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Synthesis of Potential Antineoplastic Anthracenedione Derivatives. I. Sugar Derivatives

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Seven 1-*O*-glycosyl derivatives of 4-[2-(2-hydroxyethylamino)ethylamino]-9,10-anthracenedione have been prepared as potential antineoplastic agents.

Doxorubicin (adriamycin)[1] and daunorubicin (daunomycin)[2] are well known as the clinically useful, antineoplastic agents and members of anthracycline antibiotics, together with carminomycin,[3] dihydrodaunomycin,[4] rhodomycin B,[5] pyrromycin,[6] and cinerubin.[7] Their cytotoxic effects are primarily due to their ability to intercalate their molecules between the base pairs of the DNA double helix.

The utilization of doxorubicin and daunorubicin is, however, limited by undesirable side effects, such as irreversible cardiotoxicity. To avoid the side effect and to improve antineoplastic activity, a series of anthracenedione derivatives having one or two aminoalkyl side chains, as model compounds of intercalating agents, have been studied by Double and Brown.[8]

Among these model compounds, bis(substituted aminoalkylamino)anthracenediones[9] and 1-hydroxy-4-[2-(2-hydroxyethylamino)ethylamino]-9,10-anthracenedione[10] (**1**) have exhibited good antineoplastic activities.[11]

Also, it has been well known that significant cytotoxic activity is always associated with aminoglycosides of the parent nucleus of anthracycline antibiotics.[12] This seems to be due to an electrostatic interaction between the phosphate group of the DNA molecules and the amino groups of a sugar moiety in the antibiotics.

While, in a series of anthracenedione derivatives, it has never been established that whether a glycosidation of the nucleus does improve its cytotoxic activity or not. To clarify this interesting problem, seven glycosides of **1** have been prepared, and their preliminary antineoplastic activity has been determined against leukemia L1210 in mice.

Results and Discussion

Preferential mono-*N*-acetylation of **1** with acetic anhydride in methanol gave 4-[2-(*N*-acetyl-2-hydroxyethylamino)ethylamino]-1-hydroxy-9,10-anthracenedione (**2**) in 74% yield. Protection of the primary hydroxyl group of **2** with trityl chloride in pyridine afforded the compound (**3**) in 90% yield. Successive acetylation of **3** with acetic anhydride in pyridine gave the two compound (**4**) and (**5**) in 59 and 33% yield, respectively. Selective *O*-deacetylation of **4** gave the aglycon (**6**) in 94% yield.

Condensation of **6** with acetobromoglucose in the presence of silver carbonate and quinoline afforded the product (**7**) in 84% yield. Detritylation of **7** with aqueous acetic acid and successive *O*-deacetylation in methanolic ammonia gave the compound (**9**). An attempt was made to remove *N*-acetyl groups on the side chain by alkaline hydrolysis, but it was failed, owing to a cleavage of the glycosidic linkage.[13]

An alternative protective group was used, instead of the acetyl group, to cleave *N*-acetyl bond under more mild conditions. Treatment of **1** with di-*t*-butyl dicarbonate resulted in a formation of 4-[2-(*N*-*t*-butoxycarbonyl-2-hydroxyethylamino) ethylamino]-1-hydroxy-9,10-anthracenedione (**10**) in 80% yield.

Tritylation of **10** gave the compound (**11**) in 77% yield. Acetylation of **11** in an appropriate conditions yielded preferentially *O*-acetyl derivative (**12**) in 95% yield. Treatment of **12** with trifluoroacetic anhydride in pyridine gave the compound (**13**) in 68% yield by causing a scission of the *O*-acetyl bond.

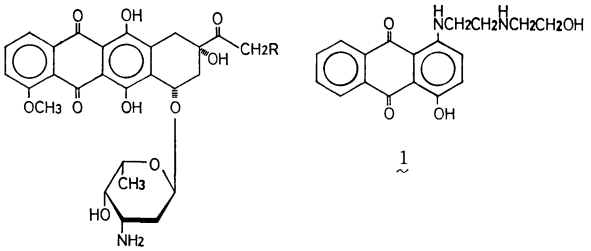
Direct *N*-acylation of **11** with trifluoroacetic anhydride in pyridine yielded a complex mixture which could not be able to isolate **13** in a good yield.

Condensation of **13** with acetobromoglucose in the presence of silver carbonate and quinoline afforded the product (**14**) in 80% yield.

Complete deprotection of **14** gave the aimed 1-(β-D-glucopyranosyloxy)-4-[2-(2-hydroxyethylamino)-ethylamino]-9,10-anthracenedione (**16**) in 48% yield. The structure of **16** was confirmed by converting **16** into hepta-*N*,*O*-acetyl derivative (**17**) which was determined by ^{1}H NMR spectroscopy.

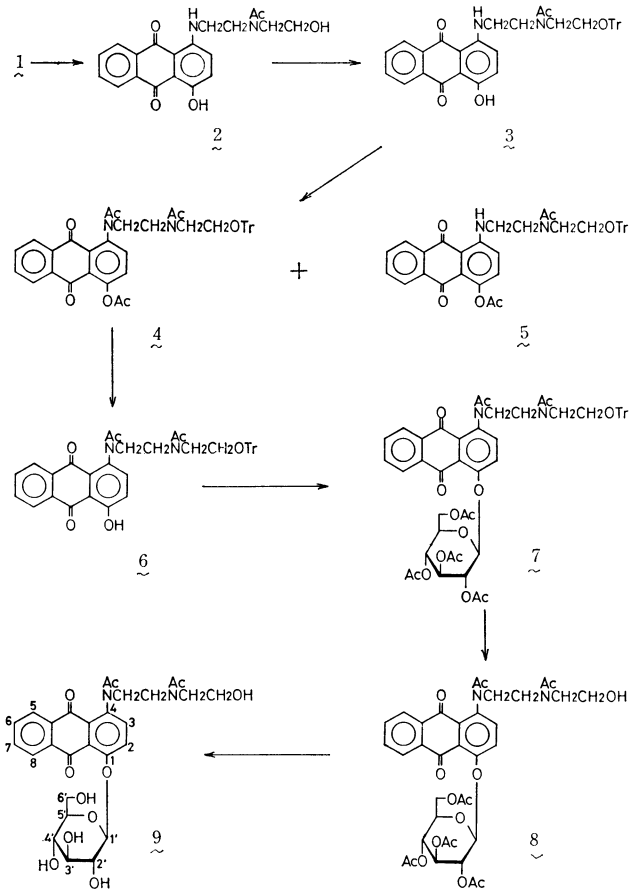
Using the same aglycon **13** and the analogous condensation procedure, six 1-*O*-glycosyl analogs have been synthesized. The sugar moieties used are β-D-galactopyranosyl, 6-deoxy-β-D-glucopyranosyl, α-L-rhamnopyranosyl, 2-acetamido-2-deoxy-β-D-glucopyranosyl, 3-acetamido-3-deoxy-β-D-glucopyranosyl and β-cellobiosyl residues.

