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Adriamycin Analogues. 2. Synthesis of 13-Deoxyanthracyclines[1]

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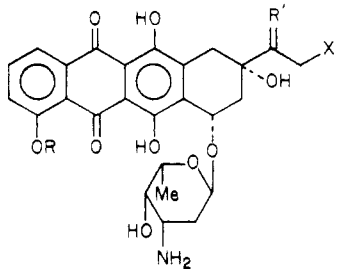
The syntheses of several 13-deoxyanthracyclines are described. Koenigs–Knorr condensation of ϵ-rhodomycinone (**12**) with the protected daunosaminyl chloride **15** afforded **14** after deprotection. Efforts to decarbomethoxylate **12**, as well as attempts to selectively deoxygenate the 13 position of daunomycinone and adriamycinone, were unsuccessful as approaches to 13-deoxyanthracyclines. However, reaction of the readily available tosylhydrazones **4** and **5**, of daunorubicin and adriamycin with $NaCNBH_3$ in acidic MeOH, afforded the 13-deoxy analogues **6** and **7** in satisfactory yield. These compounds retained antitumor activity, being comparable to the parent compounds in both efficacy and potency in the P-388 mouse leukemia screen. The ϵ-rhodomycinone glycoside **14** was less active than **6** and **7**.

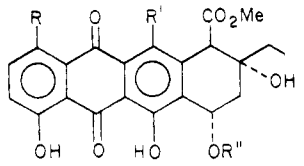
The anthracycline antibiotics, daunorubicin[2] (**1**),

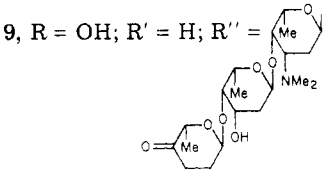


1, R = Me; R′ = O; X = H
2, R = Me; R′ = O; X = OH
3, R = X = H; R′ = O
4, R = Me; R′ = NNHTS; X = H
5, R = Me; R′ = NNHTS; X = OH
6, R = Me; R′ = H_2; X = H
7, R = Me; R′ = H_2; X = OH
8, R = Me; R′ = NNHCOPh; X = H

adriamycin[3] (**2**), and carminomycin[4] (**3**), show significant antineoplastic activity against a variety of experimental tumors with daunorubicin and especially adriamycin having clinical utility against human cancer. However, chemotherapy employing these agents is hampered by a number of undesirable side effects, the most serious being dose-related cardiotoxicity.[5] As part of our efforts to prepare related compounds having improved therapeutic properties, we now report the results of our studies of a number of synthetic approaches to 13-deoxyanthracyclines.

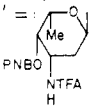
The antitumor agents **1**–**3** differ from the majority of the naturally occurring anthracyclines by the presence of the carbonyl function of C-13,[6] which is one of the principal sites of in vivo metabolism of **1** and **2**.[7] Lacking the carbonyl function at C-13, the 13-deoxy analogues might possibly display biological properties markedly different from the parent compounds and, in fact, the 13-deoxyanthracyclines, cinerubin A (**9**)[8] and aclacinomycins A and B (**10** and **11**),[9] have already demonstrated several interesting biological properties. Besides possessing potent antitumor activity, aclacinomycin A is reported to be substantially less cardiotoxic than adriamycin as determined by ECG monitoring of hamsters,[9] while cinerubin was found to possess low but reproducible activity against an adriamycin-resistant subline of P-388 leukemia.[10]





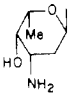
9, R = OH; R′ = H; R″ =

12, R = R″ = H; R′ = OH
13, R = H; R′ = OH; R″ =

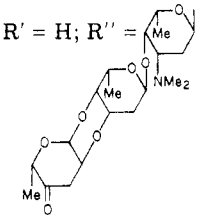


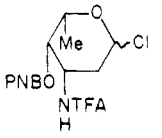
10, R = R′ = H; R″ = R″ in structure **9**

