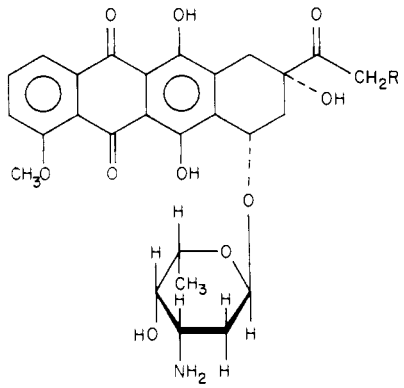
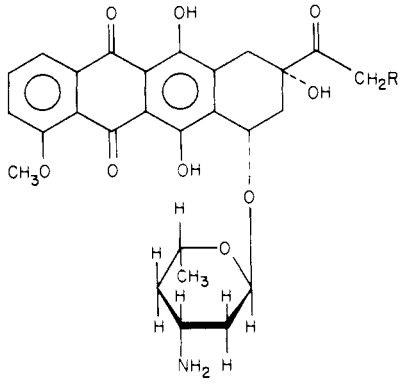
Synthesis and Antitumor Activity of 4′-Deoxydaunorubicin and 4′-Deoxyadriamycin

Sir:

The antibiotics daunorubicin (1) and adriamycin (2), whose effectiveness for the therapy of different human tumors is well established,[1] are glycosides belonging to the anthracycline family of antibiotics. In order to develop new antitumor agents, analogues of 1 and 2, in which the amino sugar residue is configurationally different with respect to the parent antibiotics, have been synthesized. It has been shown that compounds, in which the sugar moiety is changed from L-lyxo to the L-arabino and L-ribo configuration, display high activity in experimental tumors in mice.[2-4] Continuing our program directed toward the semisynthesis of analogues of the antitumor anthracyclines modified in the daunosamine residue, we now report the synthesis and biological activity of 4′-deoxydaunorubicin (3) and 4′-deoxyadriamycin (4). In these new compounds the natural amino sugar, daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), is replaced by the corresponding 4-deoxy analogue (3-amino-2,3,4,6-tetradeoxy-L-*threo*-hexose), an amino sugar previously unknown and obtained by us from methyl *N*-trifluoroacetyldaunosaminide (5).[3]

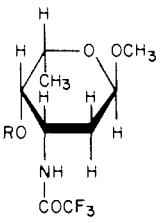


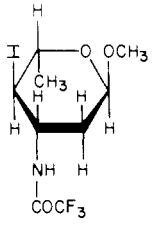
1, R = H
2, R = OH

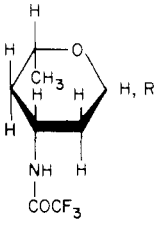


3, R = H
4, R = OH

The treatment of 5 (5 g, 0.019 mol) with 4-*p*-bromobenzenesulfonyl chloride (15 g, 0.058 mol) in pyridine (25 °C, 96 h) gave 8.3 g (92% yield) of the corresponding 4-*p*-bromobenzenesulfonyl derivative 6: mp 170–172 °C; $[\alpha]_D$ −113.7° (*c* 0.78, $CHCl_3$). Anal. ($C_{15}H_{17}F_3BrNO_6S$) C, H. This compound (5 g, 0.01 mol), by treatment with NaI (2.8 g, 0.019 mol) in methyl ethyl ketone at refluxing temperature for 5 h, gave the 4-iodo derivative 7 (3.2 g, 84% yield): mp 194–195 °C; $[\alpha]_D$ −100° (*c* 0.1, $CHCl_3$); *m/e* 367 (M^+); ^1H NMR ($CDCl_3$–Me_2SO-d_6, 2:1) δ 1.46 (d, J = 6.0 Hz, CH_3-C_5), 3.38 (s, CH_3O), and 4.83 (t, J = 2.5 Hz, C-1 H). Anal. ($C_9H_{11}F_3INO_3$) C, H. The reduction of 7 in the presence of Adams catalyst, followed by acid hydrolysis (3.5 N AcOH for 3 h at 90 °C), gave 2,3,4,6-tetradeoxy-3-trifluoroacetamido-L-*threo*-hexopyranose (8) in 90% overall yield: mp 159–160 °C; at equilibrium $[\alpha]_D$ = −80° (*c* 0.1, $CHCl_3$); *m/e* 210 (M − OH); ^1H NMR (Me_2SO-d_6) δ 1.03 (d, J = 6.0 Hz, CH_3-C_5 α anomer), 1.09 (d, J = 6.0 Hz, CH_3-C_5 β anomer), 1.2–1.9 (m, C-2 H_2 and C-4 H_2), 4.6 (dd, J = 2.0 Hz, J' = 9 Hz, C-1 H ax), 5.17 (br s, W_H = 6 Hz, C-1 H eq), 6.08 (dd, J' = 4 Hz, J'' = 1 Hz, C-1 OH ax), and 6.46 (d, J = 7 Hz, C-1 OH eq). Anal. ($C_8H_{12}F_3NO_3$) C, H. Para nitrobenzoylation of 8 with *p*-nitrobenzoyl chloride in pyridine followed by treatment with dry hydrogen chloride gave the 1-chloro derivative 9 in quantitative yield. Compound 9 was used for the coupling reaction without purification owing to its instability.