The preliminary determination of antineoplastic activity against leukemia L1210 in mice revealed that the glycosidation of the 1-*O*-hydroxyl group in **1** was

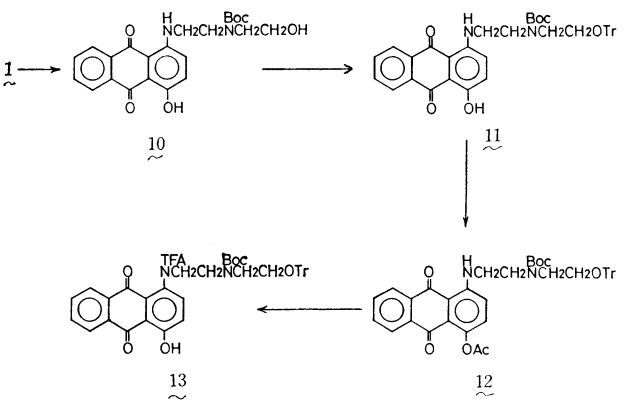


Doxorubicin R=OH
Daunorubicin R=H

Scheme 1.



Scheme 2.

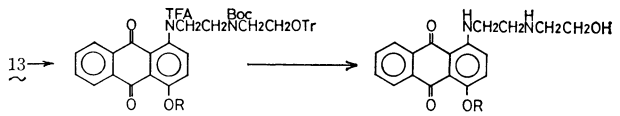


Scheme 3.

not hopeful in the production of large increase of life span in the leukemia L1210 transplanted mice. Details of the determination of antineoplastic activity will be reported elsewhere.

Experimental

General Methods. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Solutions were concentrated under reduced pressure below 50 °C. The optical rotation were measured on a Japan Spectroscopic DIPL-SL polarimeter. The IR spectra were recorded with a Hitachi 225 spectrophotometer and expressed in reciprocal centimeters. The UV spectra were measured with a Japan Spectroscopic UVIDEC-1



14 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl
16 *β*-D-glucopyranosyl
18 2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl
24 *β*-D-galactopyranosyl
19 2,3,4-tri-*O*-acetyl-6-deoxy-*β*-D-glucopyranosyl
25 6-deoxy-*β*-D-glucopyranosyl
20 2,3,4-tri-*O*-acetyl-*α*-L-rhamnopyranosyl
26 *α*-L-rhamnopyranosyl
21 2,2′,3,3′4′,6,6′-hepta-*O*-acetyl*β*-cellobiosyl
27 *β*-cellobiosyl
22 2-acetamide-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl
28 2-acetamide-2-deoxy-*β*-D-glucopyranosyl
23 3-acetamide-2,4,6-*O*-acetyl-3-deoxy-*β*-D-glucopyranosyl
29 3-aceiamide-3-deoxy-*β*-C-glucopyranosyl

Scheme 4.

spectrophotometer. ^{1}H NMR spectra were taken on a Varian EM-390 (90 MHz) spectrometer in chloroform-*d* with reference to tetramethylsilane as an internal standard. The chemical shifts are given in *δ*-values and *J*-values given are of first-order. TLC was performed on precoated silica gel 60 F-254 plaques (Merk, Darmstadt; 0.25 mm thickness). The silica gel used for a column chromatography was Wakogel C-200 (Wako Pure Chemical Co. Ltd.).

*4-[2-(N-Acetyl-2-hydroxyethylamino)ethylamino]-1-hydroxy-9,10-anthracenedione (**2**).* To a stirred solution of **1** (100 mg) in methanol (6 ml), acetic anhydride (0.3 ml) was added at room temperature. After 45 min, the solution was stand at 0—5 °C overnight. The products were collected by filtration and recrystallized from ethanol to give 84 mg (74%) of **2**, mp 149—150 °C; UV ($CHCl_3$) 253 (log *ε*, 4.56), 287 (3.89), 555 (4.09), 593 nm (4.04). ^{1}H NMR (pyridine-d_5): *δ*=2.27 (3H, s, NAc), 7.21 (1H, s, H-3), 7.32 (1H, s, H-2), 7.53—7.78 (2H, m, H-6 and 7), 8.18—8.43 (2H, m, H-5 and 8), 10.45 (1H, bs, aromatic NH).

Found: C, 63.92; H, 5.44; N, 7.15%. Calcd for $C_{20}H_{20}N_2O_5 \cdot 1/2\,H_2O$: C, 63.65; H, 5.61; N, 7.42%.

*4-[2-[N-Acetyl-2-(trityloxy)ethylamino]ethylamino]-1-hydroxy-9,10-anthracenedione (**3**).* To a stirred solution of **2** (1.00 g) in pyridine (90 ml), trityl chloride (4.53 g) was added at 50 °C. After 65 h, the mixture was concentrated, and the residue was dissolved in chloroform. The chloroform solution was washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on a column using 1:3 (v/v) ethyl acetate–toluene. Fractions homogeneous (R_f 0.36) on TLC in the same solvent were combined and concentrated. The residue was recrystallized from chloroform–petroleum ether to give 1.49 g (90%) of **3**, mp 238—240 °C; UV ($CHCl_3$) 556 (log *ε*, 4.24), 594 nm (4.21). ^{1}H NMR: *δ*=2.13 (3H, s, NAc), 3.20—3.73 (8H, m, CH_2 of side chain), 7.13—7.43 (17H, m, H-2,3 and $C(C_6\underline{H}_5)_3$), 7.65—7.83 (2H, m, H-6 and 7), 8.23—8.40 (2H, m, H-5 and 8), 10.28 (1H, bs, aromatic NH), 13.68 (1H, s, 1-OH).

Found: C, 74.83; H, 5.66; N, 4.42%. Calcd for $C_{39}H_{34}N_2O_5 \cdot H_2O$: C, 74.50, H, 5.77; N, 4.46%.