14, R = H; R′ = OH; R″ =



11, R = R′ = H; R″ =





15

Chemistry. ϵ-Rhodomycinone (**12**),[11] a fermentation by-product, was received as a gift from Bristol Laboratories. We hoped that this aglycon would afford a facile and economic route to 13-deoxyanthracyclines. The Koenigs–Knorr condensation of **12** with four 1 molar equiv portions of 1-chloro-3-*N*-trifluoroacetyl-4-*O*-*p*-nitrobenzoyldaunosamine (**15**)[12] afforded stereospecifically the α-glycoside **13**. The crude product was treated with aqueous NaOH in THF at 0 °C to effect removal of the sugar-protecting groups. The glycoside **14** could be separated from the now water-soluble sugar by-products of the coupling reaction by solvent extraction and was isolated as the HCl salt in 70% yield from **12**.

Attempts to use the aglycon **12** as a starting material for the synthesis of novel aglycons have been unsuccessful. As

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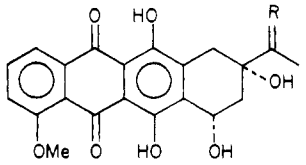
would be expected of an axial carbomethoxy group flanked by two ortho substituents,[13] the methyl ester function of **12** was quite resistant to base hydrolysis. Efforts to directly decarbomethoxylate **12** under a variety of conditions were also unsuccessful, and this approach was abandoned.

An obvious route to 13-deoxyanthracyclines is the reductive deoxygenation of the 13-carbonyl of daunorubicin, adriamycin, or their aglycons. While the chemical literature describes several methods for the deoxygenation of the keto function, this approach is complicated by the presence of other easily reducible functionalities, such as the oxygen function at C-7 and the quinizarin nucleus of the aglycon. These problems were apparent in our unsuccessful attempts to deoxygenate daunomycinone **16** via



16, R = O
17, R = $-SCH_2CH_2S-$
18, R = NNHTs
19, R = H_2

a modified Clemensen procedure[14] or desulfurization of the dithioketal **17**.

The deoxygenation of carbonyl compounds via reduction of their tosylhydrazones with $NaCNBH_3$ has been shown to be an efficient and general procedure.[15] Daunomycinone (**16**) was converted to the tosylhydrazone **18** in 85% yield. Reaction of **18** with 5 molar equiv of $NaCNBH_3$ in 1:1 sulfolane–DMF containing 1% *p*-toluenesulfonic acid at 100 °C afforded 13-deoxydaunomycinone (**19**) in 18% yield.

The poor yield of **19** appeared to rule out this procedure as a practical route to 13-deoxyanthracyclines especially since the coupling of the aglycon with the sugar moiety was still required. However, the possibility of performing the deoxygenation directly on the glycosides appeared attractive. The 13-tosylhydrazones, **4** and **5**, of the parent antibiotics were prepared in 94 and 95% yields, respectively. Reaction of **4** with excess $NaCNBH_3$ in refluxing MeOH containing 1% *p*-toluenesulfonic acid afforded 13-deoxydaunorubicin (**6**) in 29% yield after silica gel chromatography. A partially identified mixture of nonpolar aglycon and 7-deoxyaglycon type materials was also formed. The 13-deoxygenated glycoside **6** was readily characterized by its ^1H NMR spectrum in which the 14-methyl group, which appeared as a singlet at δ 1.85 in **4**, was now a triplet at δ 0.93 coupled to the new methylene group. The reaction of **5** under identical conditions afforded 13-deoxyadriamycin (**7**) in 33% yield. The structures of **6** and **7** were also confirmed by the absence of sulfonyl and 13-carbonyl absorption in their IR spectra.

Results and Discussion

Table I presents a comparison of the test data from the parent compounds and the anthracycline derivatives prepared in this study. The 13-deoxy derivatives **14**, **6**, and **7** showed similar effects on the stabilization of helical DNA to thermal denaturation as determined by their ΔT_m values. However, these values are less than those of **1** and **2**, indicating a somewhat decreased ability to bind to DNA. The ΔT_m values for the tosylhydrazones **4** and **5** were lower, possibly due to inhibition of intercalation by the steric bulk of the hydrazone function.

All of the derivatives inhibited nucleic acid synthesis in cultured L1210 cells, with the 13-deoxy derivatives **6** and **7** being nearly as potent as the parent compounds. Again the tosylhydrazones **4** and **5**, while displaying significant inhibition, were much less active than the other compounds.

