NEW ADRIAMYCIN ANALOGS

SYNTHESIS AND ANTITUMOR ACTIVITY OF 14-SUBSTITUTED 7-*O*-(3,4-DI-*O*-ACETYL-2,6-DIDEOXY-α-L-*lyxo*-HEXOPYRANOSYL)DAUNOMYCINONES*

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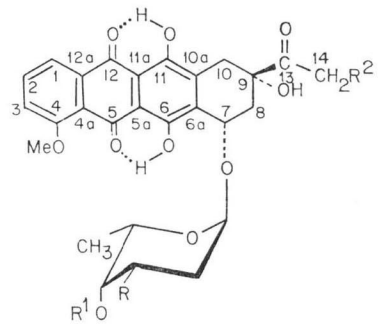
The 14-azido-, 14-thiocyanato-, 14-acetoxy-, and 14-acetylthio- derivatives of 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone were synthesized by displacement reactions conducted on the corresponding 14-bromide. The *in vivo* antitumor activities of the products were compared with that of the 14-hydroxyl derivative in the murine P-388 lymphocytic leukemia assay. The 14-acetoxy derivative was highly active and of low toxicity; the other products showed negligible or low activities.

Work from this laboratory has shown[2] that the analogue of daunorubicin (daunomycin, **1**, NSC-82151) in which the 3′-amino group has been replaced by hydroxyl (3′-desamino-3′-hydroxydaunorubicin, **3**, NSC-284682) and also its 3′,4′-diacetate **4** (NSC-283158) retain high *in vivo* antitumor activity in a range of standard test-systems in mice, and manifest much lower toxicity, including cardiotoxicity, than the parent antibiotic **1**. Likewise, the 14-hydroxylated analogue of **4** (compound **5**, NSC-307990)[3], which may be regarded as the 3′,4′-diacetate of a doxorubicin (adriamycin, **2**, NSC-123127) congener in which the 3′-amino group has been replaced by hydroxyl, displays[4] high *in vivo* antitumor activity in a wide range of murine screens; its activity is higher than that of **3** and **4**, and its acute toxicity is much lower than that of doxorubicin (**2**).



Based on the observation that hydroxylation at position 14 leads to enhancement of biological activity[5,6] (**2** is more active than **1**; **5** is more active[4] than **4**), the present study was initiated to provide, on a comparative basis, data for the effect on biological activity of halogen, nitrogen, sulfur, and acyloxy substituents at C-14 in structure **4**. It is shown that activity is markedly attenuated or abolished by bromo, azide, thiocyanato, or acetylthio groups at C-14, but full activity and low toxicity are retained in the 14-acetoxy derivative (**9**).

	R	R^1	R^2
1	NH_2	H	H
2	NH_2	H	OH
3	OH	H	H
4	OAc	Ac	H
5	OAc	Ac	OH
6	OAc	Ac	Br
7	OAc	Ac	N_3
8	OAc	Ac	SCN
9	OAc	Ac	OAc
10	OAc	Ac	SAc

* For a preliminary report of this work, see reference 1.

Chemical Synthesis

Compounds **7**~**10** variously substituted at C-14 were prepared from the readily available[4] 14-bromo-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**6**) by treatment[7] with sodium (or potassium) azide, thiocyanate, acetate, and thioacetate, respectively. The reactions were conducted at ~25°C in dry acetone (3: 1 acetone - ethanol with potassium thioacetate to increase the solubility). The reactions leading to azide **7**, thiocyanate **8**, and thiolacetate **10** were complete in <0.5 hour; the (less nucleophilic) acetate ion predictably[8,9] took longer (~36 hours at 25°C, 1 hour at boiling point) for the conversion into acetate **9**.

The structures assigned to compounds **7**~**10** were evident from analytical data (see Experimental section) and from ^{1}H NMR (Table 1), ^{13}C NMR (Table 2), and IR spectral data. The azide **7** showed characteristic IR absorption at 2120 cm^{-1} and the ^{13}C signal of C-14 in **7** (at 54.6 ppm) is ~20 ppm upfield of its position[4] in the precursor bromide **6**. Thiocyanate **8** had a characteristic IR band at 2160 cm^{-1}, and its ^{13}C NMR spectrum showed an additional carbon signal (*S*C*N*) at 111.2 ppm; the chemical shift of C-14 was 40.5 ppm. The protons at C-14 were nonequivalent and resonated as an AB pattern with chemical shifts of 4.52 and 4.40 ppm, respectively.