*1-Acetoxy-4-[N-acetyl-2-[N-acetyl-2-(trityloxy)ethylamino]ethylamino]-9,10-anthracenedione (**4**) and 1-Acetoxy-4-[2-[N-acetyl-2-(trityloxy)ethylamino]ethylamino]-9,10-anthracenedione (**5**).* To a solution of **3** (300 mg) in pyridine (10 ml), acetic anhy-

dride (8 ml) was added. After 24 h at 100 °C, the mixture was concentrated, and the residue was dissolved in ethyl acetate. The solution was washed with sat. $NaHCO_3$ solution, H_2O dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on the column using 15:1 (v/v) benzene–ethyl acetate. Fractions homogeneous (R_f 0.22) on TLC in 3:1 (v/v) benzene–ethyl acetate were concentrated and recrystallized from methanol to give 203 mg (59%) of **4**, mp 168—170 °C; UV ($CHCl_3$) 320 (log ε, 3.97), 348 (4.04), 408 nm (3.73); IR (KBr) 1765 (phenolic Ac), 1710 (aromatic NAc), 1655 (quinone), 1625 cm^{-1} (NAc). ^1H NMR; δ=2.20 (3H, s, NAc), 2.48 (3H, s, phenolic Ac), 2.62 (3H, s, aromatic NAc), 3.22—3.67 (6H, m, NAc-$CH_2C\underline{H}_2NAcC\underline{H}_2C\underline{H}_2OTr$), 4.25—4.55 (2H, m, NAc-$C\underline{H}_2CH_2NAc$), 7.09—7.48 (16H, m, aromatic protonand and $C(C_6\underline{H}_5)_3$), 7.53—7.73 (2H, m, aromatic protons), 7.82—8.00 (1H, m, aromatic proton), 8.23—8.48 (2H, m, H-5 and 8).

Found: C, 74.06; H, 5.34; N, 3.78%. Calcd for $C_{43}H_{38}N_2O_7$: C, 74.34; H, 5.51; N, 4.03%.

Fractions homogeneous (R_f 0.38) on TLC in 3:1 (v/v) benzene–ethyl acetate were concentrated and the residue was recrystallized from methanol to give 106 mg (33%) of **5**, mp 146—148 °C; UV ($CHCl_3$) 249 (log ε, 4.52), 277 (3.99), 321 (3.77), 508 nm (3.83); IR (KBr) 1775 (phenolic Ac), 1670 (quinone), 1635 cm^{-1} (quinone and NAc). ^1H NMR: δ=2.12 (3H, s, NAc), 2.39 (3H, s, phenolic Ac), 3.18—3.52 (8H, CH_2 of side chain), 7.09—7.42 (17H, m, H-2,3 and $C(C_6\underline{H}_5)_3$), 7.52—7.73 (2H, m, H-6 and 7), 8.00—8.22 (2H, m, H-5 and 8), 9.95 (1H, bs, aromatic NH).

Found: C, 73.79; H, 5.79; N, 4.04%. Calcd for $C_{41}H_{36}N_2O_6\cdot H_2O$: C, 73.42; H, 5.71; N, 4.18%.

*4-[N-Acetyl-2-[N-acetyl-2-(trityloxy)ethylamino]ethylamino]-1-hydroxy-9,10-anthracenedione (**6**).* To a stirred solution of **4** (150 mg) in ethanol (10 ml), 1 M NaOH (1 M=1 mol dm^{-3}) solution (8 ml) was added. After 24 h, 1 M HCl solution (8 ml) was added to the mixture. Pecipitated solids were collected, washed with water, and dissolved in chloroform. After drying over anhydrous Na_2SO_4, the solution was concentrated, and the residue was purified on a column using 10:1 (v/v) benzene–ethyl acetate. Fractions homogeneous (R_f 0.20) in 3:1 (v/v) benzene–ethyl acetate were combined and concentrated. The residue was recrystallized from ethanol to give 132 mg (94%) of **6**, mp 257—258 °C; UV ($CHCl_3$) 313 (log ε, 4.36), 348 (4.42), 503 nm (4.23); IR (KBr) 1710 cm^{-1} (aromatic NAc), 1650 (quinone), 1625 (quinone and NAc). ^1H NMR: δ=2.18 (3H, s, NAc), 2.70 (3H, s, aromatic NAc), 3.20—3.67 (6H, m, $NAcCH_2C\underline{H}_2$-$NAcC\underline{H}_2C\underline{H}_2OTr$), 4.27—4.53 (2H, m, $NAcC\underline{H}_2CH_2NAc$), 7.10—7.47 (16H, m, aromatic proton and $C(C_6H_5)_3$), 7.57—7.77 (2H, m, aromatic protons), 7.92—8.07 (1H, m, aromatic proton), 8.30—8.57 (2H, m, H-5 and 8).

Found: C, 75.57; H, 5.62; N, 4.04%. Calcd for $C_{41}H_{36}N_2O_6$: C, 75.44; H, 5.56; N, 4.29%.

*1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4-[N-acetyl-2-[N-acetyl-2-(trityloxy)ethylamino]ethylamino]-9,10-anthracenedione (**7**).* To a solution of **6** (100 mg) in quinoline (3 ml) and benzene (3 ml), acetobromoglucose (202 mg) and silver carbonate (218 mg) were added in the dark. The mixture was stirred for 47 h at room temperature, the insoluble materials were removed by filtration, and then the filtrate was diluted with benzene. The solution was washed with 5% H_2SO_4, sat. $NaHCO_3$ solution and water. After drying over anhydrous Na_2SO_4, the solution was concentrated, and the residue was purified on a column using 3:1 (v/v) benzene–ethyl acetate. Fractions homogeneous (R_f 0.28) on TLC in 1:1 (v/v) benzene–ethyl acetate were concentrated and the residue was resolidified with benzene–hexane to give 127 mg (84%) of **7**, mp 123—129 °C; $[\alpha]_D^{22}$ −17.1° (*c* 0.55, $CHCl_3$); UV (EtOH) 325 (log ε, 4.24), 348 (4.28), 430 nm (4.04). ^1H NMR: δ=2.03 (6H, s, Ac×2), 2.08 (3H, s, Ac), 2.18 (6H, s, Ac×2), 2.62 (3H, s, aromatic NAc), 3.19—3.63 (6H, m, $NAcCH_2C\underline{H}_2NAcC\underline{H}_2C\underline{H}_2$-OTr), 3.83 (1H, m, H-5′), 4.13—4.47 (4H, m, $NAcC\underline{H}_2$-CH_2NAc and H-6′), 5.03—5.47 (4H, m, H-1′, 2′, 3′, and 4′), 7.06—7.40 (16H, m, aromatic proton and $C(C_6\underline{H}_5)_3$), 7.50—7.70 (2H, m, aromatic protons), 7.77—7.90 (1H, m, aromatic proton), 8.30—8.43 (2H, m, H-5 and 8).

