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Note

Adriamycin analogues. Preparation of 7-*O*-(D-ribofuranosyl)-daunomycinone and -adriamycinone

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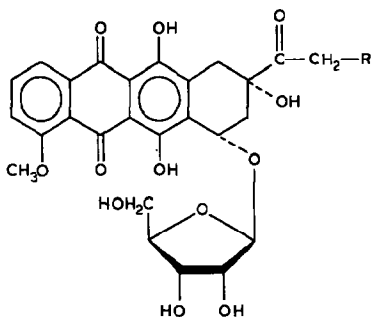
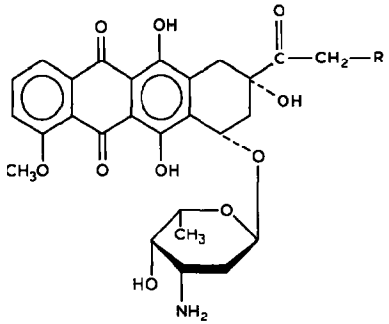
This report describes the preparation of 7-*O*-(β-D-ribofuranosyl)daunomycinone (**1**) and 7-*O*-(β-D-ribofuranosyl)adriamycinone (**2**), desamino glycoside-ring-contracted analogues of the clinically important antitumor antibiotics daunorubicin (**3**) and adriamycin (doxorubicin, **4**), respectively. These products are of interest in connection with structure–activity studies on anthracycline antitumor drug action relative to DNA-binding properties. While DNA-binding is widely considered[1,2] to be responsible for the antitumor properties of **3** and **4**, we have previously established[3–6] that certain DNA-nonbinding *N*-(trifluoroacetyl)-adriamycin 14-alkanoates have therapeutic properties superior to those of the parent antibiotics in animals and humans.

In exploring other anthracycline structural variants, we have recently shown that the 7-*O*-(3-amino-3,5-dideoxy-D-ribofuranosyl) derivatives of daunomycinone and adriamycinone, which may be viewed as ring-contracted isosteres of **3** and **4**,



1, R = H
2, R = OH



3, R = H (daunorubicin)
4, R = OH (adriamycin)

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retain high growth-inhibitory activity, while binding to a lesser extent with DNA than the parent antibiotics[7,8]. The reported[9] biological activity of the desamino-hexopyranose analogue of **3** provided the impetus for our synthesis and biological evaluation of deaminofuranoside analogues, as described in this paper.