The anthracyclines were assayed in vivo against transplanted P-388 lymphocytic leukemia in the mouse. The presence of the 10-carbomethoxy function of **14** seems to be deleterious as **14** is both less active and less potent than **6**. The tosylhydrazones **4** and **5**, despite their rather mediocre in vitro activities, did show high in vivo activity, albeit at higher doses than the parent compounds. This is possibly due to hydrolysis of the hydrazone moiety under physiological conditions to regenerate the parent compounds. A precedent for this is the hydrolysis of the benzoylhydrazone function of rubidazone (**8**) and its analogues which has been observed under approximate physiological conditions.[16] The other 13-deoxy analogues **6** and **7** retained high activity at low doses.

The results of this study indicate that the 13-carbonyl function is not intrinsically required for the biological activity of **1** and **2**. Analogues **6** and **7** are comparable both in terms of efficacy and potency to the parent compounds, but further evaluation is required to determine if **6** and **7** offer any advantage.

Experimental Section

Solvent extracts of aqueous solutions were dried over anhydrous Na_2SO_4. Solutions were concentrated under reduced pressure using a rotary evaporator. All melting points are uncorrected. Infrared spectra (Nujol, Beckman IR-4 instrument) were obtained by the Pharmaceutical Analyses Department of SRI under the direction of Dr. Peter Lim. Measurements of 100-MHz NMR spectra were performed by Mr. L. Cary using a Varian XL-100 spectrometer with Me_4Si as an internal standard. Elemental microanalyses were provided by the microanalytical laboratory of Stanford University.

Thin-layer chromatograms (TLC) were obtained on silica gel GF 250-μ plates (Analtech). Preparative layer chromatograms (PLC) were obtained on 20 × 20 × 0.2 cm silica gel 60 F-254 plates (E. Merck). Column chromatography were performed with Bio-Sil A 200–305 mesh (Bio-Rad) or E. Merck prepacked silica gel 60 columns.

(7*S*,9*R*,10*R*)-7-[(3′-Amino-2′,3′,6′-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-10-carbomethoxy-9-ethyl-7,8,9,10-tetrahydro-4,6,9,11-tetrahydroxy-5,12-naphthacenedione Hydrochloride (14). ε-Rhodomycinone (**12**, 1.07 g, 2.50 mmol), $Hg(CN)_2$ (5.0 g), $HgBr_2$ (2.4 g), and powdered molecular sieve 3A (12.0 g) were placed in THF (250 mL) and stirred at 50–55 °C for 1 h. Four 2.50-mmol portions of freshly prepared 1-chloro-3-*N*-trifluoroacetyl-4-*O*-*p*-nitrobenzoyldaunosamine (**15**) in CH_2Cl_2 (25 mL) were added to the reaction mixture at 0, 3, 20, and 25.5 h, while stirring was continued at 50–55 °C. The chloro sugar was prepared by bubbling anhydrous HCl into a cold (0 °C) suspension of 1,4-di-*O*-*p*-nitrobenzoyl-3-*N*-trifluoroacetyldaunosamine (1.35 g, 2.50 mmol) for 5 min. The mixture was allowed to stand at 0 °C for 10 min and filtered to remove the *p*-nitrobenzoic acid. The filtrate was evaporated, redissolved in CH_2Cl_2 (25 mL), and added to the reaction mixture. Additional $Hg(CN)_2$ (5.2 g), $HgBr_2$ (2.4 g), and powdered molecular sieve 3A (12.0 g) were added to the reaction mixture at 20 h. Stirring at 50–55 °C was continued for 2.5 h after the last addition, for a total reaction time of 28 h. The reaction mixture was allowed to cool to 23 °C and filtered, and the precipitate washed with CH_2Cl_2 (50 mL). The combined filtrate was evaporated. The residue was triturated with $CHCl_3$ (250 mL) and filtered, and the filtrate was washed with 30% KI (3 × 160 mL), saturated $NaHCO_3$ (150 mL), and H_2O (800 mL), dried, and evaporated.