Found: C, 66.94; H, 5.60; N, 2.67%. Calcd for $C_{55}H_{54}N_2O_{15}$: C, 67.20; H, 5.54; N, 2.85%.

*1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4-[N-acetyl-2-(N-acetyl-2-hydroxyethylamino)ethylamino]-9,10-anthracenedione (**8**).* A solution of **7** (600 mg) in 80% aqueous acetic acid (10 ml) was heated for 40 min at 100 °C. The solution was concentrated and the residue was purified on a column using 1:10 (v/v) ethanol–toluene. Fractions homogeneous (R_f 0.20) on TLC in 1:5 (v/v) ethanol–toluene were combined and concentrated. The residue was resolidified with benzene–hexane to give 367 mg (81%) of **8**. ^1H NMR: δ=2.03 (6H, s, Ac×2), 2.10 (3H, s, Ac), 2.15 (3H, s, Ac), 2.18 (3H, s, Ac), 2.58 (3H, s, aromatic NAc), 3.42—3.95 (7H, m, H-5′ and $NAcCH_2C\underline{H}_2NAcC\underline{H}_2C\underline{H}_2OTr$), 4.12—4.60 (4H, m, H-6′ and $NAcC\underline{H}_2CH_2NAc$), 5.00—5.47 (4H, m, H-1′, 2′, 3′, and 4′), 7.47—7.90 (4H, m, H-2,3,6, and 7), 8.17—8.38 (2H, m, H-5 and 8).

*4-[N-Acetyl-2-(N-acetyl-2-hydroxyethylamino)ethylamino]-1-(β-D-glucopyranosyloxy)-9,10-anthracenedione (**9**).* A solution of **8** (300 mg) in methanolic ammonia (5 ml) was stirred for 24 h at 0—5 °C. The solution was concentrated and the residue was washed with hot methanol to give 203 mg (88%) of **9** as yellow solid, mp 218—220 °C; UV (H_2O) 225 (log ε, 4.65), 314 (4.01), 352 (4.07), 427 nm (3.88). ^1H NMR (pyridine-d_5): δ=2.20 (3H, s, NAc), 2.77 (3H, s, aromatic NAc), 5.33 (1H, d, *J*=7.5 Hz, H-1′), 7.40—7.55 (2H, m, H-2 and 3), 7.87—8.05 (2H, m, H-6 and 7), 8.22—8.43 (2H, m, H-5 and 8).

Found: C, 58.88; H, 5.45; N, 4.64%. Calcd for $C_{28}H_{32}N_2O_{11}$: C, 58.74; H, 5.63; N, 4.89%.

*4-[2-[N-(t-Butoxycarbonyl)-2-hydroxyethylamino]ethylamino]-1-hydroxy-9,10-anthracenedione (**10**).* To a stirred solution of **1** (1.00 g) in 1 M NaOH solution (8 ml) and dioxane (12 ml), di-*t*-butyl dicarbonate (2.00 g) was added. After 1 h, 1 M HCl solution (8 ml) was added to the mixture and the solution was extracted with ethyl acetate. The Organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified on a column using 2:1 (v/v) benzene–ethyl acetate. Fractions homogeneous (R_f 0.26) on TLC in 1:1 (v/v) benzene–ethyl acetate were concentrated to give 1.04 g (80%) of **10** as amorphous solid; UV ($CHCl_3$) 253 (log ε, 4.58), 291 (3.88), 558 (4.11), 608 nm (4.07). ^1H NMR: δ=1.47 (9H, s, Boc), 2.57 (1H, bs, $CH_2CH_2O\underline{H}$), 3.28—3.55 (6H, m, $NHC\underline{H}_2$-$C\underline{H}_2N(Boc)C\underline{H}_2CH_2OH$), 3.73 (2H, t, *J*=4.5 Hz, $CH_2C\underline{H}_2$-OH), 7.10 (2H, d, *J*=3.0 Hz, H-2 and 3), 7.52—7.72 (2H, m, H-6 and 7), 8.05—8.22 (2H, m, H-5 and 8), 10.13 (1H, bs, aromatic NH), 13.47 (1H, s, 1-OH).

Found: C, 64.93; H, 6.13; N, 6.32%. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.93; H, 5.92; N, 6.58%.

*4-[2-[N-(t-Butoxycarbonyl)-2-(trityloxy)ethylamino]ethylamino]-1-hydroxy-9,10-anthracenedione (**11**).* To a stirred solution of **10** (966 mg) in pyridine (30 ml), trityl chloride (1.89 g) was added. After 24 h at 50 °C, the mixture was poured into ice-cooled water, and the precipitates were collected. The product was purified on a column using 1:3 (v/v) ethyl

acetate–hexane. Fractions homogeneous (R_f 0.56) on TLC in the same solvent were concentrated, and the residue was recrystallized from hexane to give 1.16 g (77%) of **11**, mp 151—152 °C; UV ($CHCl_3$) 254 (log ε, 4.45), 294 (3.65), 559 (3.68), 601 nm (3.64). ^1H NMR: δ=1.30—1.56 (9H, m, Boc), 3.03—3.56 (8H, m, CH_2 of side chain), 7.00—7.40 (17H, m, H-2,3 and C($C_6\underline{H}_5$)$_3$), 7.50—7.70 (2H, m, H-6 and 7), 8.10—8.27 (2H, m, H-5 and 8), 10.18 (1H, bs, aromatic NH), 13.47 (1H, s, 1-OH).

Found: C, 75.40; H, 6.32; N, 4.13%. Calcd for $C_{42}H_{40}N_2O_6$: C, 75.42; H, 6.03; N, 4.19%.