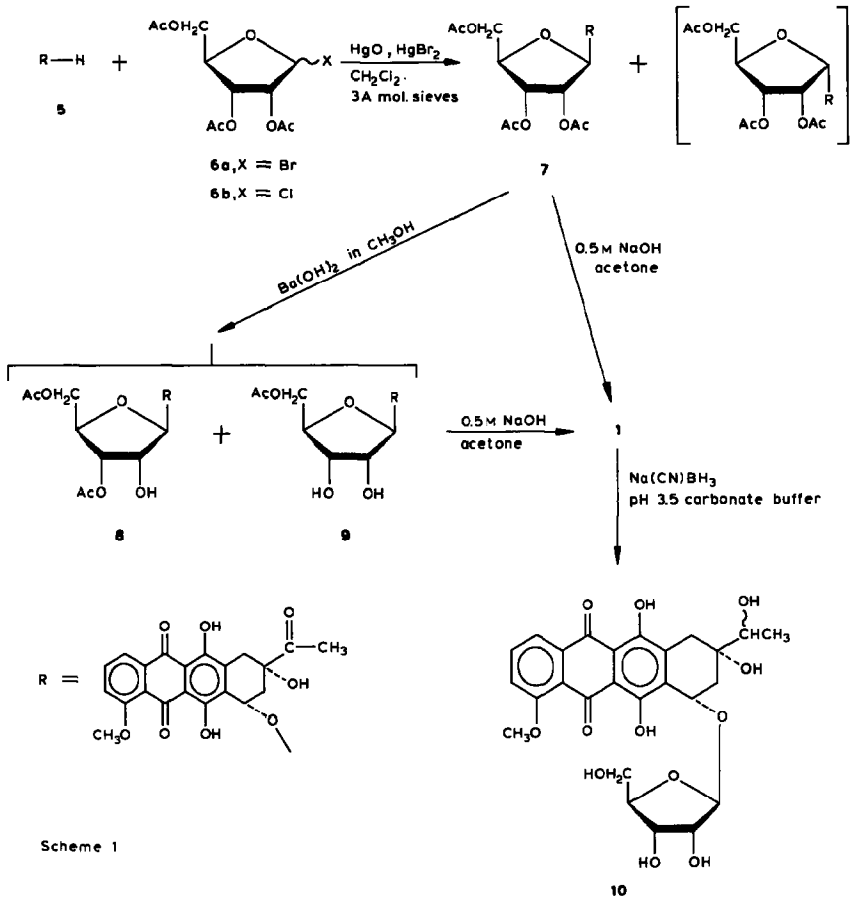
RESULTS AND DISCUSSION

The synthetic strategy used involved coupling of a protected ribofuranosyl halide with aglycons derived from **3** and **4**, separation of anomeric coupling products, as necessary, and removal of protecting groups. The commercially available 2,3,5-tri-*O*-acetyl-D-ribofuranose was converted into the corresponding 1-bromide, **6a**, by the bromotrimethylsilane bromination method previously described by us[10]. The aglycons of **3** and **4**, daunomycinone (**5**) and adriamycinone, respectively, were obtained by mild acid hydrolysis of the parent antibiotics. Based upon previous experience[2,8,11,12] the side-chain of adriamycinone was derivatized to **11**, before coupling, to protect it from the alkaline conditions subsequently needed to deprotect the sugar. We have found the *p*-anisyldiphenylmethyl protecting group, as suggested by Vishnuvajjala *et al.*[13] to be ideal for this purpose because of its lack of proton n.m.r. signals in the diagnostically important anomeric region and its ease of removal under acidic conditions mild enough to preserve the glycoside linkage.

Coupling of **5** with **6a** (Scheme 1) under Koenigs–Knorr conditions afforded a 3:1 mixture of anomers as monitored by l.c., although only a single product could be isolated in near-quantitative yield. The chloro sugar analog **6b** was tried in an attempt to achieve isolable yields of the other anomer. Reaction of **5** with **6b** was slower than with the corresponding bromide, but did indeed afford, at least in the early stages of the reaction, a higher proportion of the (apparent) unstable anomer, as evidenced chromatographically (l.c.). However, once again, only the thermodynamically more-stable anomer could be isolated.

No simple explanation can be offered to explain why the less-stable anomer, evidenced chromatographically during the reaction, could not be isolated. Only one product, the β anomer (see later), could be recovered from these reactions, even when the reaction was terminated in the early stages, at which time the second compound was maximally demonstrable. Two possibilities exist, (*1*); that the less-stable anomer is rapidly converted into the more-stable product during the course of the reaction, or on subsequent work-up, or (*2*); that under the reaction conditions the less-stable product decomposes back to aglycon and sugar, with the aglycon then reacting with excess halo sugar to continuously enrich the yield of the more-stable anomer. As the aglycon **5** was detectable by l.c. essentially throughout the entire course of the reaction, it is not possible to choose between these alternative hypotheses.

Methanolic barium hydroxide caused only partial deprotection of the coupled product **7**. While not rigorously established, the resultant diacetate has been