The 14-acetate **9** showed the anticipated 3-proton OAc resonance (2.20 ppm) and the associated ^{13}C carbonyl-group signal (170.3 ppm), and the chemical shift of C-14 (66.1 ppm) is in line with expectation. The thiolacetate **10** showed its carbonyl band (1695 cm^{-1}) as expected[10,11] at lower wavenumber than that for the oxygenated analogue. Likewise, the thiolacetate group gave a ^{1}H NMR signal (2.40 ppm) at lower field[12] than the acetoxyl group. The protons at C-14 in **10** resonated at relatively high field (4.39 and 4.08 ppm), as did C-14 (35.9 ppm). The thiolacetate group showed ^{13}C signals at 194.4 (C=O) and 30.2 (CH_3COS) ppm.

For consolidation of all signal assignments for the glycon portion of compounds **7**~**10**, the ^{1}H and ^{13}C NMR spectra of a suitable model compound, methyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside[13] (**11**) were recorded, and the corresponding spectral data are incorporated in Tables 1 and 2.

Biological Activity

The importance of the 14-substituent for biological activity in the natural anthracyclines is underscored by comparing daunorubicin (**1**) with its 14-hydroxylated analogue, doxorubicin (**2**), which is more active[6,14] as an antitumor agent. Likewise, comparison of 3′-desamino-3′-hydroxydaunorubicin diacetate (**4**) with its 14-hydroxy analogue **5** again shows the latter to be the more active[4]. As illustrated by the *in vivo* test data for the murine P-388 screen given in Table 3, introduction of other substituents at C-14 in the parent structure **4** markedly modifies activity. Athough hydroxylation at C-14 (compound **5**) increases activity, introduction of bromide (compound **6**), or acetylthio (compound **10**) completely abolishes detectable activity. Introduction of azide (compound **7**) or thiocyanate (compound **8**) causes a notable decrease in activity; these compounds manifested no activity at 50 mg/kg, but marginal activity was evident at higher doses (125~200 mg/kg). Only in the case of the 14-acetoxyl derivative **9** was high activity retained; this compound exhibited activity comparable to that of 3′-desamino-3′-hydroxydoxorubicin diacetate (**5**) and demonstrably greater than that of the non-14-hydroxylated analogue **4**. It is very probable that nonspecific esterases bring about conversion *in vivo* of the acetyl-

Table 1. ^{1}H NMR spectra data for 14-substituted 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinones (**7**～**10**) and methyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (**11**)[a].

Compound	H-1 ($J_{1,2}$) ($J_{1,3}$)	H-2	H-3 ($J_{2,3}$)	H-1′ ($J_{1',2'a}$)	H-7	H-4′ ($J_{3',4'}$)	H-3′ ($J_{2'a,3'}$) ($J_{2'e,3'}$)	9-OH	H-14A ($J_{14A,14B}$)	H-14B	H-5′ ($J_{4',5'}$)
7	8.05 bd (7.7) (~1)	7.79 app. t	7.40 bd (8.2)	5.63 bnd (3.4)	5.33 bs	5.23 bs (2.7)[b]	5.04 ddd (12.0) (4.7)	←4.50 s, 3H→			4.19 bq
8	8.04 bd (7.7) (~1)	7.79 app. t	7.40 bd (7.8)	5.64 bnd (2.8)	5.35 bs	5.23 bs	5.05 ddd	4.69 s	4.52 d (17.0)	4.40 d	4.20 bq
9	8.03 dd (7.7) (1.1)	7.78 app. t	7.39 dd (8.5)	5.61 bnd (3.6)[c]	5.29 m	5.24 bnd (2.9)[b]	5.06 ddd (12.5) (5.1)	4.48 s	5.33 d (18.0)	5.10 d	4.25 bq
10	8.03 bd (7.7) (~1)	7.77 app. t	7.39 bd (8.6)	5.63 bnd (3.4)	5.29 m	5.24 bs (2.6)[b]	5.08 ddd (12.9) (5.0)	4.54 s	4.39 d (17.6)	4.08 d	4.31 bq
11	—	—	—	4.86 dd (3.7)	—	5.17 nm	5.22 ddd (12.2) (5.4) ($J_{3',4'}$2.9)	—	—	—	4.04 qd (1.2)