*1-Acetoxy-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-ethylamino]-9,10-anthracenedione (**12**).* Compound **11** (100 mg) was acetylated with acetic anhydride (3 ml) and pyridine (6 ml) for 20 h. The mixture was concentrated and the residue was purified on a column using 1:3 (v/v) ethyl acetate–hexane. Fractions homogeneous (R_f 0.25) on TLC in the same solvent were concentrated and the residue was recrystallized from hexane to give 101 mg (95%) of **12**, mp 85—88 °C; UV ($CHCl_3$) 250 (log ε, 4.66), 278 (4.19), 319 (4.03), 511 nm (4.01); IR (KBr) 1765 cm^{-1} (phenolic Ac), 1690 (NBoc), 1655 (quinone), 1630 (quinone). ^1H NMR: δ=1.27—1.48 (9H, m, Boc), 2.40 (3H, s, phenolic Ac), 3.03—3.63 (8H, m, CH_2 of side chain), 7.00—7.47 (17H, m, H-2,3 and C($C_6\underline{H}_5$)$_3$), 7.52—7.77 (2H, m, H-6 and 7), 8.00—8.28 (2H, m, H-5 and 8), 10.00 (1H, bs, aromatic NH).

Found: C, 74.34; H, 6.22; N, 3.84%. Calcd for $C_{44}H_{42}N_2O_7$: C, 74.35; H, 5.96; N, 3.94%.

*4-[2-[N-(t-Butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)ethylamino]-1-hydroxy-9,10-anthracenedione (**13**).* To a ice-cooled solution of **12** (300 mg) in pyridine (10 ml), trifluoroacetic anhydride (0.6 ml) was added with stirring, and the mixture was stirred for 21 h at room temperature. The mixture was poured into ice cold water, and the precipitates were filtered off. The product was purified on a column using 1:8 (v/v) ethyl acetate–hexane. Fractions homogeneous (R_f 0.45) on TLC in 1:3 (v/v) ethyl acetate–hexane were concentrated and solidified with hexane to give 276 mg (86%) of **13** as amorphous solid; UV ($CHCl_3$) 257 (log ε, 4.59), 338 (3.60), 402 nm (3.82); IR (KBr) 1700 (C=O, broad), 1640 (quinone). ^1H NMR: δ=1.30 (9H, s, Boc), 7.03—7.52 (17H, m, H-2,3 and C($C_6\underline{H}_5$)$_3$), 7.63—7.83 (2H, m, H-6 and 7), 8.07—8.30 (2H, m, H-5 and 8), 13.10 (1H, s, 1-OH).

Found: C, 68.83; H, 5.42; N, 3.44%. Calcd for $C_{44}H_{39}N_2F_3O_7$: C, 69.10; H, 5.14; N, 3.66%.

*1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)ethylamino]-9,10-anthracenedione (**14**).* To a stirred solution of **13** (1.35 g) in quinoline (5 ml) and benzene (5 ml), acetobromoglucose (2.18 g) and silver carbonate (916 mg) were added. After 54 h in the dark, the reaction mixture was filtered and the filtrate was diluted with benzene. The solution was washed with 5% H_2SO_4 solution, H_2O, sat. $NaHCO_3$ solution, H_2O, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified on the column using 7:1 (v/v) benzene–ethyl acetate and 1:3 (v/v) ethyl acetate–hexane. Fractions homogeneous (R_f 0.52) on TLC in 1:1 (v/v) ethyl acetate–hexane were concentrated and recrystallized from cyclohexane to give 1.55 g (80%) of **14**, mp 113—118 °C; $[\alpha]_D^{23}$ −28.7° (*c* 0.53, $CHCl_3$); UV (EtOH) 255 (log ε, 4.55), 347 nm (3.68). ^1H NMR: δ=1.30 (9H, s, Boc), 2.02 (9H, s, Ac×3), 2.15 (3H, s, Ac), 4.98 (4H, m, H-1′2′,3′, and 4′), 7.07—7.43 (17H, m, H-2,3 and C($C_6\underline{H}_5$)$_3$), 7.56—7.73 (2H, m, H-6 and 7), 7.93—8.12 (2H, m, H-5 and 8).

Found: C, 63.85; H, 5.45; N, 2.38%. Calcd for $C_{58}H_{57}N_2F_3O_{16}$: C, 63.61; H, 5.25; N, 2.56%.

*1-(β-D-Glucopyranosyloxy)-4-[2-(2-hydroxyethylamino)ethylamino]-9,10-anthracenedione (**16**).* Compound **14** (241 mg) was dissolved in trifluoroacetic acid (1 ml) under ice cooling and stirred at room temperature. The mixture was concentrated and the residue was purified on a column using 5:1 (v/v) benzene–ethanol. Fractions homogeneous (R_f 0.34) on TLC in 1:3 (v/v) benzene–ethanol were concentrated to give 116 mg of **15** as amorphous solid. The solid was dissolved in methanolic ammonia (5 ml) and the solution was stirred overnight at 0—5 °C. Precipitated solids were collected and washed with ethyl acetate–methanol to give 52 mg (48% from **14**) of **16**, mp 211—218 °C; UV (MeOH) 248 (log ε, 4.56), 280 (3.93), 526 nm (3.87); IR (KBr) 1640 cm^{-1}, 1630 (quinone).

Found: C, 58.42; H, 5.78; N, 5.52%. Calcd for $C_{24}H_{28}N_2O_9 \cdot 1/4\,H_2O$: C, 58.47; H, 5.83; N, 5.68%.

*2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4-[N-acetyl-2-(N-acetyl-2-aceloxyethylamino)ethylamino]-9,10-anthracenedione (**17**).* Compound **16** (10 mg) was acetylated with acetic anhydride (1.5 ml) and pyridine (1.5 ml) at 100 °C. The mixture was diluted with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residue was solidified with benzene–hexane to give 13 mg (81%) of **17**, mp 102—112 °C; $[\alpha]_D^{23}$ −19.0° (*c* 0.62, $CHCl_3$); UV (EtOH) 208 (log ε, 4.91), 230 (4.92), 311 (4.31), 346 (4.34), 421 nm (4.12). ^1H NMR: δ=2.03 (3H, s, Ac), 2.05 (6H, s, Ac×2), 2.10 (3H, s, Ac), 2.17 (6H, s, Ac×2), 2.63 (3H, s, aromatic NAc), 3.45—3.91 (5H, m, $NAcCH_2C\underline{H}_2$-$NAcC\underline{H}_2CH_2OAc$ and H-5′), 4.10—4.66 (6H, m, $NHAc$-$C\underline{H}_2CH_2NAcCH_2C\underline{H}_2OAc$ and H-6′), 5.01—5.44 (4H, m, H-1′,2′,3′, and 4′), 7.49—7.93 (4H, m, H-2,3,6, and 7), 8.20—8.43 (2H, m, H-5 and 8).

