STRUCTURES OF HALOMICINS A AND C

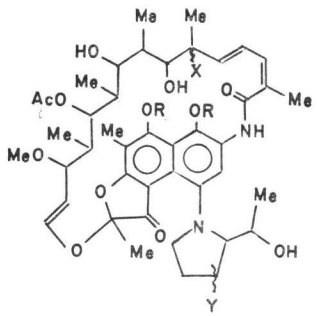
Sir:

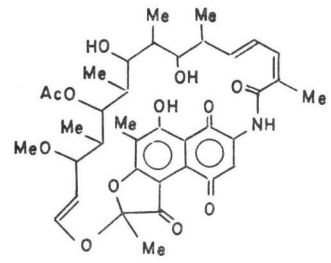
Halomicins (A→D) belong to the group of ansamycin antibiotics and are produced by *Micromonospora halophytica*[1]. They are highly active against gram-positive bacteria. We have disclosed[2] earlier the structure of halomicin B (**1**). In this communication we report the high resolution mass spectral fragmentation of halomicin B di-O-methyl ether (**2**) (see Chart 1) and its application in the elucidation of the structures of halomicins A (**3**) and C (**4**). Both of these components were produced in extremely small amounts in the fermentation and were isolated from the antibiotics complex using preparative TLC. Due to the scarcity of the material the investigations of the stereochemical details of these antibiotics were limited.

Halomicin A (**3**) is a yellow crystalline solid $C_{43}H_{58}N_2O_{13}$, m.p. 192~194°C, $[\alpha]_D$ +100.5°, λ_{max} 234(48,000), 302(16,700) and 419 nm(14,160). Mass spectrum[3] of **3** $(M+1)^+$ peak at *m/e* 811 and its fragmentation pattern parallels that of halomicin B di-O-methyl ether (**2**) and showed ions *d*, *e* and *f* at *m/e* 596, 508 and 386, respectively, indicating that halomicin A has an extra hydroxyl group in the pyrrolidine ring.

On treatment with nitrous acid halomicin A (**3**) yielded rifamycin S (**5**) and a basic compound (**6**) which was converted immediately into a tritosylate (**7**), $C_{27}H_{31}NO_8S_3$, m.p. 140~141°C, $[\theta]^{228}$ +17,500. Mass spectrum of **7** besides showing a weak molecular ion peak at *m/e* 593 showed peaks at *m/e* 438 ($M-C_7H_7SO_2$), 422 ($M-C_7H_7SO_3$) and 394 ($M-CH_3CH\text{-}OSO_2\text{-}C_6H_4\text{-}CH_3$). NMR spectrum of **7** besides showing the presence of three tosyl groups showed signals at δ 1.34 (*d*, J 7Hz, methyl), 1.7~2.2 (m, 2H, H_4), 2.8~3.18 (m, 2H, H_5), 3.66 (1H, broad dd, J= ~ 3Hz, H_2), 4.8~5.0 (2H, H_3 and H_6; octet and a degenerate doublet).

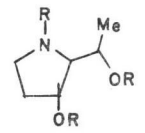
Halomicin C (**4**) is a yellow amorphous solid, $C_{43}H_{58}N_2O_{13}$ (M^+ 810) $[\alpha]_D$ +153°, ν_{max} 3350, 3300, 1705, 1250, 1670 cm^{-1}, λ_{max} 237 (38,300), 301 (10,900) and 420 nm (16,400). On methylation with diazomethane halomicin C gave a mixture of products from which halomicin C di-O-methyl ether (**8**) was obtained as yellow amorphous compound, $C_{45}H_{62}N_2O_{13}$, $[\alpha]_D$ + 320°. Besides showing the molecular ion peak at *m/e* 838 the mass spectrum of **8** also showed strong peaks at *m/e* 536 and 398 for ions *g* and *c* respectively. Halomicin C di-O-methyl ether (**8**) also showed prominent loss of *m/e* 17 (OH) and *m/e* 45 (CH_3CHOH) from the molecular ion and also from ions *g* and *c*. The loss of *m/e* 45 parallels that of halomicin B and its dimethyl ether fragmentation which has been shown by

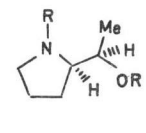




(5)