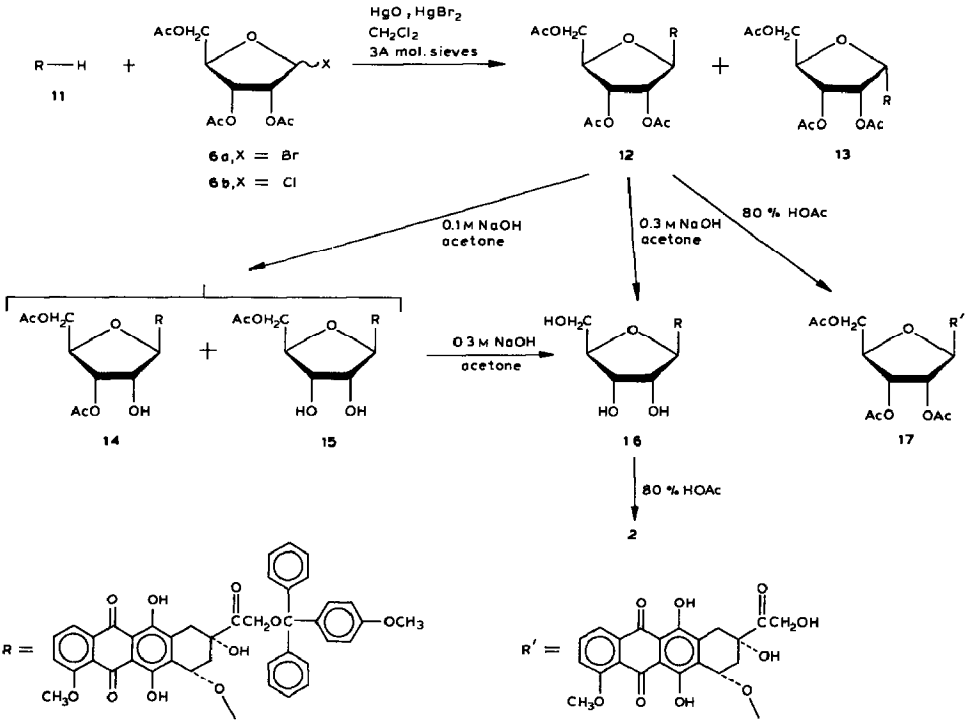
Scheme 1

assigned structure **8**, and the monoacetate structure **9**, based upon chemical considerations. Complete deprotection of **7** to afford **1** was accomplished with 0.1M sodium hydroxide in acetone; compounds **8** and **9**, separately or together as a mixture, could be treated similarly to give **1**.

Compound **1** was reduced to the corresponding 13-dihydro derivative **10** by means of sodium cyanoborohydride, without affecting the glycoside linkage. Compound **10** is structurally related to daunorubicinol, the biologically active principal metabolite of **3**.

In contrast to **5**, coupling of the side-chain-protected adriamycin aglycon **11** with halo sugar gave stable anomeric products (Scheme 2). With the bromo sugar **6a**, the major anomer was favored by 5:1; use of the chloro sugar **6b** gave the less-favored anomer in a somewhat higher proportion (3:2). Thin-layer and liquid-chromatographic monitoring during the reaction indicated that some loss of the *p*-anisyldiphenylmethyl protecting group had occurred, and, indeed, the 7-*O*-(tri-*O*-acetyl-β-D-ribofuranosyl) derivative (**17**) of adriamycinone was found among the products. The anomeric products **12** and **13** were separated by preparative t.l.c.,

and the predominant product (**12**) was *O*-deacetylated. Use of 0.1M sodium hydroxide, which fully deblocked the daunomycinone coupling-products, converted **12** into a mixture of the fully deprotected compound **16**, the monoacetate **15**, and the diacetate **14** (detected by t.l.c., but not isolated). Treatment of **12** with stronger base (0.3M sodium hydroxide in acetone) led directly to **16**; similar treatment of **15** also gave **16**. Removal of the *p*-anisyldiphenylmethyl protecting group of **16** with 80% acetic acid in the cold afforded the desired target compound **2**. Use of these same conditions with **12** afforded the acetylated adriamycinone riboside **17**.



Scheme 2

Anomeric assignment of the products was based upon n.m.r. data and the Karplus relationship[14], as previously discussed[7,8]. Assignment is generally easier when both anomers are available. Thus, with **12** and **13**, the clear appearance of a sharp singlet at δ 5.50 for H-1′ of the major product led to assignment of **12** as the β anomer; the minor coupled product showed a doublet at δ 5.78, with a coupling constant ($J_{1',2'}$) of 4 Hz, leading to its designation as the α anomer (Scheme 2). The stable product formed in the reaction of **5** with **6a** similarly showed a sharp singlet for H-1′ at δ 5.58 and was accordingly assigned the β-anomeric configuration **7** (Scheme 1).

Attempted alkaline hydrolysis of **13** with 0.1M sodium hydroxide gave a complex mixture. As our interest was in the β anomer **2**, analogous to **4**, further work with **13** was not pursued.