Compound	H-10e ($J_{8e,10e}$)	H-10ax ($J_{10ax,10e}$)	H-8e ($J_{8e,8ax}$)	H-8ax ($J_{7,8ax}$)	H-2′a	H-2′e ($J_{2'a,2'e}$)	H-6′ ($J_{5',6'}$)	6-OH, 11-OH	OMe	OAc
7	3.27 bd (<1.5)	2.98 d (18.9)	2.34 bd (14.6)	2.22 dd (3.9)	2.16—1.79 m		1.22 d (6.9)	13.22, 13.99 s	4.09 s	1.94, 2.17 s
8	3.29 bd	2.94 d (18.9)	2.38 bd (14.2)	2.25 dd (3.9)	2.09 m	1.87 m	1.23 d (6.5)	13.20, 13.98 s	4.09 s	1.95, 2.17 s
9	3.28 dd (1.5)	3.00 d (18.8)	2.47 bd (14.3)	2.20—1.98 m		1.86 bdd (13.1)[d]	1.23 d (6.6)	13.20, 13.97 s	4.08 s	1.94, 2.17, 2.20 s
10	3.31 bd	3.01 d (18.9)	2.52 bdt (14.4)	2.20	———	—1.81 m	1.24 d (6.5)	13.22, 13.98 s	4.08 s	1.94, 2.17, 2.40 s[g]
11	—	—	—	—	2.04 dt	1.84 ddt (12.5) ($J_{1',2'e}$1.5)[e] ($J_{2'e,4'}$1.0)[f]	1.15 d (6.6)	—	3.34 s	1.98, 2.15 s

[a] Spectra recorded at 200 MHz in chloroform-*d*. Spin couplings (Hz) are given in parentheses. Signal multiplicities: app, apparent; b, broadened; d, doublet; m, multiplet; n, narrow; q, quartet; s, singlet; t, triplet.

[b~f] Coupling constants were measured from spectra decoupled at: [b] H-5′ or H-2′e; [c] H-2′e; [d] H-3′; [e] H-4′; [f] H-5′. [g] SAc.

Table 2. ^{13}C NMR chemical-shift data (δ) for compounds **7**~**11**[a].

C atom	Compound				C atom	Compound				
	7	**8**	**9**	**10**		7	**8**	**9**	**10**	**11**[c]
1	120.0	119.9	119.9	120.0	10	34.1	34.2	33.6	34.0	
2	135.9	135.9	135.8	135.9	13	207.9	205.1	206.6	207.1	
3	118.8	118.7	118.5	118.7	14	54.6	40.5	66.1	35.9	
4	161.3	161.1	161.1	161.3	OMe	56.8	56.7	56.7	56.8	54.9
6	156.3	156.0	156.2	156.5	1′	101.1	100.9	101.2	101.3	98.7
11	155.7	155.4	155.7	156.0	2′	29.8	29.7	29.7	29.9	30.0
5	187.2	187.0	187.0	187.3	3′	66.5	66.3	66.5	66.6	66.9
12	186.8	186.7	186.5	186.9	4′	69.5[b]	69.4[b]	69.5[b]	69.7[b]	70.0
4a	121.1	120.9	120.8	121.2	5′	66.3	66.3	66.1	66.3	64.7
5a	111.8	111.7	111.5	111.7	Me-5′	16.7	16.7	16.6	16.7	16.5
11a	111.6	111.5		111.6	OAc	20.8	20.8	20.8	20.9	20.9
6a	135.7	135.4	135.5	135.8	OAc	20.7	20.7	20.7	20.8	20.7
10a	133.7	133.3	133.9	134.5	C=O	170.7	170.5	170.6	170.8	170.8
12a	133.6	133.2	133.5	133.9	C=O	170.1	169.9	170.3	170.1	170.1
7	69.7[b]	69.4[b]	70.0[b]	70.2[b]	C=O			169.9	194.4	
8	35.4	35.5	35.4	35.8	SAc				30.2	
9	77.4	77.5	77.3	77.4	SCN		111.2			

[a] All spectra were recorded in chloroform-*d*. Spectra of **7**, **10**, and **11** were recorded at 50 MHz, those of **8** and **9** at 20 MHz. Chemical-shift assignments are based on off-resonance decoupling plus single frequency, selective heteronuclear decoupling (compounds **7**, **8**, **9**, and **11**) and by comparison with literature values.[15,16] Assignments bracketed are not specifically differentiated.