The residue was stirred for 5 h at 0 °C in 0.1 N NaOH–THF (1:1, 1.3 L), neutralized with 0.1 N HCl (600 mL), and extracted with $CHCl_3$ (3 × 400 mL). The extracts were combined, washed with saturated $NaHCO_3$ (2 × 200 mL) and water (3 × 200 mL), dried, and evaporated.

The residue was dissolved in $CHCl_3$–ether (1:1, 100 mL) and cooled to 0 °C. Ethereal HCl (5.80 mL of a 0.40 M anhydrous solution, 2.33 mmol) was added at 0 °C with vigorous stirring.

Table I. Comparison of Test Data for Daunorubicin, Adriamycin, and Analogues Prepared in the Present Study

Drug	ΔT_m,[a] °C	Nucleic acid syn inhibn,[a] ED_{50}, μM		Antitumor act. in mice[b]			
				P-388, qd 1-9		P-388, qd 5, 9, 13	
		DNA	RNA	Dose, mg/kg	T/C[c] (n)	Dose, mg/kg	T/C (n)
Dnr (1)	11.2	0.66	0.33	1.56	148 ± 35 (8)	16	127 ± 11 (17)
				0.78	167 ± 27 (8)	8	134 ± 6 (17)
				0.39	153 ± 9 (8)	4	131 ± 13 (17)
				0.20	144 ± 9 (8)		
Adm (2)	13.4	1.5	0.58	1.56	176 ± 72 (8)	16	130 ± 10 (4)
				0.78	197 ± 26 (8)	8	157 ± 21 (17)
				0.39	174 ± 14 (8)	4	142 ± 14 (17)
				0.20	160 ± 7 (8)	2	133 ± 14 (17)
						1	133 ± 4 (5)
14	7.6	5.6	2.6	12	141		
				8	140		
				5.3	139		
				4	132		
				3.5	130		
				1.5	127		
4	3.4	18	13	25	179		
				12.5	153		
				6.25	136		
				3.13	139		
5	2.3	13	7.5	12.5	125		
				6.25	171		
				3.13	137		
6	50	1.3	0.84	3.13	160 ± 3 (2)	18.8	140
				1.56	160 ± 9 (2)	9.4	132
				0.78	134 ± 1 (2)	4.7	131
				0.39	140 ± 9 (2)		
7	6.15	1.8	1.1	6.25	153	37.5	147
				3.13	164 ± 1 (2)	18.8	147
				1.56	156 ± 2 (2)	9.4	154
				0.78	161 ± 3 (2)	4.7	128
				0.39	140 ± 11 (2)		

[a] ΔT_m and ED_{50} values were determined by the method described in ref 1b except that the drugs were initially dissolved in a volume of Me_2SO that resulted in a final Me_2SO concentration of 5 and 1%, respectively, in the assay medium. This modification greatly aided solubilization and did not affect assay results according to extensive control experiments. [b] Assays arranged through the Drug Research and Development Program, Division of Cancer Treatment, National Cancer Institute. BDF or CDF mice are injected ip with 10^6 P-388 lymphocytic leukemia cells on day 0 and are treated ip on days 1-9 or days 5, 9, 13 with the specified drug dose. For detailed protocols, see R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, 3 (2), 9 (1972). [c] Ratio of average survival times of treated mice to untreated controls in percent. The average survival time of untreated controls is approximately 11 days. Activity is defined as values of T/C ≥ 125.

Additional ether (350 mL) was added and the mixture was kept at 0 °C for 3.5 h. The precipitate was collected, washed with ether, and dried to afford 1.08 g (72%) of **14**: IR 2.95 (OH), 5.00 ($-NH_3^+$), 5.78 (C=O), 6.50 μm (quinone); UV–visible λ_{max} (MeOH) 235 nm (ε 33 910), 254 (20 806), 296 (5493), 492 (15 224), 510 (11 582), 527 (10 000); NMR (Me_2SO-d_6) δ 1.18 (m, 6, 14-H_3 and 6′-H_3), 1.3–2.3 (m, 6, 13-H_2 and 2′-H_2), 3.70 (s, 3, CO_2Me), 4.16 (s, 1, 10-H), 4.98 (br s, 1, 7-H), 5.37 (br s, 1, 1′-H), 7.35 (d, 1, 3-H), 7.73 (m, 2, 1-H and 2-H); TLC (4:1 $CHCl_3$–MeOH) R_f 0.40. Anal. ($C_{28}H_{31}NO_{11}$·HCl·H_2O) C, H, N.

