NEW ANTHRACYCLINE GLYCOSIDES OBTAINED BY THE NITROUS ACID DEAMINATION OF DAUNORUBICIN, DOXORUBICIN AND THEIR CONFIGURATIONAL ANALOGUES

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(Received for publication March 15, 1985)

The new anthracyclines 7-*O*-(2,3,5-trideoxy-3-*C*-formyl-α-L-*threo*-pentofuranosyl)daunomycinone (**8**) and -adriamycinone (**10**) have been obtained upon nitrous acid deamination of daunorubicin and doxorubicin respectively. Deamination of the L-*ribo* analogue of daunorubicin (**6**) gave a mixture of 2,3,6-trideoxy-L-*glycero*-hexopyranosid-4-ulose (α-L-cinerulosyl) (**11**) and 2,6-dideoxy-α-L-*arabino*-hexopyranosyl (**12**) glycosides. The corresponding adriamycinone glycosides **13** and **14**, obtained by deamination of the doxorubicin L-*ribo* analogue **7**, were found to display an outstanding antileukemic activity in mice.

The synthesis of analogues of daunorubicin (**1**) and doxorubicin (**2**) in which the amino sugar moiety is functionally and/or configurationally modified is of great pharmacological and practical interest.[1,2] Particularly some analogues modified at the C-4′ position show more favorable pharmacological properties and/or a wider spectrum of activity, such as 4′-epidoxorubicin (epirubicin) (**4**)[3] which, after extensive clinical trials,[4] is now used as anticancer drug in several countries.

Other configurational analogues have been previously prepared in our laboratories such as 3′-epidaunorubicin (**5**),[5] 3′,4′-diepidaunorubicin (**6**)[6] and 3′,4′-diepidoxorubicin (**7**),[7] in which the natural 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose (L-daunosamine) has been replaced by the corresponding L-*xylo* and L-*ribo* (L-ristosamine) isomers.

In order to explore the potential value of the nitrous acid deamination for obtaining other modifications in the amino sugar moiety, we applied this reaction to daunorubicin (**1**), doxorubicin (**2**) and their configurational analogues **3**～**7**.

In this paper we report the preparation, structure elucidation and preliminary biological data of new deaminoanthracyclines, namely 3-*C*-formylpentofuranosyl (**8**～**10**)[8] and hexopyranosyl (**11**～**14**)[9] glycosides.

Chemical Synthesis

Treatment of daunorubicin hydrochloride (**1**)[10] with sodium nitrite in dilute acetic acid solution under controlled conditions for pH and temperature gave an insoluble red precipitate in an almost quantitative yield. The structure assigned to the deamination product as 7-*O*-(2,3,5-trideoxy-3-*C*-formyl-α-L-*threo*-pentofuranosyl)daunomycinone (**8**) was supported by spectroscopical data (mass, ^{1}H and ^{13}C NMR spectra).

Compound **8** was slowly converted, in pyridine at room temperature, into the corresponding

Table 1. ^{1}H NMR data for compounds **8**~**14**.[a]

	8	**9**	**10**	**11**	**12**	**13**	**14**
H-1[b]	7.91	7.89	7.94	8.06	8.04	8.05	8.04
H-2[b]	7.68	7.71	7.70	7.78	7.78	7.79	7.78
H-3[b]	7.28	7.34	7.31	7.39	7.38	7.39	7.39
4-OCH_3	4.03	4.06	4.04	4.09	4.12	4.09	4.08
H-7	5.23	5.19	5.26	5.41	5.38 (2.5, 4.1)	5.42	5.30 (2.3, 4.0)
H-8ax	2.8~1.8	2.4~2.0	2.8~1.8	2.5~1.7	2.14 (2.5, 15.0)	2.5~1.7	2.15 (4.0, 14.8)
H-8eq					2.45 (2.5, 4.1, 15.0)		2.36 (2.1, 2.3, 14.8)
9-OH	4.66	4.22	—[c]	4.62	4.58	—[c]	—[c]
H-10ax	2.77 (19.0)	2.66 (19.0)	2.95 (19.0)	2.97 (19.0)	3.05 (18.9)	3.17	3.03 (19.0)
H-10eq	3.07 (2.0, 19.0)	3.05 (19.0)	3.20 (2.0, 19.0)	3.25 (2.0, 19.0)	3.33 (2.5, 18.9)		3.28 (2.1, 19.0)
H-14	2.39	2.46	4.72	2.41	2.42	4.71	4.77
H-1′	5.78 (1.0, 5.0)	5.84	5.76 (1.5, 5.5)	5.67 (6.0, 6.0)	5.59 (1.2, 4.0)	5.62 (6.0, 6.0)	5.50 (1.2, 4.1)
H-2′ax	2.8~1.8	2.4~2.0	2.8~1.8	2.5~1.7	1.81 (4.0, 11.5, 13.1)	2.5~1.7	1.72 (4.1, 11.9, 13.4)
H-2′eq					2.14 (1.2, 5.0, 13.1)		2.12 (1.2, 5.0, 13.4)
H-3′	3.10	2.67	3.05	2.5~1.7	3.84 (5.0, 9.0, 11.5)	2.5~1.7	3.71 (5.0, 9.0, 11.9)
H-4′	4.65	4.67	4.59		3.25 (9.0, 9.6)		3.15 (9.0, 9.4)
3′-CHO	9.68 (2.5)	9.71 (2.0)	9.66 (2.5)				
4′-CH_3	1.36 (6.8)	1.40 (6.8)	1.36 (6.7)				
H-5′				4.40 (6.5)	3.95 (6.2, 9.6)	4.30 (6.5)	3.78 (6.2, 9.4)
5′-CH_3				1.36 (6.5)	1.45 (6.2)	1.36 (6.5)	1.34 (6.2)
6-OH	13.79	13.88	13.81	14.01	14.01	14.01	14.01
11-OH	13.06	13.04	13.09	13.29	13.29	13.26	13.27