[b] Assignments for C-4′ and C-7 may be interchanged.

[c] ^{13}C NMR data for methyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside(**11**) are included for comparison.

ated compounds **5** and **9** into the same, active product. The differential biological-transport properties of **5**, **9**, and their common deacetylation product may, however, result in significant differences in the physiological behavior of the three compounds as potential agents for use in cancer chemotherapy.

The work here underscores the significance of the oxygenated substituent at C-14 for antitumor activity in these anthracyclines, and demonstrates that introduction of halogen, nitrogen, or sulfur at this position is unlikely to lead to compounds of antitumor activity higher than that of the 14-*O*-substituted derivatives.

Experimental

TLC was performed on precoated plastic sheets (0.2 mm) and glass plates (0.25 mm) of silica gel 60F-254 (E. Merck, Darmstadt, G.F.R.); zones of colorless compounds were detected by UV light and by spraying the plates with 0.1 M ceric sulfate in 2 M sulfuric acid, with subsequent heating. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. IR spectra were recorded with a Perkin-Elmer 457 grating spectrophotometer. ^1H NMR spectra were determined by Dr. O. MOLS at 200 MHz for solutions in chloroform-*d* with a Bruker WP-200 spectrometer. ^{13}C Spectra were recorded by Dr. C. COTTRELL at 20 MHz with a Bruker WP-80 instrument and by Dr. O. MOLS at 50 MHz with a Bruker WP-200 spectrometer. Chemical shifts refer to an internal standard of tetramethylsilane (δ=0.00). Elemental analyses were performed by Dr. O. MOLS.

Table 3. Activity[a] of 14-substituted 7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinones **4**~**10** on P388 lymphocytic leukemia in mice.[b]

Compound	NSC NO.	Substituent at C-14	Dose (mg/kg)	T/C (%)[c]	Activity criteria[e]
4	283158	H	200.00 100.00	186 155	P
5	307990	OH	50.00 25.00 12.50	211, 269[d] 183, 192[d] 163, 137[d]	P
6	307989	Br	50.00	105	F
7	327475	N_3	50.00 125.00	101 124[d]	F P
8	328006	SCN	50.00 200.00	108 123[d]	F P
9	335043	OAc	50.00 25.00	261 177	P
10	327473	SAc	50.00 125.00	101 100[d]	F F

[a] Data obtained under the auspices of the National Cancer Institute, Division of Cancer Treatment, Drug Research and Development Branch.

[b] CDF_1 mice were injected i.p. with 10^6 P388 lymphocytic leukemia cells on day 0 and treated i.p. on days 5, 9, and 13 with the drug dose specified. Toxic deaths were not observed in any of the tests.

[c] Ratio of median survival time expressed as percent of untreated controls.

[d] Data from second series of tests.

[e] P passed, F failed.

14-Azido-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**7**, NSC-327475)

To a solution of 14-bromo-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone[4] (**6**, 345.8 mg, 0.5 mmole) in acetone (20 ml) was added sodium azide (156.7 mg, 2.4 mmole) and the mixture was stirred vigorously for 0.5 hour at ~25°C. TLC (benzene - acetone, 6: 1, developed twice) showed conversion of **6** into a single, slightly more-polar product (Rf 0.41). The mixture was poured into water (100 ml) and the product extracted with dichloromethane. The organic layer was washed with water, dried (magnesium sulfate) and evaporated under diminished pressure. Crystallization of the residue from acetone (sufficient to dissolve the sample), ethyl ether, and hexane gave a red solid that was dried at 50°C/0.3 mmHg; yield 290 mg (89%), m.p. 135°C, $[\alpha]_D^{23}$ +230°, $[\alpha]_{578}^{23}$ +284° (*c* 0.024, $CHCl_3$); ν_{max}^{KBr} 3480 (OH), 2120 (N_3), 1746 (C=O), 1622, and 1583 cm^{-1} (H-bonded quinone).

