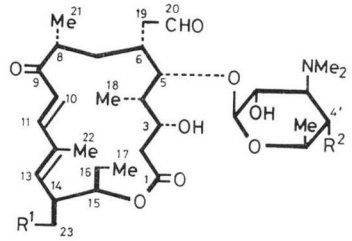
SYNTHESES OF 23-DIALKYLAMINO DERIVATIVES OF MYCAMINOSYL TYLONOLIDE AND 4′-DEOXYMYCAMINOSYL TYLONOLIDE EFFECTIVE AGAINST GRAM-NEGATIVE BACTERIA

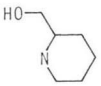
Sir:

In a previous communication[1] we reported the syntheses and antibacterial activities of 23-halo and 23-*O*-substituted mycaminosyl tylonolides and 4′-deoxymycaminosyl tylonolides and it was shown that the 23-modifications gave rise to an increase in the antibacterial activity of mycaminosyl tylonolide (**1a**) and 4′-deoxymycaminosyl tylonolide (**1b**). This paper describes the syntheses of 23-dialkylamino derivatives as an extension of the previous work.

A typical synthetic procedure is as follows. 23-Deoxy-23-iodomycaminosyl tylonolide diethyl acetal (**2a**; compound **16b** in the previous paper[1]) or 4′,23-dideoxy-23-iodomycaminosyl tylonolide diethyl acetal (**2b**; **16a** in the previous paper[1]) described in the previous paper[1] was treated with dimethylamine (*ca.* 8 molar equivalents for **2a** and **2b**) in acetonitrile (*ca.* 20 v/w of the starting material) at 80°C in a sealed tube. After 30 minutes, another portion of dimethylamine (*ca.* 8 molar equiv.) in acetonitrile (as a 5 M solution) was added and the reaction was continued for further 30 minutes at the same temperature. (In some other cases, the reaction was carried out with a single addition of dialkylamine.) Concentration gave a syrup, which was dissolved in chloroform. The solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium sulfate, dried (Na_2SO_4), and concentrated to give a chromatographically homogeneous solid. The 23-*N*-dialkylated product was then hydrolyzed (20°C, 1 hour) with a mixture of 0.1 M aqueous hydrochloric acid and acetonitrile (40 and 20 v/w of the solid, respectively) and, after neutralization with sodium hydrogen carbonate, the product was extracted with chloroform. The crude deacetalated product was subjected to silica gel column chromatography (in most cases the solvent mixture of chloroform - methanol - 28% aqueous ammonia, 20~30: 1: 0.1 was used as the developer) to give pure 23-deoxy- (**3a**, 84%) or 4′,23-dideoxy-23-dimethylaminomycaminosyl tylonolide (**3b**, 80%).

Fig. 1.



	R^1	R^2
1a	OH	OH
1b	〃	H
3a	NMe_2	OH
3b	〃	H
4a	$N(CH_2Me)_2$	OH
4b	〃	H
5a	$N(CH_2CH_2Me)_2$	OH
6a	$N(CH_2CH_2CH_2Me)_2$	OH
7a	$N(CH_2CHMe_2)_2$	OH
7b	〃	H
8b	$N(CH_2)_4$	H
9a	$N(CH_2)_5$	OH
9b	〃	H
10b	$N(CH_2)_6$	H
11b	$N(CH_2)_7$	H
12a	$NMeC_6H_{11}$	OH
13a	$NMeCH_2C_6H_5$	OH
14a	$NMeCH_2CH_2C_6H_5$	OH
15b		H
16b		H
17b		H
18b		H

3a: $[\alpha]_D^{23}$ +18° (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.85 (3H, s, 22-Me), 2.22 (6H, s, C(23)NMe_2), 2.54 (6H, s, C(3′)NMe_2), 4.28 (1H, d, J=7.5 Hz, H-1′), 4.78 (1H, m, H-15), 5.80 (1H, d, $J_{13,14}$=10 Hz, H-13), 6.30 (1H, d, $J_{10,11}$=16 Hz, H-10), 7.42 (1H, d, H-11), 9.80 (1H, s, H-20); *Anal*, Found (Calcd. for $C_{33}H_{56}N_2O_9$): C, 63.70 (63.44); H, 9.02 (9.03); N, 4.25 (4.48).