[a] Chemical shifts in ppm (δ) obtained from $CDCl_3$ solutions. In parentheses coupling constants in Hz.

[b] For all compounds: $J_{1,2}$=8.0 Hz, $J_{1,3}$=1.0 Hz, $J_{2,3}$=8.0 Hz.

[c] Signal not observed.

ax; axial, eq; equatorial.

Table 2. ^{13}C NMR chemical shifts (ppm) for compounds **8**, **9**, **11**, **13** and **14**.[a]

C	**8** (Acetone-d_6)	**9** (Acetone-d_6)	**11** ($CDCl_3$)	**13** ($CDCl_3$)	**14** ($CDCl_3$·CD_3OD)
1	119.5	119.4	118.4	118.5	119.3
2	136.0	136.0	135.7	135.8	136.5
3	119.5	119.4	119.8	119.8	120.3
4	161.5	161.5	—[b]	161.0	161.6
5	186.9	(186.8)	—[b]	187.0	(187.3)
6	(156.4)	[156.6]	—[b]	(155.6)	155.7
7	68.9	68.5	69.3	69.0	68.8
8	35.5	35.8	35.3	35.8	36.3
9	76.7	76.6	76.7	76.6	77.0
10	33.1	32.8	33.3	33.9	33.9
11	(155.6)	[155.6]	—[b]	(156.1)	158.7
12	186.9	(186.4)	—[b]	187.0	(187.6)
13	211.5	211.8	210.5	213.8	214.2
14	24.1	24.4	24.7	65.4	65.4
4-OCH_3	56.4	56.4	56.6	56.6	57.0
1′	106.2	106.5	100.2	100.3	101.4
2′	33.3	34.3	27.8	27.6	38.0
3′	52.7	57.2	33.3	33.1	69.8
3′-CHO	191.7	201.8			
4′	75.4	74.3	210.5	210.3	69.8
4′-CH_3	16.6	20.4			
5′			71.2	71.3	77.9
5′-CH_3			14.8	14.9	17.8

[a] Values in parentheses may be interchanged. Data for the aromatic quaternary carbons are not given.
[b] Signal not detected due to low signal/noise ratio.

erythro epimer **9**, owing to a ready enolization of the aldehyde function. Conversion of **8** into **9** was also simply achieved by passing a chloroform solution of **8** through a silica gel column buffered at pH 7.

Compound **8** was also obtained upon deamination of 4′-epidaunorubicin (**3**)[3] and 3′-epidaunorubicin (**5**).[5]

Ring contraction also occurred in the deamination of doxorubicin (**2**)[11] and 4′-epidoxorubicin (**4**)[3] both giving 7-*O*-(2,3,5-trideoxy-3-*C*-formyl-α-L-*threo*-pentofuranosyl)adriamycinone (**10**), whose ^1H NMR spectrum was almost super-imposable to that of **8** with the exception of protons at C-14 (see Table 1).

The presence of a furanose sugar moiety in compounds **8** and **9** was readily confirmed by the ^{13}C chemical shifts values for the corresponding anomeric carbons[12] (see Table 2).

Deamination of 3′,4′-diepidaunorubicin (**6**)[6] gave in good yield a mixture of two products (**11** and **12**) which were isolated in comparable amounts after silica gel column chromatography. The less polar product (**11**) showed in the IR spectrum a relevant increase in the intensity of the carbonyl absorption band at 1725 cm^{-1} when compared with that of daunorubicin (**1**).[10] Compounds **11** and **12** gave upon mild acid hydrolysis (0.1 N HCl, 85°C for 30 minutes) the same aglycone, daunomycinone,[13] but different sugar constituents which were identified by TLC analysis as 2,3,6-trideoxy-L-*glycero*-4-hexulose (L-cinerulose A, from an acidic hydrolysate of aclacinomycin A)[14] from **11**, and 2,6-dideoxy-L-*arabino*-hexose (authentic sample prepared from L-rhamnose)[15] from **12**.

