9-*O*-ESTERS OF NODUSMICIN

Sir:

Nodusmicin (**1**) is a 10-membered macrolide antibiotic which possesses modest antibacterial activity against staphylococci[1]. When the 9-hydroxyl group is esterified with pyrrole-2-carboxylic acid, the antibiotic is known as nargenicin A_1 (**2**)[2].* This antibiotic is much more potent to staphylococci than nodusmicin. We now disclose the conversion of nodusmicin to nargenicin A_1 and the formation of other antibacterially potent 9-*O*-esters of nodusmicin.

When **1** was treated with pyrrole-2-carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) in THF[3], **2** was isolated in 8.1% yield. In addition, 18-*O*-pyrrole-2′-carbonylnodusmicin (**3**) (10.0% yield) and 9,18-*O*-dipyrrole-2′-carbonylnodusmicin (**4**) (4.1% yield) were also isolated and identified.**

In order to attain a more efficient process, the reactive 18-hydroxyl of nodusmicin was blocked as the *t*-butyldimethylsilyl ether so that esterification would be directed to the 9-hydroxyl. When nodusmicin was treated with *t*-butyldimethylsilyl chloride in the presence of imidazole[4] in methylene chloride, 18-*O*-*t*-butyldimethylsilyl ether **5** was obtained in high yield. In addition 9,18-disilyl ether **6** was isolated in varying amounts. Structural assignments were made on the basis of ^{13}C NMR data which are summarized in Table 1. Introduction of the 18-*O*-silyl ether into nodusmicin to give silyl ether **5** produced a downfield shift in the ^{13}C NMR spectrum for C-18, but no change for carbons 9 and 11, indicating the substituent to be at C-18. Disilyl ether **6** showed a downfield shift for C-18 and also for C-9 indicative of a 9, 18-disilyl ether. In addition to the assignments shown in Table 1, compounds **5** and **6** gave absorptions characteristic of mono and di-*t*-butyldimethylsilyl ethers, respectively. Note that carbons adjacent to the *O*-silyl ethers remained essentially unchanged. These assignments were confirmed by evaluation of 200 MHz ^1H NMR spectra.

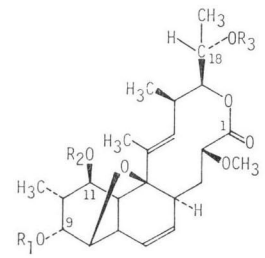
* As suggested by WHALEY[1], macrolide style numbering, in which the carbonyl carbon is C-1, is used for these antibiotics.

** New compounds gave acceptable ^{13}C NMR spectra and high resolution mass spectra including measurement of the exact mass of M^+.

Esterification of silyl ether **5** with acid chlorides-pyridine, or preferably with carboxylic acids, DCC, and DMAP followed by unblocking with Bu_4NF afforded 9-*O*-esters indicated in Table 2. In addition to 9-*O*-esters, varying amounts of 11-*O*-esters and 9,11-*O*-diesters were isolated in low yield.

^{13}C NMR was definitive for establishing structure of these esters. For example, chemical shifts for benzoate esters **7**, **8**, and **9** are included in Table 1. Ester **7** exhibited a downfield shift of the carbon 9 and an upfield shift of the adjacent

Chart 1.



1 $R_1 = R_2 = R_3 = H$

2 R_1 = pyrrole-2-CO; $R_2 = R_3 = H$

3 $R_1 = R_2 = H$; R_3 = pyrrole-2-CO

4 $R_1 = R_3$ = pyrrole-2-CO; $R_2 = H$

5 $R_1 = R_2 = H$; $R_3 = -Si$

6 $R_2 = H$; $R_1 = R_3 = -Si$

7 R_1 = benzoyl; $R_2 = H$; $R_3 = -Si$

8 $R_1 = H$; R_2 = benzoyl; $R_3 = -Si$

9 $R_1 = R_2$ = benzoyl; $R_3 = -Si$

Table 1. ^{13}C NMR shifts for nodusmicin derivatives.

Carbon	Chemical shift δ(ppm)					
	1	**5**	**6**	**7**	**8**	**9**
C-8	85.3	85.4	84.8	83.3	84.6	83.5
C-9	72.6	72.6	73.6	75.2	72.4	74.7
C-10	50.3	50.3	49.4	50.3	47.1	46.9
C-11	75.5	75.5	75.8	75.8	78.6	78.4
C-12	36.1	36.2	35.6	35.5	35.4	36.1
C-17	79.2	79.4	79.1	78.4	79.9	79.8
C-18	66.0	68.2	67.7	68.3	68.6	68.6
C-19	21.4	21.4	21.4	21.3	21.3	21.4

Referenced to Me_4Si; Solvent, acetone-d_6.

Table 2. Antibacterial activity of 9-*O*-esters of nodusmicin.

9-*O*-Substituent	MIC (mcg/ml)[a]		
	S. aureus UC-76	*S. aureus*[b] UC-6685	*S. aureus*[b] UC-6690
H (nodusmicin)	125	250	250
Pyrrole-2′-carbonyl (nargenicin A_1)	0.125	0.175	0.175
Pyrrole-3′-carbonyl[c]	0.39	0.39	0.78
Benzoyl	>250	>250	>250
Thiophene-3′-carbonyl	0.5	0.25	0.5
Thiophene-2′-carbonyl	3.9	3.9	3.9
Furane-3′-carbonyl	0.5	0.25	0.5
Furane-2′-carbonyl	7.8	7.8	7.8
4-Methylpyrrole-2′-carbonyl	0.78	0.78	0.78
Nicotinoyl	250	250	250
Picolinoyl	>250	>250	>250
Isonicotinoyl	>250	>250	>250
Pyrrole-2′-acetyl	>100	>100	>100
Pyrrole-2′-acryloyl	>50	>50	>50
L-Prolyl	31.5	62.5	62.5
Δ-3′-L-Prolyl	12.5	12.5	12.5
N-Methylpyrrole-2′-carbonyl	>250	>250	>250

[a] Minimum inhibitory concentrations were determined in Bacto Brain Heart Infusion, Difco.
[b] Staphlococci resistant to multiple antibiotics.
[c] This compound was prepared by a different process which will be the subject of a future communication.

C-8, while C-11 remains unchanged indicating the presence of a new substituent at C-9. Similarly ester **8** showed a downfield shift for C-11 and smaller upfield shifts for adjacent carbons 10 and 12. Both C-9 and C-11 were shifted downfield in the spectrum of diester **9**.

Antibacterial testing data for 9-*O*-esters of nodusmicin expressed as minimum inhibitory concentrations (MIC) are found in Table 2. MIC's *vs.* an antibiotic-susceptible and two antibiotic-resistant strains of staphylococci are given. Several structure-activity relationships are apparent. Five membered heterocyclic acids gave esters with *in vitro* antistaphylococcal activity equal to or approaching that of nargenicin A_1, with the 3′-carbonyl esters being more potent than 2′-carbonyl esters. The various pyridine carboxylic acids gave esters of low activity. Substitution of methyl on nitrogen, moving the carboxyl group away from the aromatic ring, or reduction of the pyrrole ring led to diminution of antibacterial activity.

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