3b: $[\alpha]_D^{23}$ +23° (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.83 (3H, s, 22-Me), 2.22 (6H, s, C (23)

Table 1. Antibacterial spectra of the products (mcg/ml).

Test organisms*	1a	1b	3a	3b	4a	4b	5a	6a	7a	7b	8b
1. *Staph. aureus* 193	1.56	1.56	0.78	0.2	1.56	0.2	0.2	0.78	3.12	<0.2	0.78
2. 〃 EMf**	>100	>100	>100	>100	>100	>100	100	50	50	50	>100
3. 〃 209P	1.56	0.2	0.39	0.2	1.56	0.2	0.2	0.39	0.78	<0.2	0.39
4. 〃 MS 8710	>100	>100	>100	>100	>100	>100	>100	>100	50	50	>100
5. 〃 MS 9351	>100	>100	>100	>100	>100	>100	>100	>100	100	100	>100
6. 〃 MS 9610	>100	>100	>100	>100	>100	>100	>100	>100	100	100	>100
7. 〃 MS 9861	3.12	1.56	3.12	0.78	25	1.56	3.12	1.56	12.5	0.39	1.56
8. 〃 MS 10246	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9. *M. luteus* PCI 1001	<0.2	<0.2	<0.2	0.2	<0.2	<0.2	<0.2	<0.2	0.2	0.2	<0.2
10. *B. subtilis* NRRL B-558	6.25	0.78	0.39	<0.2	0.39	<0.2	0.2	<0.2	0.78	0.2	0.78
11. *Coryn. bovis* 1810	12.5	0.78	0.78	0.2	0.78	<0.2	<0.2	<0.2	<0.2	<0.2	0.39
12. *E. col* NIHJ	6.25	1.56	1.56	0.2	3.12	0.2	1.56	6.25	50	3.12	0.78
13. 〃 K-12	25	25	6.25	1.56	6.25	1.56	6.25	12.5	100	6.25	3.12
14. 〃 〃 R-5	25	12.5	3.12	0.78	3.12	0.78	3.12	12.5	50	0.78	1.56
15. 〃 〃 ML 1629	100	25	6.25	1.56	12.5	6.25	12.5	25	>100	12.5	3.12
16. 〃 〃 ML 1410	100	12.5	1.56	0.39	3.12	0.39	3.12	6.25	25	0.39	1.56
17. 〃 〃 〃 R81	100	25	12.5	1.56	25	1.56	12.5	25	50	6.25	3.12
18. 〃 〃 LA290 R55	25	3.12	0.78	0.2	1.56	0.2	0.78	1.56	6.25	3.12	1.56
19. *Kl. pneumoniae* PCI 602	3.12	0.39	0.39	<0.2	0.78	<0.2	0.39	0.78	3.12	0.78	0.78
20. *Sh. dysenteriae* JS 11910	0.39	0.2	0.2	<0.2	0.2	<0.2	0.2	0.2	0.39	0.39	<0.2
21. *Sal. enteritidis* 1891	1.56	3.12	0.78	<0.2	1.56	0.39	0.78	1.56	3.12	6.25	0.39
22. *Sal. typhi* T-63	50	25	3.12	1.56	6.25	1.56	6.25	25	50	12.5	3.12
23. *Enter. aerogenes* ATCC 13048 (MS-1)	>100	100	12.5	6.25	50	6.25	25	100	>100	12.5	25
24. *Providencia* sp. Pv 16	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
25. *Serratia marcescens*	>100	100	50	12.5	100	25	50	100	>100	50	12.5
26. *Proteus vulgaris* OX-19	50	12.5	3.12	1.56	3.12	0.78	3.12	12.5	25	12.5	1.56
27. *Ps. aeruginosa* A3	50	50	100	100	>100	100	>100	>100	>100	>100	100
Mean MIC for No. 1~11	16.1	8.03	8.03	4.85	11.7	4.55	4.85	4.85	7.08	2.75	7.54
Mean MIC for No. 12~27	28.4	11.4	4.41	1.31	7.42	1.63	5.48	12.0	33.8	6.52	3.12

* Agar dilution streak method (nutrient agar, 37°C, 17 hours)