The corresponding adriamycinone glycosides **13** and **14** were obtained in comparable yield upon

Table 3. Effect on HeLa cells viability *in vitro*.[a]

Compound	ID_{50} (ng/ml)[b]
Daunorubicin·HCl (**1**)	12
8	320
9	1,750
11	350
12	60
Doxorubicin·HCl (**2**)	11
10	140
13	40
14	25

[a] HeLa cells were exposed to the drugs for 24 hours, then plated. Colonies number was evaluated 5 days later.
[b] Calculated on dose-effect lines.

deamination of **7**.[7] Acid hydrolysis of both products gave adriamycinone[11] in addition to L-cinerulose A from **13** and 2,6-dideoxy-L-*arabino*-hexose from **14**.

The structures assigned to **11** and **13** as 7-*O*-(2,3,6-trideoxy-α-L-*glycero*-hexopyranosid-4-ulose)daunomycinone and -adriamycinone and to **12** and **14** as 7-*O*-(2,6-dideoxy-α-L-*arabino*-hexopyranosyl)daunomycinone and -adriamycinone respectively, were fully supported by analytical and spectroscopical data.

After completion of this work,[8,9] compounds **12** and **14** were also prepared by glycosidation of daunomycinone and of 14-*O*-(*tert*-butyldiphenylsilyl)adriamycinone with 3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl chloride.[16,17]

Biological Activity

Cytotoxicity on HeLa cells of the new anthracyclines was compared to that of daunorubicin and doxorubicin and the results are reported in Table 3. With the exception of the doxorubicin analogues **13** and **14**, all the new glycosides were found to be remarkably less cytotoxic than the parent antibiotics.

All the new anthracyclines were also tested against the P388 lymphocytic leukemia in mice in comparison with daunorubicin and doxorubicin. The results, reported in Tables 4 and 5, indicate

Table 4. Activity of daunorubicin analogues against P388 leukemia in mice.[a]

Compound	Dose[b] (mg/kg)	T/C (%)	LTS[c]	Toxic deaths[d]
Daunorubicin·HCl (**1**)[e]	2.9	170	0/37	0/37
	4.4	167	0/32	0/38
	6.6	157	0/38	19/38
Daunorubicin·HCl (**1**)[f]	4.4	170	0/10	0/10
	6.6	160	0/10	6/10
8[f]	50	168	0/8	0/8
	100	163	0/5	0/5
	200	190	0/5	0/5
9[f]	50	110	0/10	0/10
	100	110	0/10	0/10
	200	125	0/9	0/9
11[f]	30	127	0/8	0/8
	60	165	0/10	2/10
	100	100	0/10	5/10
12[f]	15	180	0/5	0/5
	20	290	0/5	0/5
	26	160	0/5	3/5

[a] BDF_1 mice received 10^6 ascites cells on day 0, ip.
[b] Single treatment ip on day 1 after tumor transplantation.
[c] Long term survivors (≥60 days).
[d] Evaluated on the basis of autoptic findings on dead mice.
[e] Dissolved or suspended in water.
[f] Dissolved in Tween 80 and diluted with 9 volumes of water.

Table 5. Antitumor activity of doxorubicin analogues against P388 leukemia in mice.[a]

Compound	Dose[b] (mg/kg)	T/C (%)	LTS[c]	Toxic deaths[d]
Doxorubicin·HCl (**2**)[f]	4.4	225	0/8	0/8
	6.6	290	1/8	0/8
	10	300	2/8	0/8
10[f]	50	163	0/9	0/9
	100	190	0/9	0/9
	200	231	1/7	1/7
13[f]	10	170	2/10	0/10
	15	180	0/8	0/8
	22.5	210	0/8	0/8
	33.7	230	1/8	0/8
Doxorubicin·HCl (**2**)[e,g]	4.4	245, 223	0/10, 0/10	0/10, 0/10
	6.6	255, 258	1/10, 0/10	0/10, 0/10
	10	345, 282	2/10, 1/10	0/10, 0/10
14[e,g]	6.6	250	1/10	0/10
	10	290	3/10	0/10
	15	>630, >658	6/10, 6/10	0/10, 1/10
	22.5	>630, >658	9/10, 5/10	0/10, 2/10
	33.7	194	3/10	5/10

[a~f] see Table 4.
[g] Data of two experiments.

that the 3-*C*-formyl-L-*threo*-pentofuranosyl analogues **8** and **10** display an activity comparable to that of the parent drugs albeit at much higher dose levels, while the L-*erythro* analogue **9** is essentially inactive. The cinerulosyl daunomycinone glycoside **11** showed some activity only at high toxic dosage. The corresponding 14-hydroxyl analogue **13**, retaining substantially the efficacy of doxorubicin at higher dose levels, was further evaluated against the Gross leukemia in mice by iv and oral route. The results, shown in Table 6, confirmed a reduced potency of **13** after iv injection; when the compound was orally administered at the same iv dose levels, it exhibited a good activity with 100% increase in average survival time. Doxorubicin displayed no activity or toxicity when given orally up to 200 mg/kg.