The key target compounds of this study, **1** and **2**, were evaluated for *in vitro* growth-inhibitory activity *vs.* a human-derived lymphoblastic leukemic cell line (CEM), according to well-established assay conditions[15]. Both compounds showed marginal growth-inhibitory activity, with ID_{50} values (concentrations producing 50% inhibition of the growth of treated cultures relative to untreated controls) of 1.90μM for **1** and 2.80μM for **2**, relative to 0.02μM for **3** and 0.06μM for **4** under identical conditions (48-h incubations, with continuous drug exposure). The level of cytotoxicity expressed by **1** and **2** in these assays was insufficient to advance these products on to *in vivo* antitumor evaluation in murine tumor model systems.

EXPERIMENTAL

General methods. — Melting points were recorded on a Kofler hot-stage with microscope and are uncorrected. I.r. spectra were determined as KBr discs with a Perkin–Elmer Model 1320 spectrophotometer. Proton-n.m.r. spectral data (Table I) were recorded at 60 MHz with a Varian EM360-L spectrometer, and additionally for compounds **1, 7**, and **9** at 250 MHz on a Bruker instrument, with tetramethylsilane as internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. T.l.c. utilized analytical silica gel G glass-backed plates (Analtech), with chloroform–methanol (9:1 by volume, system *A*), chloroform–methanol (19:1, system *B*), or petroleum ether–ethyl acetate (3:7, system *C*) as irrigant. Analytical l.c. determinations utilized a Waters Associates Model 202 chromatograph, with a U6K universal loop-injector and dual-model M6000-A solvent-delivery pumps controlled by a Model 660 programmer; the column material was μBondapak/phenyl, operating in reverse-phase, with linear gradient-elution (32–65% acetonitrile in ammonium formate buffer, pH 4.0, at 3.5 mL/min over 6 min). Signals were monitored by means of flow-fluorescence detection (Schoeffel Model FS 970 fluorescence detector, excitation wavelength 484 nm, emission cut-off at 580 nm). Preparative separations were done by gravity-flow column chromatography on silicic acid (Biosil A, Biorad), by preparative t.l.c. using silical gel G Uniplates (Analtech), and by l.c., using a preparative (1 in. o.d. × 1 ft.) column packed with silica gel mounted in the foregoing Waters Associates instrument and operating in normal phase, with simultaneous signal detection by u.v. (254 nm) and refractive index. Moisture- or oxygen-sensitive reactions were carried out in flame-dried glassware under nitrogen.

2,3,5-Tri-O-acetyl-D-ribofuranosyl bromide (**6a**). — 2,3,5-Tri-*O*-acetyl-D-ribofuranose (500 mg, Pfanstiehl Laboratories) was dissolved in 3 mL of alcohol-free dry dichloromethane and cooled to 0°. Bromotrimethylsilane (500 μL) was added in a stream through a microsyringe and the mixture was stirred for 10 min at 0°, and then for 3 h at room temperature. When t.l.c. (system *A*) showed conversion of all starting material into a more-polar product, the solvent was removed on a rotary evaporator at room temperature; removal of the remaining volatiles was ensured by applying high vacuum for 1 h. The product, a colorless syrup, was utilized in coupling reactions soon after preparation.

TABLE I

PROTON MAGNETIC RESONANCE SPECTRAL DATA[a]

Assignment	**1**[b,c]	**2**[d]	**7**[b]	**9**[b]	**10**[c]
Aromatic protons	7.30–7.90, 3H	7.33–8.00, 3H	7.25–7.85, 3H	7.30–8.00, 3H	7.23–8.03, 3H
H-7	4.95, m, 1H	4.98, m, 1H	5.19, m, 1H[e]	5.10, m, 1H	5.08, m, 1H
H-14	2.33, 3H	4.70, 2H	2.37, 3H	2.40, 3H	1.33, d (6), 3H
4-OMe	3.95, 3H	3.91, 3H	4.03, 3H	4.02, 3H[e]	4.00, 3H
Trityl-OMe					
H-1′[f]	5.23, 1H	5.20, 1H	5.58, 1H	5.40, 1H	5.25, 1H
H-2′	4.22, d (5), 1H	4.10, m, 1H	5.20, 1H[e]	4.22, dd, (5.1), 1H	4.20, m, 1H
H-3′	4.07, t (5), 1H	4.03, m, 1H	5.20, 1H[e]	4.04, m, 1H[e]	4.10, m, 1H
H-5′	3.55, m, 2H	3.60, m, 2H	4.25, 2H	3.85, m, 2H	3.60, m, 1H
OAc (2′, 3′, and/or 5′)			2.05, 2.08, 2.10, 3H ea.	2.07, 3H	
Phenolic OH	13.10, 13.85 1H ea.		13.07, 13.83 1H ea.	13.03, 13.83	