Found: C, 58.44; H, 5.18; N, 3.27%. Calcd for $C_{38}H_{42}N_2O_{16}$: C, 58.31; H, 5.41; N, 3.85%.

*Condensation of **13** with Halogen Sugars.* Halogen sugars of galactose,[14] 6-deoxyglucose,[15] L-rhamnose,[16] cellobiose,[17] 2-acetamido-2-deoxyglucose,[18] 3-acetamido-3-deoxyglucose,[19] were prepared according to the authentic methods. The reaction procedure was analogous as described in the preparation of **14**.

*1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyloxy)-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)ethylamino]-9,10-anthracenedione (**18**).* Compound **18** was obtaine in 93% yield from **13** and showed a spot at R_f 0.45 on TLC in 1:1 (v/v) ethyl acetate–hexane; mp 118—125 °C; $[\alpha]_D^{20}$ −5.9° (*c* 1.05, $CHCl_3$); UV (EtOH) 225 (log ε, 4.83), 258 (4.75), 350 nm (3.80). ^1H NMR: δ=1.31 (9H, s, Boc), 2.02 (6H, s, Ac×2), 2.17 (6H, s, Ac×2), 7.07—7.43 (17H, m, H-2,3 and C($C_6\underline{H}_5$)$_3$), 7.48—7.75 (2H, m, H-6 and 7), 7.83—8.20 (2H, m, H-5 and 8).

Found: C, 63.57; H, 5.43; N, 2.41%. Calcd for $C_{58}H_{57}N_2F_3O_{16}$: C, 63.61; H, 5.25; N, 2.56%.

*1-(2,3,4-Tri-O-acetyl-6-deoxy-β-D-glucopyranosyloxy)-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)-ethylamino]-9,10-anthracenedione (**19**).* Compound **19** was obtained in 91% yield from **13** and showed a spot at R_f 0.42 on TLC in 1:3 (v/v) ethyl acetate–toluene; mp 146—148 °C; $[\alpha]_D^{24}$ −24.8° (*c* 1.16, $CHCl_3$); UV ($CHCl_3$) 256 (log ε, 4.62), 350 nm (3.71). ^1H NMR: δ=1.30 (12H, bs, Boc and H-6′), 2.00 (6H, s, Ac×2), 2.10 (3H, s, Ac), 4.67—5.47 (4H, m, H-1′,2′,3′, and 4′), 6.90—7.80 (19H, m, H-2,3,6,7 and C($C_6\underline{H}_5$)$_3$), 7.80—8.23 (2H, m, H-5 and 8).

Found: C, 65.05; H, 5.54; N, 2.53%. Calcd for $C_{56}H_{55}N_2F_3O_{14}$: C, 64.86; H, 5.35; N, 2.70%.

1-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyloxy)-4-[2-[N-(t-

*butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)ethylamino]-9,10-anthracenedione (**20**).* Compound **20** was obtained in 42% yield from **13** and showed a spot at R_f 0.47 on TLC in 1:3 (v/v) ethyl acetate–toluene; mp 115—119 °C; $[\alpha]_D^{24}$ −24.6° (*c* 1.00, $CHCl_3$); UV ($CHCl_3$) 256 (log ε, 4.67), 354 nm (3.75). ^1H NMR δ=1.21 (3H, d, $J_{5',6'}$= 6.0 Hz, H-6'), 1.31 (9H, s, Boc), 2.03 (6H, (6H, s, Ac×2), 2.16 (3H, s, Ac), 6.97—7.77 (19H, m, H-2,3,6,7, and $C(C_6\underline{H}_5)_3$), 7.80—8.27 (2H, m, H-5 and 8).

Found: C, 64.68; H, 5.35; N, 2.76%. Calcd for $C_{56}H_{55}N_2F_3O_{14}$: C, 64.86; H, 5.35; N, 2.70%.

*1-(2,2',3,3',4',6,6'-Hepta-O-acetyl-β-cellobiosyloxy)-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)-ethylamino]-9,10-anthracenedione (**21**).* Compound **21** was obtained in 66% yield from **13** and showed a spot at R_f 0.45 on TLC in 1:3 (v/v) ethyl acetate–toluene; mp 131—139 °C; $[\alpha]_D^{27}$ −31.1° (*c* 0.52, $CHCl_3$); UV (EtOH) 214 (log ε, 4.61), 254 (4.51), 341 nm (3.70). ^1H NMR: δ= 1.30 (9H, s, Boc), 1.93 (3H, s, Ac), 1.97 (3H, s, Ac), 2.00 (3H, s, Ac), 2.07 (9H, s, Ac×3), 2.13 (3H, s, Ac), 6.91—7.43 (17H, m, H-2,3 and $C(C_6\underline{H}_5)_3$), 7.53—7.79 (2H, m, H-6 and 7), 7.87—8.13 (2H, m, H-5 and 8).

Found: C, 60.51; H, 5.45; N, 1.95%. Calcd for $C_{70}H_{73}N_2F_3O_{24}$: C, 60.78; H, 5.31; N, 2.03%.

*1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)ethylamino]-9,10-anthracenedione (**22**).* Compound **22** was obtaine in 82% yield from **13** and showed a spot at R_f 0.32 on TLC in 1:3 (v/v) ethyl acetate–chloroform; mp 148—150 °C; $[\alpha]_D^{21}$ +29.2° (*c* 1.06, $CHCl_3$); UV ($CHCl_3$) 256 (log ε, 4.64), 345 nm (3.71). ^1H NMR: δ= 1.32 (9H, s, Boc), 2.00 (3H, s, Ac), 2.03 (6H, s, Ac×2), 2.07 (3H, s, Ac), 6.43 (1H, d, *J*=9.0 Hz, N$\underline{H}$Ac), 7.07—7.47 (17H, m, H-2,3 and $C(C_6\underline{H}_5)_3$), 7.50—7.85 (2H, m, H-6 and 7), 7.90—8.20 (2H, m, H-5 and 8).

