TETRAHYDROPYRANYL DERIVATIVES OF DAUNOMYCIN AND ADRIAMYCIN

Sir:

The baumycins were found in culture filtrates of a daunomycin-producing strain[1]. In preliminary tests of the activity on L-1210, baumycin A1 exhibited stronger activity than adriamycin or daunomycin. This was not repeated in other laboratories where a second sample was tested. Moreover, the yield of baumycin A1 was very small. Consequently, the simplest 4′-O-glycosidic derivative, that is, 4′-O-tetrahydropyranyladriamycin was prepared. One of the diastereomers of this glycosidic derivative was found to have greater activity than either adriamycin or daunomycin. It had lower toxicity by LD_{50} and electrocardiographic toxicity tests. As reported by Dr. MATHÉ[2] in the next paper, he obtained results suggesting a low delayed cardio toxicity.

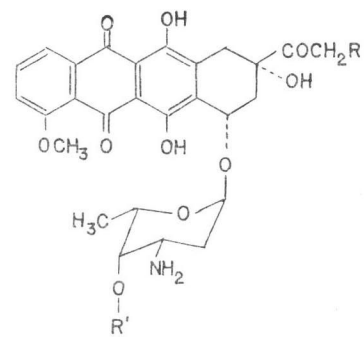
In this paper, the chemical synthesis, properties and the L-1210-inhibiting activities of two diastereomers of 4′-O-tetrahydropyranyl derivatives of daunomycin and adriamycin are reported.

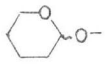
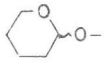
Treatment of daunomycin (**I**) hydrochloride (60 mg) in dry N,N-dimethylformamide (5 ml) with 3,4-dihydro-2*H*-pyrane (1 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid at room temperature for 47 hours produced the 4′-O-tetrahydropyranyl derivatives **IIa** and **IIb**, each of which was isolated as the free base by silica gel chromatography; **IIa**: mp 193~196°C (dec.), $[\alpha]_D^{22}$ +125° (*c* 0.2, $CHCl_3$), found: C 60.82, H 6.27, N 2.24, calcd. for $C_{32}H_{37}NO_{11}\cdot H_2O$: C 61.04, H 6.24, N 2.22; **IIb**: mp 190~193°C (dec.), $[\alpha]_D^{22}$ +162.5° (*c* 0.2, $CHCl_3$), found: C 61.48, H 6.37, N 1.97. Compound **IIb** (Rf 0.65) moves faster than **IIa** (Rf 0.46) on Silica gel G (E. Merck, $60F_{254}$) tlc with chloroform-methanol (10: 1) as the developing solvent.

Treatment of adriamycin (**III**) hydrochloride (130 mg) in dry N,N-dimethylformamide (10 ml) with 3,4-dihydro-2*H*-pyrane (2 ml) in a manner similar to that described above resulted in a mixture of 14,4′-bis(O-tetrahydropyranyl) adriamycins (**IVa**, **IVb**) and 14-O-tetrahydropyranyladriamycin (**V**). These compounds were isolated by preparative silica gel tlc using chloroform-methanol (15: 1) as the developing solvent: **IVa**, 16 mg; **IVb**, 14 mg; and **V**, 35 mg. Compound **V** had a mp 195~202°C (dec.) and $[\alpha]_D^{24}$ +162.5° (*c* 0.2, $CHCl_3$). Compounds **IVa** and **IVb** were diastereomeric mixtures of the 14-O-tetrahydropyranyl groups. The 14-O-tetrahydropyranyl groups in **IVa** and **IVb** were removed by treatment with methanolic 0.005 N *p*-toluenesulfonic acid solution at room temperature for an hour to yield 4′-O-tetrahydropyranyladriamycin derivatives **VIa** and **VIb** as free bases of single compounds, respectively; **VIa**: mp 172~177°C (dec.), $[\alpha]_D^{25}$ +165°±15° (*c* 0.2, $CHCl_3$), Rf 0.32 on silica gel tlc with chloroform - methanol (10: 1), found: C 59.65, H 6.33, N 2.21, calcd. for $C_{32}H_{37}NO_{12}\cdot H_2O$: C 59.52, H 6.10, N 2.17; **VIb**: mp 188~192°C (dec.), $[\alpha]_D^{25}$ +175°±25° (*c* 0.2, $CHCl_3$), Rf 0.49 on tlc, found: C 59.71, H 6.24, N 2.05.

The effects of tetrahydropyranyl derivatives on L-1210 were tested in comparison with daunomycin and adriamycin: 10^5 tumor cells were inoculated into CDF_1 mice (20±1 g) intraperitoneally. Varied amounts (100, 50, 25, 12.5, 6.25 and 3.13 μg/mouse/day) of each of the two diastereomers of 4′-O-tetrahydropyranyldauno-

Fig. 1.