** Erythromycin-resistant strain

Table 1. continued

Test organisms*	9a	9b	10b	11b	12a	13a	14a	15b	16b	17b	18b	Kanamycin A
1. *Staph. aureus* 193	0.78	0.78	<0.2	0.2	1.56	0.39	0.39	1.56	0.39	0.78	0.2	0.2
2. 〃 EMf**	>100	>100	25	12.5	>100	12.5	100	>100	>100	>100	100	0.2
3. 〃 209P	0.39	0.39	<0.2	<0.2	0.2	0.2	0.2	0.78	0.39	0.2	0.2	0.78
4. 〃 MS 8710	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	0.78
5. 〃 MS 9351	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	0.78
6. 〃 MS 9610	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	0.78
7. 〃 MS 9861	1.56	1.56	0.78	0.78	6.25	0.39	25	6.25	0.78	0.78	0.78	3.12
8. 〃 MS 10246	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
9. *M. luteus* PCI 1001	<0.2	<0.2	<0.2	<0.2	<0.2	0.39	<0.2	<0.2	<0.2	<0.2	<0.2	0.39
10. *B. subtilis* NRRL B-558	0.39	0.39	<0.2	0.39	<0.2	1.56	25	1.56	0.39	0.39	<0.2	<0.2
11. *Coryn. bovis* 1810	0.39	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	6.25	<0.2	0.39	0.39	12.5
12. *E. coli* NIHJ	0.78	0.78	0.39	0.39	1.56	3.12	6.25	3.12	3.12	0.78	6.25	0.78
13. 〃 K-12	3.12	3.12	0.78	0.78	12.5	12.5	50	25	25	3.12	12.5	1.56
14. 〃 〃 R-5	1.56	1.56	0.78	0.78	6.25	12.5	25	6.25	12.5	1.56	12.5	>100
15. 〃 〃 ML1629	3.12	1.56	1.56	1.56	6.25	12.5	25	25	25	12.5	50	>100
16. 〃 〃 ML1410	3.12	0.78	0.78	0.78	3.12	6.25	12.5	12.5	12.5	1.56	12.5	1.56
17. 〃 〃 〃 R81	3.12	1.56	1.56	1.56	6.25	12.5	25	25	25	6.25	50	>100
18. 〃 〃 LA290 R55	1.56	0.78	0.78	0.39	1.56	0.78	1.56	3.12	3.12	0.78	3.12	12.5
19. *Kl. pneumoniae* PCI 602	0.78	1.56	0.39	0.2	<0.2	0.2	0.39	25	3.12	0.39	0.78	0.39
20. *Sh. dysenteriae* JS 11910	<0.2	<0.2	<0.2	<0.2	<0.2	0.39	0.39	0.2	0.39	0.78	0.78	3.12
21. *Sal. enteritidis* 1891	0.78	0.39	<0.2	<0.2	<0.2	0.78	1.56	6.25	12.5	0.39	6.25	1.56
22. *Sal. typhi* T-63	3.12	6.25	1.56	1.56	6.25	12.5	25	25	25	6.25	50	1.56
23. *Enter. aerogenes* ATCC 13048 (MS-1)	12.5	12.5	6.25	6.25	50	25	50	100	100	25	>100	6.25
24. *Providencia* sp. Pv 16	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	12.5
25. *Serratia marcescens*	25	12.5	12.5	6.25	25	25	100	100	100	50	>100	25
26. *Proteus vulgaris* OX-19	1.56	0.78	0.78	0.39	3.12	3.12	6.25	12.5	12.5	3.12	25	0.2
27. *Ps. aeruginosa* A3	100	100	100	100	100	100	>100	>100	100	>100	>100	50
Mean MIC for No. 1~11	7.08	6.24	3.12	3.54	6.24	4.85	9.70	13.3	5.50	6.24	4.55	1.14
Mean MIC for No. 12~27	3.40	2.62	1.63	1.37	4.22	6.52	13.0	16.9	16.2	4.61	20.1	6.52

* Agar dilution streak method (nutrient agar, 37°C, 17 hours)
** Erythromycin-resistant strain

NMe_2), 2.31 (6H, s, C(3′)NMe_2), 4.23 (1H, d, H-1′), 4.78 (H-15), 5.80 (H-13), 6.32 (H-10), 7.45 (H-11), 9.83 (H-20); the splitting patterns of H-15, -13, -10, -11 and -20 were quite similar to those of the corresponding protons of **3a**; *Anal.* Found (Calcd. for $C_{33}H_{56}N_2O_8$): C, 65.21 (65.10); H, 9.16 (9.27); N, 4.37 (4.60).