Found: C, 63.44; H, 5.44; N, 3.85%. Calcd for $C_{58}H_{58}N_3F_3O_{15}$: C, 63.67; H, 5.34; N, 3.84%.

*1-(3-Acetamido-2,4,6-tri-O-acetyl-3-deoxy-β-D-glucopyranosyloxy)-4-[2-[N-(t-butoxycarbonyl)-2-(trityloxy)ethylamino]-N-(trifluoroacetyl)ethylamino]-9,10-anthracenedione (**23**).* Compound **23** was obtained in 62% yield from **13** and showed a spot at R_f 0.24 on TLC in 1:1 (v/v) ethyl acetate–chloroform; mp 182—186 °C; $[\alpha]_D^{21}$ +10.8° (*c* 1.01, $CHCl_3$); UV (EtOH) 211 (log ε, 4.61), 254 (4.52), 346 nm (3.63). ^1H NMR: δ=1.34 (9H, s, Boc), 1.85 (3H, s, Ac), 2.07 (3H, s, Ac), 2.19 (6H, s, Ac×2), 7.10—7.52 (17H, m, H-2,3 and $C(C_6\underline{H}_5)_3$), 7.56—7.96 (2H, m, H-6 and 7), 8.01—8.32 (2H, m, H-5 and 8).

Found: C, 63.75; H, 5.50; N, 3.72%. Calcd for $C_{58}H_{58}N_3F_3O_{15}$: C, 63.67; H, 5.34; N, 3.84%.

*Deprotection of **18**, **19**, **20**, **21**, **22**, and **23**.* Deprotection was worked up with trifluoroacetic acid and methanolic ammonia analogously as described in the preparation of **16**.

*1-(β-D-Galactopyranosyloxy)-4-[2-(2-hydroxyethylamino)ethylamino]-9,10-anthracenedione (**24**).* Compound **24** was obtained in 52% yield from **18**; mp 202—205 °C; IR (KBr) 1655 cm^{-1} and 1630 (quinone).

Found: C, 58.02; H, 5.73; N, 5.44%. Calcd for $C_{24}H_{28}N_2O_9 \cdot 1/2\,H_2O$: C, 57.94; H, 5.88; N, 5.63%.

*1-(6-Deoxy-β-D-glucopyranosyloxy)-4-[2-(2-hydroxyethylamino)-ethylamino]-9,10-anthracenedione (**25**).* Compound **25** was obtained in 26% yield from 19; mp 175—180 °C; IR (KBr) 1655 cm^{-1} and 1630 (quinone).

Found: C, 58.50; H, 5.84; N, 5.38%. Calcd for $C_{24}H_{28}N_2O_8 \cdot H_2O$: C, 58.76; H, 6.17; N, 5.71%.

*4-[2-(2-Hydroxyethylamino)ethylamino]-1-(α-L-rhamnopyranosyloxy)-9,10-anthracenedione (**26**).* Compound **26** was obtained in 39% yield from 20; mp 162—164 °C; IR (KBr) 1655 cm^{-1} and 1630 (quinone).

Found: C, 58.69; H, 5.94; N, 5.79%. Calcd for $C_{24}H_{28}N_2O_8 \cdot H_2O$: C, 58.76; H, 6.17; N, 5.71%.

*4-[2-(2-Hydroxyethylamino)ethylamino]-1-(β-cellobiosyloxy)-9,10-anthracenedione (**27**).* Compound **27** was obtained in 43% yield from **21**; mp 198—206 °C; IR (KBr) 1645 cm^{-1} and 1620 (quinone).

Found: C, 53.79; H, 5.80; N, 4.26%. Calcd for $C_{30}H_{38}N_2O_{14} \cdot H_2O$: C, 53.88; H, 6.03; N, 4.19%.

*1-(2-Acetamido-2-deoxy-β-D-glucopyranosyloxy)-4-[2-(2-hydroxyethylamino)ethylamino]-9,10-anthracenedione (**28**).* Compound **28** was obtained in 53% yield from **22**; mp 186—189 °C; IR (KBr) 1650 cm^{-1} and 1625 (quinone).

Found: C, 57.24; H, 5.83; N, 7.31%. Calcd for $C_{26}H_{31}N_3O_9 \cdot H_2O$: C, 57.03; H, 6.08; N, 7.67%.

*1-(3-Acetamido-3-deoxy-β-D-glucopyranosyloxy)-4-[2-(2-hydroxyethylamino)ethylamino]-9,10-anthracenedione (**29**).* Compound **29** was obtained in 40% yield from **23**; mp 118—121 °C; IR (KBr) 1650 cm^{-1} and 1625 (quinone).

Found: C, 58.18; H, 5.88; N, 7.30%. Calcd for $C_{26}H_{31}N_3O_9 \cdot 1/2\,H_2O$: C, 57.99; H, 5.99; N, 7.80%.

*Acetylation of **24**, **25**, **26**, **27**, **28**, and **29**.* Acetylation was worked up with acetic anhydride and pyridine at room temperature.

*1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyloxy)-4-[2-(N-acetyl-2-acetoxyethylamino)ethylamino]-9,10-anthracenedione (**30**).* Compound **30** was obtained in 81% yield from **24** and showed a spot at R_f 0.54 on TLC in 1:1 (v/v) acetone–toluene; mp 85—98 °C; UV (EtOH) 206 (log ε, 4.43), 247 (4.61), 316 (3.74), 511 nm (3.89). ^1H NMR: δ=1.99 (6H, s, Ac× 2), 2.01 (3H, s, Ac), 2.15 (3H, s, Ac), 2.19 (3H, s, Ac), 7.09—7.29 (2H, m, H-2 and 3), 7.37—7.74 (2H, m, H-6 and 7), 7.94—8.23 (2H, m, H-5 and 8).

Found: C, 58.05; H, 5.53; N, 3.62%. Calcd for $C_{36}H_{40}N_2O_{15}$: C, 58.38; H, 5.44; N, 3.62%.