	R	R′
DM (I)	H	H
4′-THP-DM(a) (IIa) and 4′-THP-DM(b) (IIb)	H	
ADM (III)	OH	H
14,4′-THP-ADM(a) (IVa) and 14,4′-THP-ADM(b) (IVb)		
14-THP-ADM (V)		H
4′-THP-ADM(a) (VIa) and 4′-THP-ADM(b) (VIb)	OH	

Abbreviations: Daunomycin = DM, Adriamycin = ADM, Tetrahydropyranyl = THP

Table 1. Antitumor activities (T/C % of the survival period) of tetrahydropyranyl derivatives of daunomycin and adriamycin on L-1210.

Compounds	Dose (μg/mouse/day)					
	100	50	25	12.5	6.25	3.13
DM-HCl (**I**)	Toxic	138*	191	145	132	118
4′-THP-DM(a) (**IIa**)	320*	>474	122	115	96	90
4′-THP-DM(b) (**IIb**)	320*	256	122	115	103	90
ADM-HCl (**III**)	180*	>458	278	373	198	131
14,4′-THP-ADM(a) (**IVa**)	154	115	109	96	103	96
14,4′-THP-ADM(b) (**IVb**)	161	109	103	103	96	115
14-THP-ADM (**V**)	142	130	126	113	110	103
4′-THP-ADM(a) (**VIa**)	—	173	180	187	120	127
4′-THP-ADM(b) (**VIb**)	>800**	>473	>427	342	171	129

Leukemia L-1210 cells (10^5) were inoculated into CDF_1 mice (20±1 g) intraperitoneally. Drugs were daily administered from day 1 to 9, intraperitoneally. Survival studies were continued up to 60 days.
* Toxic ** 5 out of 6 survived.

Table 2. Antitumor activities of 4′-tetrahydropyranyladriamycin (**VIb**) and adriamycin (**III**) on L-1210.

Injection	Compounds		Dose (μg/mouse/day)					
			320	160	80	40	20	10
Once*	4′-THP-ADM-(b) (**VIb**)	T/C(%)	>370	>337	>212	219	150	124
		30 days survivor	6/6	5/6	1/6	0/6	0/6	0/6
	ADM (**III**)	T/C (%)		>290	191	144	127	121
		30 days survivor		3/6	0/6	0/6	0/6	0/6
3 times**	4′-THP-ADM-(b) (**VIb**)	T/C (%)	>370	>370	>281	>274	152	132
		30 days survivor	5/6	6/6	2/6	3/6	0/6	0/6
	ADM (**III**)	T/C (%)		263	>259	>292	142	126
		30 days survivor		0/6	2/6	2/6	0/6	0/6

Leukemia L-1210 cells (10^5) were inoculated into CDF_1 mice (20±1 g) intraperitoneally.
* Drugs (hydrochlorides) were intraperitoneally administered one time, 24 hours after the inoculation of cells.
** Drugs (hydrochlorides) were intraperitoneally administered three times on day 1, 5 and 9.

mycin (**IIa** and **IIb**) or 4′-O-tetrahydropyranyladriamycin (**VIa** and **VIb**) were administered intraperitoneally, daily for 9 days, from one day after inoculation of tumor cells. As shown in Table 1, compound **VIb**, one of the 4′-O-tetrahydropyranyladriamycins had the greatest activity. The 14-O-tetrahydropyranyl derivatives (**IVa**, **IVb** and **V**) of adriamycin were weakly active. As shown in Table 2, one- or three-dose therapy of **VIb** had strong therapeutic effects.

The intravenous LD_{50} of the most active derivative, **VIb**, was 27.8 mg/kg. This is approximately one-third the toxicity of adriamycin (10 mg/kg).

Electrocardiographic toxicity determined by administering **VIb** at 1.56, 3.13 and 6.25 mg/kg to hamsters indicated about one-fourth the toxicity of adriamycin. Administration of 3.13 mg/kg of adriamycin produced slight toxicity in 2/5 hamsters and 6.25 mg/kg caused marked changes in all hamsters; 6.25 mg/kg of **VIb** caused a slight changes comparable to 1.56 mg/kg of adriamycin. Accordingly, the actue cardiac toxicity of **VIb** was found to be significantly lower than that of adriamycin.

The results described above indicated that one of the 4′-O-tetrahydropyranyl derivatives of

adriamycin is an interesting compound that should be investigated further. The 4′-O-glycosidic derivatization may give other interesting derivatives. Additional studies on other derivatives will be reported in the future.

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