Daunomycinone 13-Ethylenedithioketal (17). Daunomycinone (**16**, 21.0 mg, 0.050 mmol) and ethanedithiol (40 μL) were placed in $CHCl_3$ (5 mL). HCl(g) was slowly bubbled into the solution for 1 h and the solution was stirred at 23 °C for 2 h. The solvent was removed, and the residue was triturated with $CHCl_3$ (20 mL) and filtered. The filtrate was evaporated, and the residue was chromatographed (PLC, 95:5 $CHCl_3$–MeOH) to afford 18.2 mg (77%) of **17**: mp 234–237 °C; IR 2.85 (OH), 6.16, 6.30 μm (H-bonded quinone); NMR ($CDCl_3$) δ 2.02 (s, 3, 14-H_3), 2.21 (m, 2, 3-H_2), 3.02 (m, 2, 10-H_2), 3.39 (s, 4, SCH_2CH_2S), 4.09 (s, 3, OMe), 5.31 (m, 1, 7-H), 7.34 (dd, 1, J = 8 Hz and J = 1 Hz, 3-H), 7.74 (t, 1, J = 8 Hz, 2-H), 8.01 (dd, 1, J = 8 Hz and J = 1 Hz, 1-H), 13.34 (s, 1, phenolic OH), 13.96 (s, 1, phenolic OH); TLC (95:5 $CHCl_3$–MeOH) R_f 0.48. Anal. ($C_{23}H_{22}O_7S_2$) C, H.

Daunomycinone 13-Tosylhydrazone (18). Daunomycinone (**16**, 15 mg, 0.038 mmol), *p*-toluenesulfonylhydrazide (9 mg, 0.048 mmol), and *p*-toluenesulfonic acid (3.0 mg) were placed in THF (5 mL) and refluxed for 2.5 h. The solvent was removed, and the residue was triturated with hot MeOH (6 mL), cooled, and filtered to afford 18.3 mg (85%) of **18**: mp 201–205 °C; IR 2.90 (OH, NH), 6.15, 6.30 (H-bonded quinone), 8.62 μm (SO_2); TLC (95:5 $CHCl_3$–MeOH) R_f 0.28. Anal. ($C_{28}H_{26}N_2O_9S$·0.25H_2O) C, H, N.

13-Deoxydaunomycinone (19). Daunomycinone (**16**, 29.2 mg, 0.073 mmol) and *p*-toluenesulfonylhydrazide (20 mg) were placed in EtOH (100 mL) and refluxed for 6 h. The solvent was removed, and the residue was placed with *p*-toluenesulfonic acid (7.0 mg) and $NaCNBH_3$ (40 mg) in 1:1 DMF–sulfolane (4 mL) and stirred at 100 °C under N_2 for 1 h. The reaction mixture was allowed to cool, quenched with saturated NH_4Cl (20 mL), and extracted with benzene (3 × 10 mL). The extracts were combined, washed with H_2O (2 × 10 mL), saturated $NaHCO_3$ (10 mL), and saturated NaCl (10 mL), dried, and evaporated. The residue was chromatographed (PLC 95:5 $CHCl_3$–MeOH) to afford 5.3 mg (19%) of **19**: IR 2.90 (OH), 6.20, 6.30 μm (H-bonded quinone); NMR δ 1.11 (t, 3, 14-H_3), 1.75 (q, 2, 13-H_2), 2.18–2.64 (m, 2, 8-H_2), 3.10–3.45 (m, 2, 10-H_2), 4.09 (s, 3, OMe), 5.29 (br s, 1, 7-H), 7.35 (dd, 1, J = 8 Hz and J = 1 Hz, 3-H), 7.76 (t, 1, J = 8 Hz, 2-H), 8.02 (dd, 1, J = 8 Hz and J = 1 Hz, 1-H), 13.30 (s, 1, phenolic OH), 13.99 (s, 1, phenolic OH); MS (12 eV) *m/e* (%) 384 M (100), 366 (88), 348 (58); TLC (95:5 $CHCl_3$–MeOH) R_f 0.33. Anal. ($C_{21}H_{20}O_7$) C, H.