*1-(2,3,4-Tri-O-acetyl-6-deoxy-β-D-glucopyranosyloxy)-4-[2-(N-acetyl-2-acetoxyethylamino)ethylamino]-9,10-anthracenedione (**31**).* Compound **31** was obtained in 66% yield from **25** and showed a spot at R_f 0.53 on TLC in 1:5 (v/v) ethanol–toluene; mp 101—103 °C; UV ($CHCl_3$) 250 (log ε, 4.53), 276 (4.00), 320 (3.72), 516 nm (3.85). ^1H NMR: δ=1.22 (3H, d, $J_{5',6'}$=3.0 Hz, H-6'), 2.00 (6H, s, Ac×2), 2.02 (3H, s, Ac), 2.10 (3H, s, Ac), 2.15 (3H, s, Ac), 4.70—5.37 (4H, m, H-1',2',3', and 4'), 7.30 (1H, d, *J*=9.0 Hz, aromatic proton), 7.52 (1H, d, *J*=9.0 Hz, aromatic proton), 7.60—7.83 (2H, m, H-6 and 7), 7.97—8.30 (2H, m, H-5 and 8), 10.11 (1H, bs, aromatic NH).

Found: C, 60.07; H, 5.62; N, 3.89%. Calcd for $C_{34}H_{38}N_2O_{13}$: C, 59.82; H, 5.61; N, 4.10%.

*1-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyloxy)-4-[2-(N-acetyl-2-acetoxyethylamino)ethylamino]-9,10-anthracenedione (**32**).* Compound **32** was obtained in 97% yield from **26** and showed a spot at R_f 0.49 on TLC in 1:5 (v/v) ethanol–toluene; mp 192—194 °C; UV ($CHCl_3$) 249 (log ε, 4.71), 276 (4.18), 320 (3.88), 514 nm (4.04). ^1H NMR: δ=1.20 (3H, d, $J_{5',6'}$=6.0 Hz, H-6'), 2.03 (3H, s, Ac), 2.06 (6H, s, Ac× 2), 2.12 (3H, s, Ac), 2.18 (3H, s, Ac), 4.93—6.00 (4H, m, H-1',2',3', and 4'), 7.13—7.50 (2H, m, H-2 and 3), 7.56—7.98 (2H, m, H-6 and 7), 8.03—8.43 (2H, m, H-5 and 8), 10.10 (1H, bs, aromatic NH).

Found: C, 59.81; H, 5.66; N, 3.87%. Calcd for $C_{34}H_{38}N_2O_{13}$: C, 59.82; H, 5.61; N, 4.10%.

*1-(2,2',3,3',4',6,6'-Hepta-O-acetyl-β-cellobiosyloxy)-4-[2-(N-acetyl-2-acetoxyethylamino)ethylamino]-9,10-anthracenedione (**33**).* Compound **33** was obtained in 86% yield from **27** and showed

a spot at R_f 0.53 on TLC in 1:3 (v/v) ethanol–toluene; mp 162—164 °C; UV (EtOH) 247 (log ε, 4.64), 271 (3.99), 316 (3.72), 509 nm (3.95). ^{1}H NMR: δ=1.97 (3H, s, Ac), 1.98 (3H, s, Ac), 1.99 (3H, s, Ac), 2.01 (3H, s, Ac), 2.07 (3H, s, Ac), 2.08 (3H, s, Ac), 2.09 (3H, s, Ac), 2.14 (3H, s, Ac), 2.17 (3H, s, Ac), 7.30 (1H, d, J=6.5 Hz, aromatic proton), 7.50 (1H, d, J=6.5 Hz, aromatic proton), 7.60—7.78 (2H, m, H-6 and 7), 8.13—8.33 (2H, m, H-5 and 8), 10.11 (1H, bs, aromatic NH).

Found: C, 55.94; H, 5.58; N, 2.58%. Calcd for $C_{48}H_{56}N_2O_{23}$: C, 56.03; H, 5.49; N, 2.72%.

*1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyloxy)-4-[2-(N-acetyl-2-acetoxyethylamino)ethylamino]-9,10-anthracenedione (**34**).* Compound **34** was obtained in 70% yield from **28** and showed a spot at R_f 0.26 on TLC in 1:2 (v/v) acetone–chloroform; mp 179—182 °C; UV ($CHCl_3$) 250 (log ε, 4.70), 280 (4.17), 319 (3.96), 514 nm (4.00). ^{1}H NMR: δ=1.99 (3H, s, Ac), 2.03 (3H, s, Ac), 2.05 (9H, s, Ac×3), 2.13 (3H, s, Ac), 3.33—3.80 (6H, m, NHC$\underline{H}_2$-C$\underline{H}_2$N(Ac)C$\underline{H}_2$CH$_2$OAc), 3.87—4.47 (6H, m, H-2′,5′,6′, and CH$_2$C$\underline{H}_2$OAc), 4.87—5.33 (3H, m, H-1′,3′,4′), 7.03 (1H, bd, J=6.0 Hz, N$\underline{H}$Ac), 7.22 (1H, d, J=9.0 Hz, aromatic proton), 7.41 (1H, d, J=9.0 Hz, aromatic proton), 7.53—7.83 (2H, m, H-6 and 7), 7.90—8.30 (2H, m, H-5 and 8), 9.93—10.20 (1H, bs, aromatic NH).

Found: C, 58.25; H, 5.60; N, 5.49%. Calcd for $C_{36}H_{41}N_3O_{14}$: C, 58.45; H, 5.59; N, 5.68%.

*1-(3-Acetamido-2,4,6-tri-O-acetyl-3-deoxy-β-D-glucopyranosyloxy)-4-[2-(N-acetyl-2-acetoxyethylamino)ethylamino]-9,10-anthracenedione (**35**).* Compound **35** was obtained in 93% yield from **29** and showed a spot at R_f 0.52 on TLC in 1:3 (v/v) ethanol–toluene; mp 96—106 °C; UV (EtOH) 205 (log ε, 4.51), 247 (4.61), 514 nm (3.91). ^{1}H NMR: δ=1.81 (3H, s, Ac), 2.05 (6H, s, Ac×2), 2.15 (3H, s, Ac), 2.18 (6H, s, Ac×2), 3.43—3.76 (6H, m, NHC$\underline{H}_2$C$\underline{H}_2$N(Ac)-CH$_2$CH$_2$OAc), 4.01—4.69 (6H, m, H-3′,5′,6′ and CH$_2$C$\underline{H}_2$-OAc), 5.06—5.60 (3H, m, H-1′,2′, and 4′), 7.37—7.82 (3H, m, aromatic protons), 8.00—8.32 (3H, m, aromatic protons), 10.06 (1H, bs, aromatic NH).

Found: C, 58.30; H, 5.68; N, 5.80%. Calcd for $C_{36}H_{41}N_3O_{14}$: C, 58.45; H, 5.59; N, 5.68%.

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