The L-*arabino*-deamino anthracyclines **12** and **14** were found remarkably more active against P388 than the parent drugs although at somewhat higher dose levels. The doxorubicin analogue **14** was further evaluated against the Gross and L-1210 murine leukemias. As reported in Table 6, the glycoside **14** showed against the Gross leukemia the same activity as doxorubicin with a reduced toxicity when given iv and also some activity by oral route. 3′-Deamino-3′-hydroxy-4′-epidoxorubicin (**14**) confirmed its remarkable activity either by ip and iv route against the L-1210 leukemia, which is relatively resistant to doxorubicin.

Discussion

The nitrous acid deamination of carbohydrate amines[18] and aminoglycoside antibiotics[19,20] provides a potentially useful method of structure elucidation and synthesis of new analogues, despite the fact that complex mixtures of products can result from rearrangements accompanying decomposition of the intermediate unstable diazonium ion.[18] Deamination of daunorubicin (**1**), doxorubicin (**2**) and their L-*arabino* isomers (**3**,**4**) resulted in an almost quantitative formation of a single ring-contracted aldehyde (**8** and **10**, respectively, as reported in Scheme 1) likely because of its high insolubility in the aqueous reaction medium. The formation of ring-contracted aldehydes as major

Table 6. Activity against L-1210 leukemia and/or Gross leukemia of compounds **13** and **14**, after single treatment on day 1.

Leukemia	Route	Treatment			T/C (%)	LTS[c]	Toxic deaths[d]
		Route	Compound	Dose (mg/kg)			
Gross[a]	iv	iv	Doxorubicin[e,g]	10	200	0/8	0/8
				13	241, 275	0/18	1/18
				16.9	233, 175	1/18	6/18
		iv	**13**[e,g]	40	185, 250	0/17	2/17
				48	116	0/10	7/10
		oral	**13**[f]	40	192	0/8	0/8
				48	200	0/8	0/8
				57.6	200	0/8	2/8
		oral	**14**[f]	26	133	0/7	0/7
				34	158	0/10	0/10
				44	158	0/10	0/10
		iv	**14**[e]	13.3	183	0/7	0/7
				26.6	225	0/8	0/8
				39.9	250	0/8	3/8
L-1210[b]	ip	ip	Doxorubicin[f]	4.4	166	0/10	0/10
				6.6	166	0/10	0/10
				10	177	3/10	0/10
			14[f]	8.8	>600	3/6	0/6
				13.3	505	3/8	0/6
				20	238	0/8	2/8
	iv	iv	Doxorubicin[f]	10	157	0/10	0/10
				13	178	0/10	0/10
				16.9	185	0/10	0/10
			14[f]	13.3	185	0/9	0/9
				20	264	0/9	0/8
				30	600	3/8	0/8

[a] C3H mice were injected with 2×10^5 leukemia cells iv.
[b] BDF_1 mice received 10^3 ascites cells on day 0 ip or iv.
[c ~ g] see Table 4.