Anal. Calcd. for $C_{31}H_{31}N_3O_{13}$: (653.605): C, 56.97; H, 4.78; N, 6.43.
Found: C, 57.19; H, 5.12; N, 5.70.

7-*O*-(3,4-Di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-14-thiocyanatodaunomycinone (**8**, NSC-328006)

To a solution of the 14-bromide **6** (305.8 mg, 0.44 mmole) in acetone (20 ml) was added potassium thiocyanate (270 mg, 2.78 mmole) and the mixture was vigorously stirred for 0.5 hour at ~25°C. TLC (benzene - acetone, 6: 1) exhibited a single spot (product **8**), slightly more polar than the starting material (**6**). The product was isolated as described in the preceding experiment. Crystallization afforded **8** as a chromatographically pure, red solid (288.6 mg, 94%) in two crops; m.p. 138°C (dec.), $[\alpha]_D^{27}$ +176°, $[\alpha]_{578}^{27}$ +206° (*c* 0.02, $CHCl_3$); ν_{max}^{KBr} 3472 (OH), 2162 (SCN), 1745 (C=O), 1622, and 1583 cm^{-1} (H-bonded quinone).

Anal. Calcd. for $C_{32}H_{31}NO_{13}S$ (669.667): C, 57.40; H, 4.67; N, 2.09; S, 4.79.
Found: C, 57.84; H, 4.76; N, 1.95; S, 4.75.

14-*O*-Acetyl-7-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)adriamycinone (**9**, NSC-335043)

To a vigorously stirred solution of the 14-bromide **6** (267.8 mg, 0.38 mmole) in acetone (20 ml)

was added sodium acetate (280 mg, 3.4 mmole). The reaction was complete after 36 hours at 25°C (TLC, benzene - acetone, 6: 1, one component, more polar than the substrate), and the product was isolated as for the two preceding reactions. The first crystallization afforded **9** as a red solid (165 mg), and the filtrate gave an additional 82 mg of **9**, total yield 95%; m.p. 141~143°C, $[\alpha]_D^{28}$ +202°, $[\alpha]_{578}^{28}$ +238° (*c* 0.02, $CHCl_3$); ν_{max}^{KBr} 3460 (OH), 1745 (C=O), 1621, and 1583 cm^{-1} (H-bonded quinone).

Anal. Calcd. for $C_{33}H_{34}O_{15} \cdot 0.5\ H_2O$ (679.63): C, 58.32; H, 5.19.
Found: C, 58.31; H, 4.86.

14-Acetylthio-7-*O*-3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*lyxo*-hexopyranosyl)daunomycinone (**10**, NSC-327473)

The bromide **6** (175 mg, 0.25 mmole) was dissolved in a mixture of acetone (12 ml) and absolute ethanol (4 ml), potassium thioacetate (124 mg, 1.05 mmole) was added, and the mixture was stirred vigorously at ~25°C. After 10 minutes, TLC (benzene - acetone, 6: 1 developed twice) showed **6** to be absent and a single, more-polar (Rf 0.42) product had been formed. The mixture was poured into water (50 ml) and the product extracted with dichloromethane. The organic layer was washed with water, dried with magnesium sulfate, and evaporated, to afford a red oil (155.4 mg) that was crystallized from a little acetone plus ethyl ether and hexane. Compound **10** was obtained as a red solid that was dried for 5 hours at 65°C and 0.3 mmHg; yield 135.5 mg (78%), m.p. 140~141°C, $[\alpha]_D^{23}$ +191°, $[\alpha]_{578}^{23}$ +205° (*c* 0.02, $CHCl_3$); ν_{max}^{KBr} 3483 (OH), 1748 (C=O), 1696 (SC=O), 1621, and 1582 cm^{-1} (H-bonded quinone).

Anal. Calcd. for $C_{33}H_{34}O_{14}S$ (686.695): C, 57.72; H, 4.99; S, 4.67.
Found: C, 57.44; H, 4.96; S, 4.67.

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