Daunorubicin 13-Tosylhydrazone Hydrochloride (4). Daunorubicin hydrochloride (**1**, 354.4 mg, 0.628 mmol) and *p*-toluenesulfonylhydrazide (213 mg) were placed in MeOH (144 mL) and allowed to stand for 7 days at 23 °C. The solvent was removed and the residue precipitated from MeOH–ether to afford 433.2 mg (94%) of **4**: IR 2.95, 3.15 (OH, NH), 6.00, 6.30 (H-bonded quinone), 8.60 μm ($-SO_2-$); NMR (Me_2SO-d_6) δ 1.18 (d, 3, 6′-H_3), 1.6–2.1 (m, 7, 8- and 2′-H_2's, 14-H_3), 2.30 (s, 3, Ar Me), 2.7–3.1 (m, 2, 10-H_2), 3.57 (m, 2, 3′- and 4′-H's), 4.03 (s, 4, OMe and 5′-H),

4.90 (br s, 1, 7-H), 5.30 (br s, 1, 1'-H), 5.44 (m, 1, 9-OH), 7.06 (d, 2, Ar H's), 7.6–8.0 (m, 5, Ar H's); UV λ_{max} (MeOH) 234 nm (ϵ 42 196), 252 (28 794), 291 (7892); $[\alpha]^{20}_D$ +320° (*c* 0.020, MeOH); TLC (30:10:1 $CHCl_3$–MeOH–H_2O) R_f 0.28. Anal. ($C_{34}H_{37}NO_{11}S\cdot HCl\cdot 2H_2O$) C, H, N.

Adriamycin 13-Tosylhydrazone Hydrochloride (5). Adriamycin hydrochloride (**2**, 1.00 g, 0.175 mmol) and *p*-toluenesulfonylhydrazide (1.00 g) were placed in MeOH (300 mL) and allowed to stand at 23 °C for 5.5 days. The solvent was removed and the residue was precipitated with MeOH–ether to afford 1.26 g (95%) of **5**: IR 2.95 (OH, NH), 6.19, 6.31 (H-bonded quinone), 8.58 μm (–SO_2–); NMR 1.6–2.4 (m, 7, 8- and 2'-H_2's, Ar Me), 2.7–3.1 (m, 2, 10-H_2), 3.56 (m, 2, 3'- and 4'-H's), 4.03 (s, 4, OMe and 5'-H), 4.33 (s, 2, 14-H_2), 4.95 (m, 1, 7-H), 5.32 (m, 2, 1-H and 9-OH), 7.2–8.0 (m, 7, Ar H's); UV λ_{max} (MeOH) 234 nm (ϵ 37 806), 252 (26 685), 291 (8285); $[\alpha]^{20}_D$ +421° (*c* 0.022, MeOH); TLC (30:10:1 $CHCl_3$–MeOH–H_2O) R_f 0.31. Anal. ($C_{34}H_{37}N_3O_{12}S\cdot HCl\cdot 2H_2O$) C, H, N.