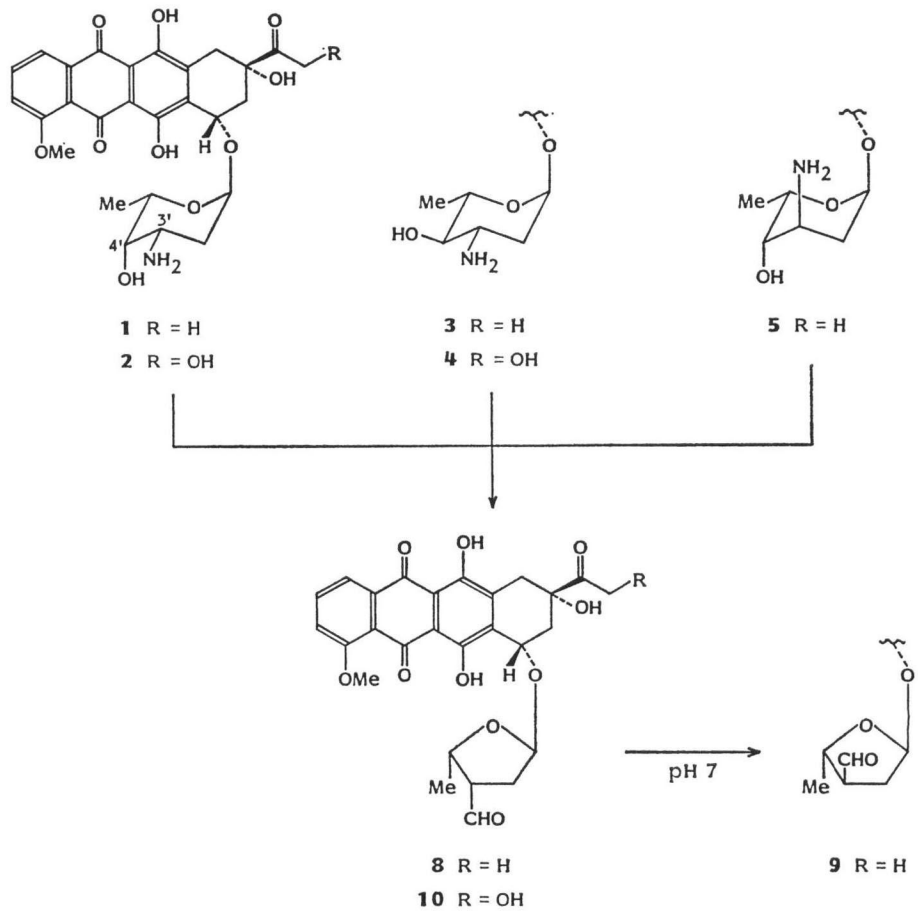
deamination products of pyranose derivatives bearing an equatorial amino group in position 3 was previously reported.[18] In the case of the daunorubicin *xylo*-conformer (**5**), whose sugar moiety adopts in solution a $^1C_4$ preferred conformation,[1] the observed formation of **8** could be explained by a $^4C_1$ chair conformation adopted by the intermediate diazonium ion.

Mechanistic considerations suggest the preferential formation of the *threo* compounds **8** and **10**; in fact the ^{13}C chemical shift data of **8** (Table 2) show an increased shielding due to steric compression for the methyl and *C*-formyl *cis* substituents, when compared with those of the corresponding *trans* groups in the *erythro* isomer **9**.[18] The assignment was also supported by 2D-NOE ^1H NMR[20] studies of **8** and **9**. The NOE correlation peak between the *C*-formyl and the methyl groups was detected in the spectrum of **8** but not in that of **9** under similar experimental conditions.

Deamination of the L-*ribo* conformers **6** and **7**, shown in Scheme 2, gave in good and comparable yields the hexopyranosid-4-ulose glycosides **11** and **13** respectively, as rearrangement products, in addition to the corresponding L-*arabino*-hexopyranosides **12** and **14** as substitution products. These results are similar to those observed for other pyranosides carrying an axial 3-amino group vicinal to an equatorial hydroxyl group.[18]

The ketosugar moiety in **11** and **13** exhibited in the ^1H NMR spectrum (see Table 1) the anomeric proton signal as a sharp triplet (J=6.0 Hz). Torsion angles between protons at C-1′ and C-2′, calculated from the Karplus curve as 30° and 144°, suggested a pseudo-boat conformation for the sugar ring.

Scheme 1.

