its methyl ester $C_{41}H_{82}O_2$ (Found: 606.6301; Calcd. 606.6314) and $C_{42}H_{84}O_2$ (620.6459; 620.6471)] with the same number of carbon atoms as **1**. The relative amounts of **1A** and **1B** can be estimated from the gas chromatograms of the saturated hydrocarbon (1.00 : 1.18) and methyl ester (1.00 : 1.47) as approximately 43 % dermostatin A and 57 % dermostatin B.

The electronic maximum of dermostatin appears at 385 nm, appropriate for a hexaene conjugated to a carbonyl group[9]. Since the conjugated lactone is the only carbonyl group in dermostatin it must be conjugated to the hexaene chromophore, thus accounting for eight of the nine double bonds or rings defined by the molecular formulas of dermostatins A and B. An additional alkene group is indicated by the seven-mole hydrogen uptake by **1**. Oxidation of tetradecahydrodermostatin with 70 % nitric acid gives 1,15-pentadecanedioic acid, as well as 1,14-tetradecanedioic acid from over-oxidation, identified by gc-ms of their dimethyl esters. Thus, partial structure **a** is defined.



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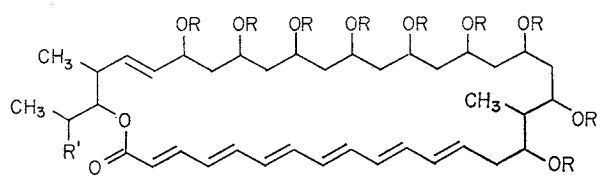
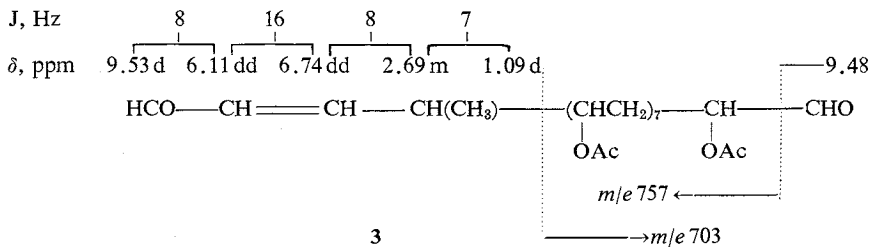


1A: R=H, R'=CH_3 **2A**: R=Ac, R'=CH_3

1B: R=H, R'=CH_2CH_3 **2B**: R=Ac, R'=CH_2CH_3

Ozonolysis of dermostatin nona-acetate (**2**) at −60°C, followed by treatment with dimethyl sulfide[10] and silica gel chromatography gave the α,β-unsaturated dialdehyde **3** ($C_{37}H_{54}O_{19}$, $[\alpha]_D^{26}$ +28.57° (*c* 0.7, $CHCl_3$) uv_{max} 220 nm, ε 10,544], whose mass spectrum showed a weak molecular ion at *m/e* 786 and stronger ions at

* Microanalyses[7] agree with the formulas given.



3

m/e 757 and 703 for loss of the groups indicated. The nmr spectrum of **3** contained the absorptions shown, as well as eight acetate methyl groups at δ 2.14 (3H), 2.04 (3H), 2.01 (6H), 1.99 (3H), 1.98 (3H), and 1.96 (6H). The positions of the eight acetoxyl groups follow from the lack of periodate uptake of dermostatin. The ninth acetoxyl of **2** must have undergone β-elimination in isolation of **3**.

Ozonolysis at −10°C, followed by hydrogenolysis over platinum oxide, steam distillation, 2, 4-dinitrophenylhydrazone formation, and preparative tlc, gave the mixed 2, 4-DNP's [mp 145~146°, uv_{max} 376 nm, ε 24,700, $M^{+\cdot}$ *m/e* 292.1178 ($C_{13}H_{16}N_4O_4$, Calcd. 292.1184) and 306.1325 ($C_{14}H_{18}N_4O_4$, Calcd. 306.1327)] of 2, 4-dimethyl-2-pentaenal and 2, 4-dimethyl-2-hexaenal[11], whose nmr spectrum assigned the structures and confirmed the mixture.

The unsaturation in the DNP's must have arisen from β-elimination of the lactone function during steam distillation. Other positions for the lactone ring are eliminated by the acetylation of the C-17, C-19, C-21, C-23, C-25, C-27, C-29, and C-31 hydroxyls (found in **3**), the inability of a lactone to form at C-15 due to the rigidity of the hexaene system, and the appearance of the C-34 methyl as a doublet in the nmr spectra of **1** and **2**.

Fitting the molecular fragments defined by **3** and **4** into partial structure **a** requires formula **1A** for dermostatin A and **1B** for dermostatin B. The present structures assigned dermostatins A and B resemble closely those assigned mycoticins A and B earlier[11], but with one extra —CH=CH— group and one extra —$CHOHCH_2$— group.

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RAMESH C. PANDEY
KENNETH L. RINEHART, Jr.
DAVID S. MILLINGTON
Roger Adams Laboratory
University of Illinois,
Urbana, Illinois 61801, U.S.A.
MALLIKARJUN B. SWAMI
Antibiotics Research Centre,
Hindustan Antibiotics, Ltd.,
Pimpri, India

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