13-Deoxydaunorubicin Hydrochloride (6). Daunorubicin 13-tosylhydrazone hydrochloride (**4**, 163.7 mg, 0.213 mmol), $NaCNBH_3$ (213 mg), and *p*-toluenesulfonic acid (150 mg) were placed in MeOH (16 mL) and refluxed under N_2 for 0.5 h. The reaction mixture was poured into saturated $NaHCO_3$–ice (20 mL) and extracted with $CHCl_3$–MeOH (9:1, 3 × 10 mL). The extracts were combined and extracted with 0.5 M citric acid (2 × 15 mL). The acid extracts were combined, neutralized with saturated $NaHCO_3$, and extracted with $CHCl_3$–MeOH (9:1, 4 × 15 mL). The extracts were combined, dried, and evaporated. The residue (12.3 mg) was dissolved in MeOH (1 mL) and cooled to 0 °C. HCl (54 μL of 0.40 M solution in ether) was added and the hydrochloride precipitated by addition of ether (30 mL). The solvent was removed and the residue chromatographed [E. Merck silica gel 60 (size A prepacked column) 30:10:1 $CHCl_3$–MeOH–H_2O] to afford 34.0 mg (29%) of **6**: IR 2.95 (OH), 6.20, 6.30 μm (H-bonded quinone); NMR (Me_2SO-d_6) δ 0.93 (t, 3, 14-H_3), 1.16 (d, 3, 6'-H_3), 1.5 (m, 2, 2'-H_2), 1.7–2.1 (m, 4, 8- and 13'-H_2's), 2.8–3.8 (m, H_2O, 10-H_2, 3'- and 4'-H's), 4.02 (s, 4, OMe and 5'-H), 4.88 (br s, 1, 7-H), 5.31 (br s, 1, 1'-H), 7.6–7.9 (m, 3, 1-, 2-, and 3-H's), 13.26 (s, 1, phenolic OH), 14.06 (s, 1, phenolic OH); UV–visible λ_{max} (MeOH) 243 nm (ϵ 31 620), 251 (26 315), 284 (10 319), 478 (9946), 495 (9969), 529 (6651); $[\alpha]^{20}_D$ +193° (*c* 0.041, MeOH); TLC (30:10:1 $CHCl_3$–MeOH–H_2O) R_f 0.39. Anal. ($C_{27}H_{31}NO_9\cdot HCl\cdot 0.5H_2O$) C, H, N.

13-Deoxyadriamycin Hydrochloride (7). Adriamycin 13-tosylhydrazone hydrochloride (**5**, 916 mg, 1.168 mmol), $NaCNBH_3$ (1.19 g), and *p*-toluenesulfonic acid (90.0 mg) were dissolved in MeOH (90 mL) and refluxed under N_2 for 0.5 h. The reaction mixture was poured into saturated $NaHCO_3$–ice (150 mL) and extracted with $CHCl_3$–MeOH (3:1, 5 × 50 ml). The aqueous portion was placed on a 2 × 40 cm column of XAD-2 resin, washed with H_2O (200 mL), and eluted with MeOH (200 mL), MeOH–benzene (1:1), and MeOH (100 mL). The eluents were combined and evaporated, and the residue was partitioned between $CHCl_3$–MeOH (3:1) and saturated $NaHCO_3$. The organic phase was separated, dried, combined with the original extract, and evaporated. The residue was dissolved in a minimum amount of $CHCl_3$–MeOH (3:1) and cooled to 0 °C. HCl (3.0 mL of a 0.4 M solution in MeOH) was added, followed by ether (100 mL). The precipitate was collected and chromatographed (E. Merck prepacked silica gel 60 column, size B, 30:10:1 $CHCl_3$–MeOH–H_2O) to afford 215.7 mg (33%) of **7**: IR 2.95 (OH), 6.18, 6.30 (H-bonded quinone), 9.82, 10.10 μm; NMR (Me_2SO-d_6) δ 1.16 (d, 3, 6'-H_3), 1.70 (m, 2, 2'-H_2), 2.07 (m, 2, 8-H_2), 2.76 (m, 2, 13-H_2), 3.09–3.76 (m, 6, 3'- and 4'-H's and 10- and 14-H_2's), 4.02 (s, 4, OMe and 5'-H), 4.85 (br s, 1, 7-H), 5.26 (br s, 1, 1'-H), 7.67 (m, 1, 3-H), 7.91 (m, 2, 1- and 2-H's), 13.26 (s, 1, phenolic OH), 14.06 (s, 1, phenolic OH); UV λ_{max} (MeOH) 237 nm (29 557), 249 (23 868), 286 (8059); $[\alpha]_D$ +151° (*c* 0.041, MeOH); TLC (30:10:1 $CHCl_3$–MeOH–H_2O) R_f 0.23. Anal. ($C_{27}H_{31}NO_{10}\cdot HCl\cdot {}^2/_3H_2O$) C, H, N.

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References and Notes

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