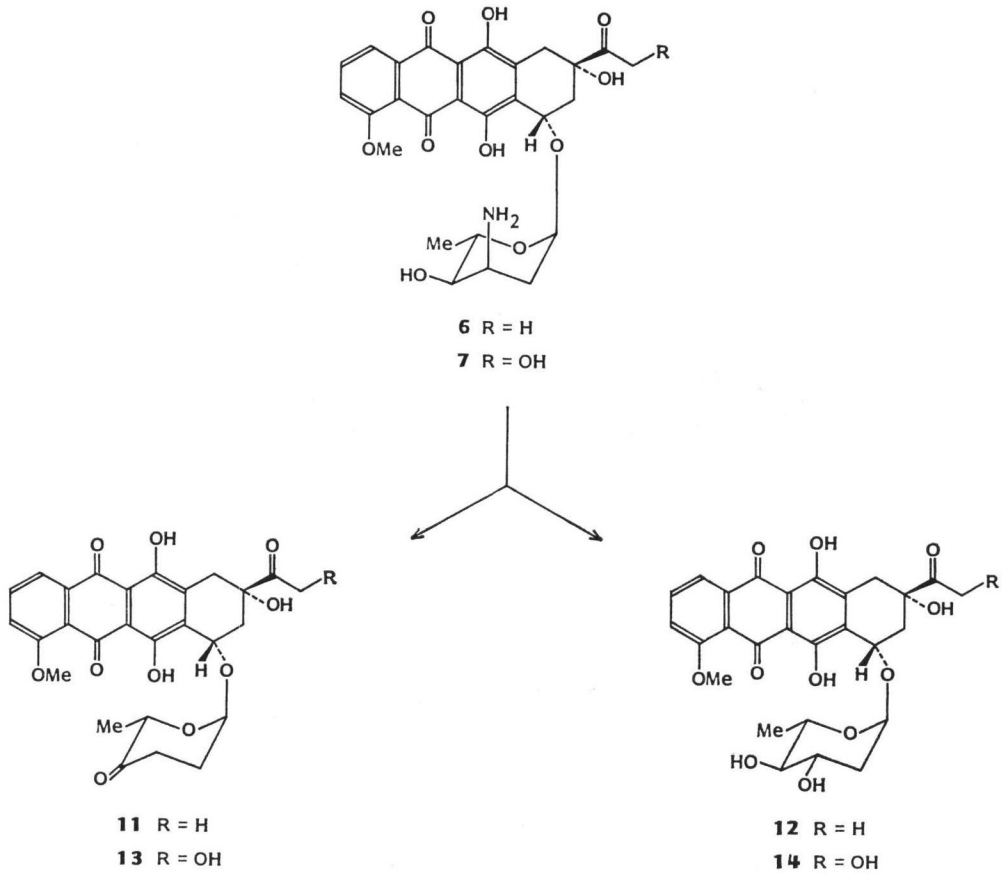


^{13}C and ^{1}H NMR data reported in the literature[14,22,23] for 4-keto-L-hexopyranoses with an analogous conformation are in good agreement with our results. Anthracyclines **12** and **14** were extensively analyzed by 2D-^{1}H NMR[24] to confirm the stereochemistry at C-3′ and C-4′ centers. The coupling patterns of H-3′ and H-5′ from the 2D-J resolved spectrum of **12** are reported in Fig. 1, from which the stereochemistry at C-3′ and C-4′ centers can be safely deduced. In the normal one dimentional ^{1}H NMR spectrum the signals of H-3′ and H-5′ are badly overlapped preventing the determination of coupling constant values.

Some daunorubicin and doxorubicin analogues, in which the natural amino sugar L-daunosamine is replaced by neutral sugar residues, have been prepared by glycosidation of the corresponding aglycones, such as β-D-*gluco*-hexopyranosyl-,[25] 2,6-dideoxy-α-L-*lyxo*-hexopyranosyl-,[26~30] 2,6-dideoxy-α- and -β-D-*ribo*-hexopyranosyl-,[26] 2-deoxy-D-*erythro*-pentopyranosyl-,[31] and 2,6-dideoxy-2-iodo-α-L-*manno* and -*talo*-hexopyranosyl glycosides.[27,32,33] Among these deamino anthracyclines, only 3′-deamino-3′-hydroxydoxorubicin,[30] its 3′,4′-di-*O*-acetyl derivative,[27] and 2′-halo-3′-hydroxyl analogues[32] displayed against some experimental tumors an activity comparable or higher than that of doxorubicin.

The nitrous acid deamination approach herein described represents a facile synthetic route to new deamino anthracyclines not readily accessible by other procedures. Furthermore the outstanding antileukemic activity of 7-*O*-(2,6-dideoxy-α-L-*arabino*-hexopyranosyl)adriamycinone (**14**) and the activity by oral route of 7-*O*-(2,3,6-trideoxy-α-L-*glycero*-hexopyranosid-4-ulose)adriamycinone (**13**)

Scheme 2.



make these new anthracyclines worthy of further investigations.

Experimental

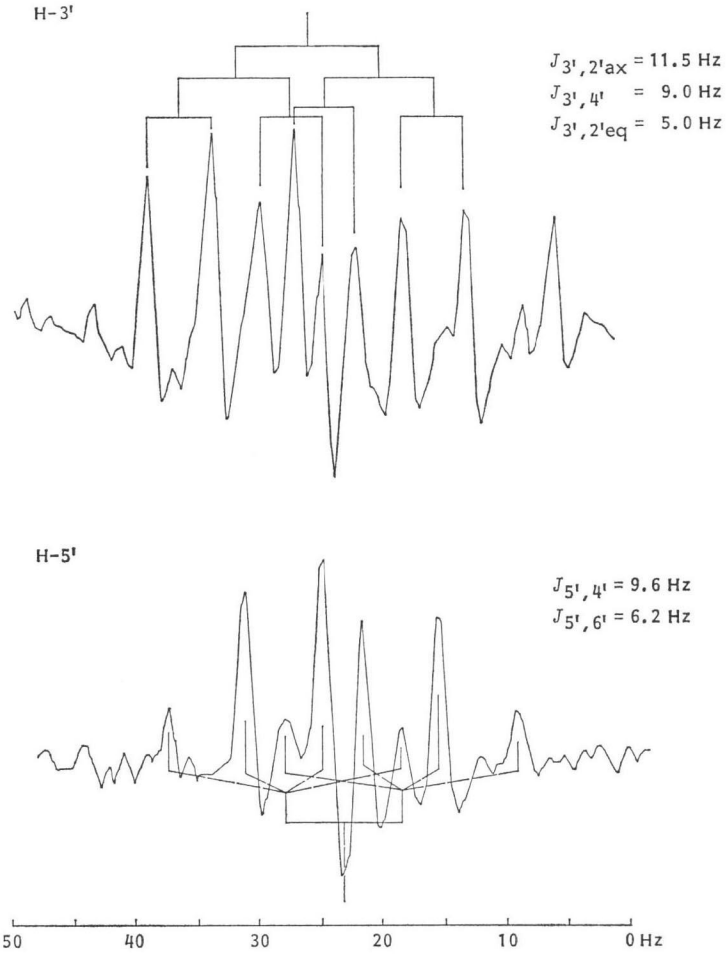
TLC was performed on precoated glass plates (0.25 mm) of silica gel 60F-254 (E. Merck, Darmstadt, GFR). Melting points, obtained with a SMP-20 apparatus (Büchi), are uncorrected. Optical rotations were measured with a Perkin-Elmer 151 polarimeter in 1 dm tubes. ^{1}H and ^{13}C NMR spectra were taken on XL-200 or CFT-20 Varian instruments and the data are reported in Tables 1 and 2. 2D-Homocorrelation, 2D-J resolved and 2D-NOE experiments were performed on the XL-200 Varian. Mass spectra were obtained on a Varian Mat 311-A spectrometer equipped with a combined EI/FD source.