Assignment	**12**	**13**	**15**[d]	**16**[c]	**17**
Aromatic protons	6.77–8.03, 17H	6.73–8.02, 17H	6.73–8.00, 17H	6.70–8.00, 17H	7.30–7.95, 3H
H-7	5.17, m, 1H[e]	5.32, m, 1H	5.13, m, 1H	5.15, m, 1H	5.20, m, 1H[e]
H-14	4.45, 2H	4.42, 2H	4.43, 2H	4.43, 2H	4.70, 2H
4-OMe	4.03, 3H	4.02, 3H	4.02, 3H	4.05, 3H	4.00, 3H
Trityl-OMe	3.80, 3H	3.78, 3H	3.78, 3H	3.80, 3H	
H-1′[f]	5.50, 1H	5.78, d	5.32, 1H	5.28, 1H	5.53, 1H
H-2′	5.17, 1H[e]	4.80, m, 1H[e]	4.22, m, 1H	4.20, m, 1H	5.20, 1H[e]
H-3′	5.17, 1H[e]	4.80, m, 1H[e]	3.98, m, 1H	4.08, m, 1H	5.20, 1H[e]
H-5′	4.25, 2H	4.23, 2H	4.28, 2H	3.88, m, 2H	4.30, m, 2H
OAc (2′, 3′, and/or 5′)	1.90, 2.03, 2.08, 3H ea.	1.78, 2.06, 2.08, 3H ea.	1.90, 3H		2.02, 2.07, 2.13, 3H ea.
Phenolic OH	13.07, 13.80 1H ea.	13.08, 13.95 1H ea.	13.12, 13.91 1H ea.		13.07, 13.93 1H ea.

[a]Recorded in $CDCl_3$ at 60 MHz, unless otherwise indicated; frequencies in p.p.m. downfield from Me_4Si as internal standard; unmarked signals denote singlets; coupling constants (in parentheses) in Hz. [b]Recorded at 250 MHz. [c]In 9:1 $CDCl_3$–Me_2SO. [d]In 2:1 $CDCl_3$–Me_2SO. [e]Overlapping signals. [f]Bandwidth at half-peak height ($\Delta\nu 1/2$) for all β-anomeric products was 2 Hz.

*2,3,5-Tri-*O*-acetyl-*D*-ribofuranosyl chloride* (**6b**). — A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranose (500 mg) in alcohol- and moisture-free dichloromethane (50 mL) was cooled to 0° in an ice bath. Dry hydrogen chloride was bubbled through this solution gently for 0.5 h or until t.l.c. (system *A*) showed conversion of all starting material into a more-polar product. The solvent was removed by distillation under vacuum at low temperature. The product, a colorless oil, was used without further purification.

*7-*O*-(2,3,5-Tri-*O*-acetyl-*D*-ribofuranosyl)daunomycinone* (**7**). — (*a*) *From bromo sugar* **6a**. Daunomycinone (**5**, 250 mg, 0.63 mmol) was dissolved in alcohol-

free dry dichloromethane (30 mL), and finely ground, preignited type 3A molecular sieves (1 g), moisture-free yellow HgO (500 mg), and $HgBr_2$ (200 mg) were added. To this mixture was added, with stirring, one-half the volume of a solution of 500 mg of **6a** in 6 mL of CH_2Cl_2. After stirring for 30 min, another batch of molecular sieves (500 mg), yellow HgO (300 mg), and $HgBr_2$ (75 mg) was added, followed by the rest of the solution of **6a**. After 10 min, l.c. indicated two peaks in the ratio of 3:1, in addition to the daunomycinone peak. Reaction was continued for another 20 min to consume all of the daunomycinone starting-material (l.c.). The mixture was filtered and the solvent was removed under diminished pressure leaving a deep-red gum, which was dissolved in CH_2Cl_2 (5 mL) and the product precipitated from 70 mL of petroleum ether. The product was collected by filtration and washed with petroleum ether to remove remaining sugar. The solid showed only one prominent peak on l.c. The crude product was purified by preparative t.l.c. (system *B*) and crystallized from $CHCl_3$–petroleum ether to give **7** (380 mg, 92%); m.p. 168–170°; ν_{max} 3500 (br), 1755, 1740, 1720, 1620, 1575, and 1230 cm^{-1}.