5, R = H
6, R = *p*-Br-C_6H_4-SO_2-

7

8, R = OH
9, R = Cl

The synthesis of glycosidic linkage was performed by treatment of daunomycinone with 9 (1.1 mmol) in methylene chloride at room temperature for 30 min, using silver trifluoromethanesulfonate[5] (1.1 mmol) as catalyst, to give stereoselectively the *N*-trifluoroacetyl derivative of 4′-deoxydaunorubicin. Removal of the protective group with 0.1 N aqueous sodium hydroxide afforded 4′-deoxydaunorubicin (3), which was isolated as the hydrochloride: single spot with R_f 0.6 on TLC and system $CHCl_3$–CH_3OH–H_2O (13:6:1 v/v); mp 160–164 °C dec; $[\alpha]_D$ +296° (*c* 0.05, methanol). Anal. ($C_{27}H_{30}ClNO_9$)H; C: calcd, 59.17; found, 58.61. The α configuration of the glycosidic linkage was assigned on the basis of the C(1)′–H NMR signal, which is a broad singlet (W_H ~ 9.5 Hz) at 5.38 (Me_2SO-d_6), a characteristic region for the α anomers in the glycosides of anthracyclines.[2,3] The corresponding adriamycin analogue 4 [mp 163 °C dec; $[\alpha]_D$ +320° (*c* 0.05, methanol); R_f 0.5 on TLC and system $CHCl_3$–CH_3OH–H_2O (13:6:1 v/v). Anal. ($C_{27}H_{30}ClNO_{10}$) C, H] was obtained from 3 in 50% yield via the 14-bromo derivative, R_f 0.65 on TLC and system $CHCl_3$–CH_3OH–H_2O (13:6:1 v/v), following a procedure already described for the chemical transformation of daunorubicin to adriamycin.[6]

The biological activity of 3 and 4 appears to be equal or improved when the compounds are compared with the parent antibiotics on L1210 leukemia in mice (Table I). Compound 4 shows noticeable activity on solid Sarcoma 180 in mice (Table II).

Table I. Activity of 4'-Deoxydaunorubicin (3) and 4'-Deoxyadriamycin (4) on L1210 Leukemia in Mice[a]

Compd	Optimal dose[b]	T/C[c]	LST[d]
Daunorubicin	2	162	
3	4	162	
Adriamycin	5	155	2/10
4	4	177	2/10

[a] Tumor inoculum 10^5 cells, ip. [b] Treatment ip on day 1 (mg/kg of body weight). [c] Average survival time expressed as percent of untreated controls. Median survival time of untreated controls was 9 days. [d] Long-term survivors (60 days). No toxic deaths were observed at optimal doses indicated.