7-*O*-(2,3,5-Trideoxy-3-*C*-formyl-α-L-*threo*-pentofuranosyl)daunomycinone (**8**)

A stirred solution of daunorubicin hydrochloride (**1**)[10] (4.5 g, 8 mmol) in water (200 ml) cooled at 0°C was treated with sodium nitrite (2.7 g, 80 mmol) and 1 N aqueous acetic acid (80 ml), added in several portions over a period of 20 minutes at such a rate that the temperature did not exceed 0°C; the pH was maintained at 3.5. After 3 hours, the reaction mixture which contained a red precipitate was brought to room temperature and filtered. The solid was washed with water and then dissolved in chloroform. The solution, dried over anhydrous magnesium sulfate and evaporated under reduced pressure, gave a red solid upon addition of *n*-hexane; yield 4.0 g (98%); mp 179~180°C (dec); $[\alpha]_D^{23}$

Fig. 1. Cross section corresponding to H-3′ (ν_H=769.08 Hz) and H-5′ (ν_H=790.10 Hz) from the 2D-J resolved ^{1}H NMR spectrum of **12** in $CDCl_3$.

The outlines are shown as phased spectra on a scale of 50 Hz. Coupling patterns and $^3J_{HH}$ values are also shown.



+178° (*c* 0.04, MeOH); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$) 233 (643), 252 (463), 290 (156), 480 (227), 496 (232) and 530 (sh 134); IR ν_{max}^{KBr} 1720 (C=O), 1620 and 1580 cm^{-1} (H-bonded quinone); FD-MS *m/z* 510 $[M]^{+\cdot}$.

Anal Calcd for $C_{27}H_{26}O_{10}\cdot H_2O$ (528.5): C 61.36, H 5.34.
Found: C 61.67, H 5.19.

7-*O*-(2,3,5-Trideoxy-3-*C*-formyl-α-L-*erythro*-pentofuranosyl)daunomycinone (**9**)

A chloroform solution (20 ml) of compound **8** (2.0 g, 4 mmol) was passed through a column of silica gel buffered at pH 7 (phosphate buffer). The chloroform effluent and the eluate with $CHCl_3$-acetone, 98: 2 contained a single constituent slightly more polar (Rf 0.20) than **8** (Rf 0.25) on TLC ($CHCl_3$-acetone, 95: 5). After concentration and precipitation upon addition of *n*-hexane, **9** was obtained as red amorphous powder; yield 1.8 g (90%); mp 120~121°C (dec); $[\alpha]_D^{23}$ +246° (*c* 0.05, MeOH). UV, IR and mass spectra were found practically superimposable to those of the *threo* analogue **8**.

7-*O*-(2,3,5-Trideoxy-3-*C*-formyl-α-L-*threo*-pentofuranosyl)adriamycinone (**10**)

The deamination procedure of daunorubicin was repeated with doxorubicin hydrochloride (**2**)[11]

(2.3 g, 4 mmol) and the reaction product **10** was isolated as a red solid; yield 1.9 g (90%); mp 150~151°C (dec); $[\alpha]_D^{23}$ +269° (*c* 0.05, $CHCl_3$); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$) 233 (620), 253 (460), 480 (222), 496 (225) and 530 (sh 140); IR ν_{max}^{KBr} 1730 (C=O), 1620 and 1580 cm^{-1} (H-bonded quinone); FD-MS *m/z* 526 $[M]^{+\cdot}$.

Anal Calcd for $C_{27}H_{26}O_{11}\cdot H_2O$: C 59.55, H 5.18.
Found: C 59.66, H 5.04.