(1) X=Y=H; R=H
(2) X=Y=H; R=CH_3
(3) X=R=H; Y=OH
(4) Y=R=H; X=OH
(8) Y=H; X=OH; R=CH_3

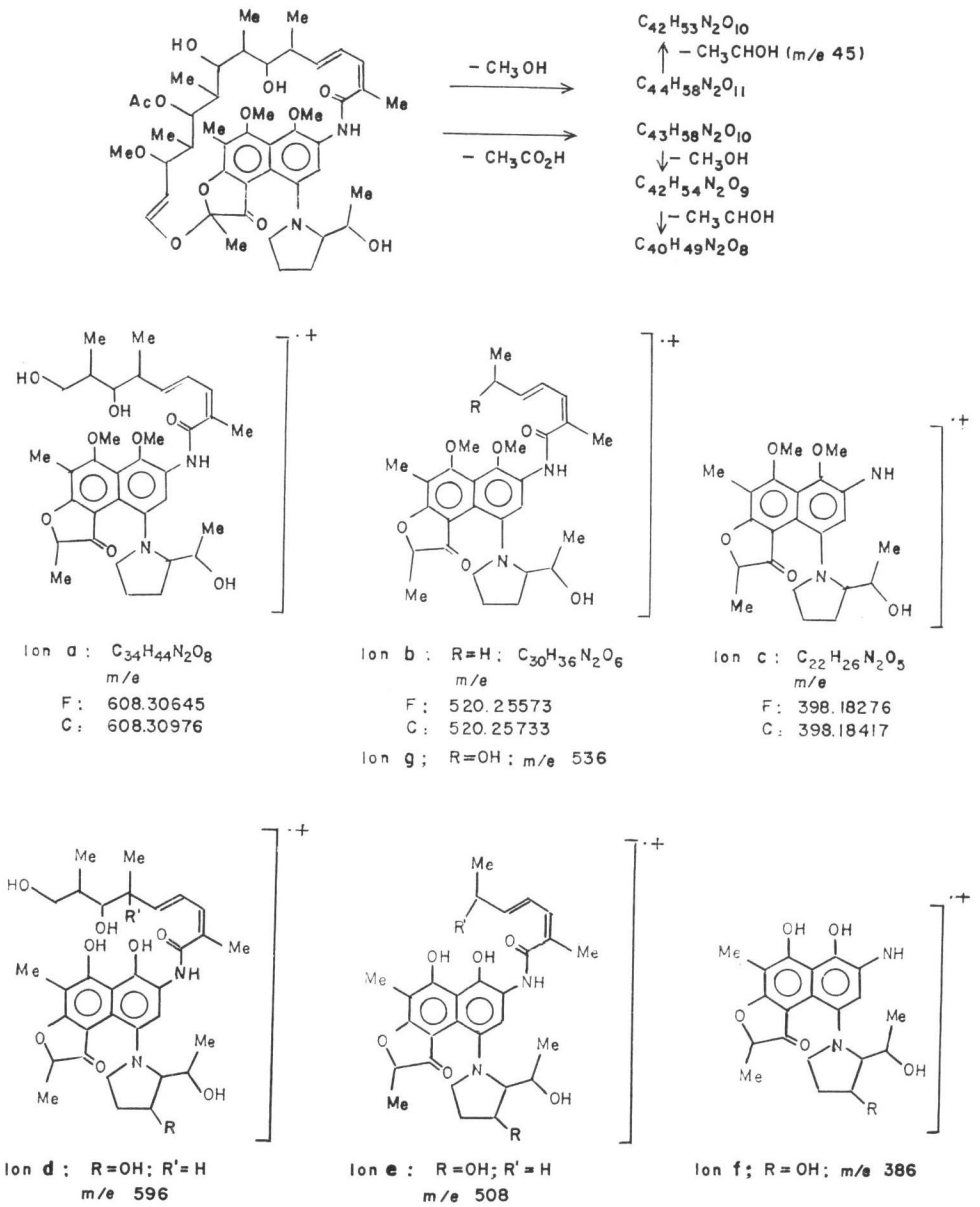




(6) R=H
(7) R=$-SO_2-C_6H_4-CH_3$

(9) R=H
(10) R=$-SO_2-C_6H_4-CH_3$

Chart 1.



high resolution mass spectrometry to be due to the loss of the hydroxy ethyl side chain of the pyrrolidine ring. It is evident, therefore, that halomicin C is 20-hydroxy halomicin B.

The NMR spectrum of the dimethyl ether of halomicin C (**8**) is consistent with the assigned structure and very similar to the n.m.r. spectrum of halomicin B di-O-methyl ether excepting that the C_{20}-methyl in **8** appeared as a singlet compared to a doublet in **2**. Degradation of halomicin C (**4**) with nitrous acid yielded a basic compound (**9**) which was characterized as a N-O-ditosylate (**10**) by direct comparison with an authentic sample[2] (m.p., m.m.p., IR, CD, mass, and NMR).

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