Anal. Calc. for $C_{32}H_{32}O_{15} \cdot 0.5\ H_2O$: C, 57.74; H, 5.01. Found: C, 57.69; H, 5.10.

(*b*) *From chloro sugar* **6b**: The coupling procedure was the same as just described, except that the reaction was performed for a total of 2 h. Initial stages of the reaction showed (l.c.) larger proportions of the unstable anomer than before, but at the end of the reaction only the stable anomer was obtained.

7-O-(3,5-di-O-acetyl-β-D-ribofuranosyl)daunomycinone (**8**) *and 7-O-(5-O-acetyl-β-D-ribofuranosyl)daunomycinone* (**9**). — The coupled product **7** (600 mg) was dissolved in acetone (40 mL) and the solution cooled in an ice bath. To this was added a solution of $Ba(OH)_2 \cdot 8\ H_2O$ in CH_3OH (7 mL of 10 g/100 mL solution). The violet solution was stirred at room temperature for 2.5 h and treated with dry CO_2 until a red color was obtained. Water (3 mL) was added and the solution extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and the solvent removed. The product showed two spots on t.l.c. (system *A*) which were separated by preparative t.l.c. The less-polar band precipitated from $CHCl_3$–petroleum ether to give **8** as an orange, amorphous powder (150 mg, 27%); ν_{max} 3500, 1745, 1720, 1618, 1580, and 1235 cm^{-1}.

Anal. Calc. for $C_{30}H_{30}O_{14} \cdot 0.5\ H_2O$: C, 57.78; H, 5.02. Found: C, 57.46; H, 4.94.

The more-polar band gave **9** (300 mg, 57%) as a red powder from $CHCl_3$–petroleum ether; m.p. 130–133°; ν_{max} 3450, 1740, 1718, 1618, 1580, and 1235 cm^{-1}.

Anal. Calc. for $C_{28}H_{28}O_{13} \cdot 1.5\ H_2O$: C, 56.09; H, 5.22. Found: C, 56.07; H, 4.92.

7-O-(β-D-Ribofuranosyl)daunomycinone (**1**). — A solution of **7** (250 mg) in acetone (10 mL) was stirred with 3 mL of 0.5M sodium hydroxide solution for 4 h, brought to pH 7.4 by the addition of solid oxalic acid, diluted with water, and extracted with $CHCl_3$. Removal of the solvent gave a deep-red syrup, which crystallized from $CHCl_3$–ether to give **1** (190 mg, 94%); m.p. 202–205° (dec.); ν_{max} 3500, 3400, 1720, 1710, 1620, and 1580 cm^{-1}.

Anal. Calc. for $C_{26}H_{26}O_{12} \cdot H_2O$: C, 56.93; H, 5.16. Found: C, 56.54; H, 5.02.

Similar treatment starting with **8** and **9** also gave **1**.

13-Dihydro-7-O-(β-D-ribofuranosyl)daunomycinone (**10**). — A solution of **1** (100 mg) in 80% acetic acid (10 mL) was adjusted to pH 3.5 by the addition of solid $NaHCO_3$, $Na(CN)BH_3$ (150 mg) was added in two portions with stirring, and the reaction was continued for 3 h, whereupon l.c. indicated complete conversion of **1** into a new product. The product was freeze-dried overnight, the residue was extracted with 4:1 $CHCl_3$–MeOH and the extract filtered. Preparative t.l.c. (system *A*, double development) of the filtrate gave a single major band, from which **10** was recovered as a deep-red solid (50 mg, 50%, from $CHCl_3$–ether); ν_{max} 3420, 1612, and 1580 cm^{-1}.

Anal. Calc. for $C_{26}H_{28}O_{12} \cdot 1.5\ H_2O$: C, 55.80; H, 5.60. Found: C, 55.65; H, 5.47.