Other 23-dialkylamino derivatives (Fig. 1) of **1a** and **1b** were prepared by procedures similar to that described above, starting from **2a** and **2b**. The reaction conditions for dialkylamination and the physico-chemical properties of the final products are described next in the order of the total amount of the reagent used (expressed as molar equivalents for the starting material), reaction temperature, reaction period [$a+a$ hour means that the same reagent (the same quantity with that used for the first time) is added after a hours], the yield of the product calculated from **2a** or **2b** after purification, optical rotation $[\alpha]_D^{23}$ (*c* 1, chloroform); in some cases, other characteristics are also shown. **4a** (diethylamine): 10 molar equiv., 80°C, 6 hours, 90%, +22°; **4b**: 10, 80°C, 3+3 hours, 61%, +28°; **5a** (di-*n*-propylamine): 5, 80°C, 20 hours, 57%, +31°; **6a** (di-*n*-butylamine): 5, 80°C, 20 hours, 68%, +28°; **7a**: 5-(diisobutylamine), 80°C, 48 hours, 74%, +49°; **7b**: 5, 80°C, 48 hours, 78%, +40°, Found (Calcd. for $C_{39}H_{68}N_2O_8$): C, 67.43 (67.60); H, 9.76 (9.89); N, 4.32 (4.04); **8b**: 5(pyrrolidine), 60°C, 80 minutes, 90%, +38°, Found (Calcd. for $C_{35}H_{58}N_2O_8$): C, 66.42 (66.22); H, 9.33 (9.21); N, 4.42 (4.41); **9a**: 5(piperidine), 80°C, 1.5 hours, 87%, +28°; **9b**: 5, 80°C, 60 minutes, 93%, +36°; **10b**: 5(hexamethyleneimine), 80°C, 60 minutes, 97%, +36°, m.p. 195~198°C (recrystallized from acetone - hexane); **11b**: 5 (heptamethylenimine), 80°C, 1.5 hours, 95%, +32°, Found (Calcd. for $C_{38}H_{64}N_2O_8$): C, 67.25 (67.42); H, 9.26 (9.53); N, 4.12 (4.14); **12a**: 5(*N*-methylcyclohexylamine), 80°C, 4 hours, 86%, +20°; **13a**: 5(*N*-methylbenzylamine), 80°C, 3 hours, 83%, −5°; **14a**: 5(*N*-methylphenethylamine), 80°C, 18 hours, 63%, +30°: **15b**: 5(*N*-methylpiperazine), 80°C, 1.5 hours, 76% +42°, ^1H NMR ($CDCl_3$): 2.30 (9H s, NMe_2 and pip. NMe); **16b**: 5(morpholine), 80°C, 2.5 hours, 87%, +32°, Found (Calcd. for $C_{35}H_{58}N_2O_9$): C, 64.53 (64.59); 8.86 (8.98); N, 4.07 (4.30); **17b**: 5(racemic 2-hydroxymethylpiperidine), 80°C, 12 hours, 65%, +40°; **18b**: 5(4-piperidone dimethylketal), 80°C, 4 hours, 76%; recrystallized from chloroform - hexane, m.p. 120~123°C, $[\alpha]_D^{23}$ +39°, Found (Calcd. for $C_{36}H_{58}N_2O_9 \cdot CHCl_3 \cdot H_2O$): C, 55.47 (55.39); H, 7.96 (7.92); N, 3.58 (3.49); Cl, 14.26 (13.26). The structures of the compounds prepared were all confirmed by their ^1H NMR spectra.

Antibacterial spectra (Table 1) of the compounds prepared show that the introduction of a dialkylamino group at C-23 of **1a** and **1b** markedly enhances the activity of the parent compounds. It is noteworthy that these compounds show strong activities against Gram-negative bacteria, as indicated by comparison of the spectra with the spectrum of kanamycin A (see the last column of Table 1). Another point which should be emphasized is that the 4′-deoxy compounds (compounds denoted as **b**) are always superior to the corresponding 4-hydroxyl compounds (denoted as **a**) in terms of the antibacterial activity, again confirming the results of the previous papers[1~3].

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