7-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulose)daunomycinone (**11**) and 7-*O*-(2,6-Dideoxy-α-L-*arabino*-hexopyranosyl)daunomycinone (**12**)

Deamination of 3′,4′-diepidaunorubicin hydrochloride (**6**)[6] (2.3 g, 4 mmol), carried out as previously described, gave a mixture of two products which were detected by TLC (Rf 0.45 and 0.05, CH_2Cl_2 - acetone, 97: 3) and extracted from the reaction mixture with chloroform. The extract, washed with water and dried over anhydrous sodium sulfate, was evaporated to a small volume and chromatographed on a silica gel column. Elution with chloroform gave, after concentration and precipitation with *n*-hexane, the less polar compound **11** as an amorphous red solid; yield 0.81 g (40%); mp 143~144°C (dec); $[\alpha]_D^{23}$ +190° (*c* 0.05, MeOH); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$) 235 (808), 253 (557), 290 (188), 480 (236), 496 (242) and 530 (sh 143); IR ν_{max}^{KBr} 1725 (C=O), 1620 and 1585 cm^{-1} (H-bonded quinone); FD-MS *m/z* 510 $[M]^{+\cdot}$.

Anal Calcd for $C_{27}H_{26}O_{10}\cdot 1/2H_2O$ (519.5): C 62.42, H 5.24.
Found: C 62.18, H 5.10.

Elution with $CHCl_3$ - acetone, 97: 3 gave the more polar compound **12** as a red powder; yield 0.74 g (35%); mp 165~170°C (dec); $[\alpha]_D^{23}$ +340° (*c* 0.025, MeOH); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$) 235 (714), 254 (509), 290 (154), 480 (226), 496 (231) and 530 (sh 142); IR ν_{max}^{KBr} 1710 (C=O), 1610 and 1570 cm^{-1} (H-bonded quinone); FD-MS *m/z* 528 $[M]^{+\cdot}$.

Anal Calcd for $C_{27}H_{28}O_{11}$ (528.5): C 61.36, H 5.34.
Found: C 61.70, H 5.07.

7-*O*-(2,3,6-Trideoxy-α-L-*glycero*-hexopyranosid-4-ulose)adriamycinone (**13**) and 7-*O*-(2,6-Dideoxy-α-L-*arabino*-hexopyranosyl)adriamycinone (**14**)

Deamination of 3′,4′-diepidoxorubicin hydrochloride (**7**)[7] (1.2 g, 2 mmol) gave two major products, detected by TLC (Rf 0.7 and 0.45, $CHCl_3$ - MeOH - water, 100: 20: 2) which were extracted with chloroform and butanol, respectively, from the reaction mixture. The chloroform extract was chromatographed on a silica gel column and the effluent, after concentration and precipitation with *n*-hexane, gave the less polar compound **13** as a red powder; yield 0.47 g (45%); mp 140~141°C (dec); $[\alpha]_D^{23}$ +145° (*c* 0.046, MeOH); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$) 235 (690), 254 (490), 290 (190), 480 (228), 496 (230) and 530 (sh 140); IR ν_{max}^{KBr} 1730 (C=O), 1620 and 1585 cm^{-1} (H-bonded quinone); FD-MS *m/z* 526 $[M]^{+\cdot}$.

Anal Calcd for $C_{27}H_{26}O_{11}\cdot H_2O$ (544.5): C 59.55, H 5.18.
Found: C 59.71, H 4.81.

Crude **14** was obtained upon concentration of the butanol extract and precipitation with *n*-hexane. Silica gel column chromatography ($CHCl_3$ - MeOH, 95: 5 elution) gave **14** in pure form as a red solid; yield 0.39 g (36%); mp 186~190°C; $[\alpha]_D^{23}$ +280° (*c* 0.046, MeOH); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$) 235 (674), 254 (478), 290 (186), 480 (223), 496 (228) and 530 (sh 148); IR ν_{max}^{KBr} 1725 (C=O), 1620 and 1585 cm^{-1} (H-bonded quinone); FD-MS *m/z* 544 $[M]^{+\cdot}$.

Anal Calcd for $C_{27}H_{28}O_{12}\cdot H_2O$ (562.5): C 57.64, H 5.37.
Found: C 57.67, H 5.05.

Acknowledgments

Thanks are due to Dr. D. BORGHI for the 2D-NOE experiments, to Drs. B. GIOIA and E. ARLANDINI for mass spectral determinations and to Mrs. C. GERONI for cytotoxicity data. We thank also Dr. R. RICHARZ of Varian Application Laboratories in Zug (Switzerland) for performing and interpreting 2D-homocorrelated and 2-DJ resolved ^1H NMR experiments with skill and dedication. This work was supported by the Istituto Mobiliare Italiano (I.M.I.).

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