Table II. Comparison of 4'-Deoxyadriamycin (4) with Adriamycin on Solid Sarcoma 180 in Mice

Compd	Dose[a]	Tumor growth[b]	T/C[c]
Adriamycin	1.6	52	95
	2	51	184
4	0.8	47	90
	1	46	143

[a] Treatment iv on days 1-5 (mg/kg/day). [b] Tumor size evaluated in live animals on day 11 after tumor implant expressed as percent of untreated controls. [c] Average survival time expressed as percent of untreated controls. Median survival time of untreated controls was 22 days.

Acknowledgments. The authors are indebted to A. Di Marco and A. M. Casazza of the Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, for the biological data; to A. Vigevani and B. Gioia for the interpretation of the ^{1}H NMR and mass spectra; and to A. Alemanni for elemental analysis.

References and Notes

(1) S. K. Carter, *J. Natl. Cancer Inst.*, **55**, 1265 (1975).
(2) F. Arcamone, S. Penco, and A. Vigevani, *Cancer Chemother. Rep.*, **6**, 123 (1975).
(3) F. Arcamone, S. Penco, A. Vigevani, S. Redaelli, G. Franchi, A. Di Marco, A. M. Casazza, T. Dasdia, F. Formelli, A. Necco, and C. Soranzo, *J. Med. Chem.*, **18**, 703 (1975).
(4) F. Arcamone, A. Bargiotti, G. Cassinelli, S. Penco, and S. Hanessian, *Carbohyd. Res.*, **46**, C3 (1976).
(5) F. Arcamone, A. Bargiotti, A. Di Marco, and S. Penco, British Patent Application 18098/75 (April 30, 1975); S. Hanessian and J. Banoub, *Carbohyd. Res.*, **44**, C14 (1975), and references cited therein.
(6) F. Arcamone, G. Franceschi, and S. Penco, U.S. Patent 3 803 124 (April 9, 1974).

Federico Arcamone,* Sergio Penco, Silvio Redaelli
Farmitalia, Ricerca Chimica, Milano, Italy

Stephen Hanessian
Department of Chemistry, University of Montreal Montreal, Quebec, Canada

Received June 23, 1976

Additions and Corrections

1968, Volume 11

Girgis M. Bebawi and J. P. Lambooy: Synthesis of Substituted 4-Dimethylaminoazobenzenes and a Study of Their Effect on *Lactobacillus casei* and *Escherichia coli*.

Page 580. In column 2, line 1, "certainty on complete" should read certainty or complete.

Page 581. In Table I under Composition, the sixth formula should be $C_{17}H_{21}N_3$, the seventh formula $C_{17}H_{21}N_3$, and the eighth formula $C_{18}H_{23}N_3$.

1975, Volume 18

W. J. Wechter, M. A. Johnson, C. M. Hall, D. T. Warner, A. E. Berger, A. H. Wenzel, D. T. Gish, and G. L. Neil: *ara*-Cytidine Acylates. Use of Drug Design Predictors in Structure–Activity Relationship Correlation.

Page 342. In column 2, line 23 should read law ($A = Ebc$, where A is the absorbance, E the molar extinction coefficient, etc.). In line 27, the equation should read

$$P = c_{O/W}/c_{W/O} = \frac{(A_O)(E_W b_W)}{(A_W)(E_O b_O)}$$

In line 29, the equation should read

$$P = A_O E_W / A_W E_O$$

Norman J. Santora and King Auyang: Non-Computer Approach to Structure–Activity Study. An Expanded Fibonacci Search Applied to Structurally Diverse Types of Compounds.

Page 960. In column 2, line 1, "point number 19" should read point number 14.

Arthur A. Santilli, Anthony C. Scotese, and John A. Yurchenco: Synthesis and Antibacterial Evaluation of 1,2,3,4-Tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid Esters, Carbonitriles, and Carboxamides.

Page 1041. To ref 7 should be added, A. A. Santilli and A. C. Scotese, U.S. Patent 3 853 864 (1974), which specifically describes the preparation of methyl 2-chloro-6-methylnicotinate.

Gilda H. Loew and J. Randal Jester: Quantum Chemical Studies of Meperidine and Prodine.

Page 1054. Figures 4 and 5 are mistakenly identical. While the captions of each are correct, Figure 4 itself is wrong. Below is the correct Figure 4.