14-O-(p-Anisyldiphenylmethyl)-7-O-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-adriamycinone (**12**) *and its α anomer* **13**. — 14-*O*-*p*-(Anisyldiphenylmethyl)adriamycinone[13] (**11**, 500 mg) was coupled as already described for **7**. The bromo sugar gave the anomer **12** and **13** in 5:1 ratio; use of the chloro sugar produced the anomers in 3:2 ratio, with the same anomer predominating in each instance. The reaction mixture showed three major spots on t.l.c., which were separated by preparative t.l.c. (system *B*). The upper band, though homogeneous by t.l.c. in solvent system *B*, showed two components by l.c., which were separated by preparative t.l.c. in system *C* (multiple development). The upper band from this second chromatography gave the minor anomer **13**, which crystallized from $CHCl_3$–petroleum ether as red–orange flakes (60 mg, 9%); ν_{max} 3460, 1745, 1735, 1620, 1580, and 1740 cm^{-1}.

Anal. Calc. for $C_{52}H_{48}O_{17} \cdot 1.5\ H_2O$: C, 64.26; H, 5.25. Found: C, 64.13; H, 5.52.

The second band from the first preparative t.l.c., which was homogeneous on l.c., gave **12** (300 mg, 44%) as an orange-red powder after precipitation from $CHCl_3$–petroleum ether; m.p. 125–127°; ν_{max} 3500, 1750, 1720, 1620, 1580, and 1730 cm^{-1}.

Anal. Calc. for $C_{52}H_{48}O_{17} \cdot 0.5\ H_2O$: C, 65.47; H, 5.14. Found: C, 65.11; H, 5.18.

The third band crystallized from $CHCl_3$–petroleum ether as a red, amorphous powder (70 mg), identical in all respects with a sample of 7-*O*-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)adriamycinone (**17**) prepared by gentle acid hydrolysis of **12**, as described later.

14-O-(p-Anisyldiphenylmethyl)-7-O-(5-O-acetyl-β-D-ribofuranosyl)adriamycinone (**15**) *and 14-O-(p-anisyldiphenylmethyl)-7-O-(β-D-ribofuranosyl)adriamycinone* (**16**). — Compound **12** (150 mg) was dissolved in acetone (30 mL) and 0.3M sodium hydroxide (3 mL) was added. The purple solution was stirred for 7 h, at which time t.l.c. indicated the absence of starting material. The solution was

cooled, made neutral with solid oxalic acid, diluted with iced water, extracted with $CHCl_3$, and dried. The solvent was removed and the product chromatographed on preparative t.l.c. plates (system *A*). The less-polar product (**15**) crystallized from $CHCl_3$–petroleum ether as a red, amorphous solid (40 mg, 29%).

Anal. Calc. for $C_{48}H_{44}O_{15} \cdot 2\ H_2O$: C, 64.28; H, 5.40. Found: C, 64.19; H, 5.24.

The more-polar band gave compound **16** (50 mg, 39%) as a red powder from $CHCl_3$–ether; m.p. 135–138°.

Anal. Calc. for $C_{46}H_{42}O_{14} \cdot 1.5\ H_2O$: C, 65.32; H, 5.37. Found: C, 65.58; H, 5.60.

Treatment of **12** or **15** with 0.3M sodium hydroxide under similar conditions afforded **16** exclusively.

7-O-(β-D-Ribofuranosyl)adriamycinone (**2**). — A solution of **16** (50 mg) in 80% acetic acid (3 mL) was stirred at 0°, refrigerated overnight and then lyophilized. The residue was purified by preparative t.l.c. to give **2** as a red solid (25 mg, 75%); m.p. 185–189° (dec.).

Anal. Calc. for $C_{26}H_{26}O_{13} \cdot 2\ H_2O$: C, 53.60; H, 5.20. Found: C, 53.28; H, 5.12.

7-O-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)adriamycinone (**17**). — Treatment of compound **12** with 80% acetic acid, as described for **2**, afforded **17** after purification by preparative t.l.c.

Anal. Calc. for $C_{32}H_{32}O_{16} \cdot 2\ H_2O$: C, 54.23; H, 5.13. Found: C, 54.27; H, 5.22.

ACKNOWLEDGMENTS

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