Nuclear Alkylation of 1,4-Diaminoanthraquinone. Synthesis of Chiral 6,11-Diaminoanthracyclinones related to Ametantrone from Carbohydrates

Susan K. Mills,[a] David J. Mincher,*[a] and Gordon Shaw[b]

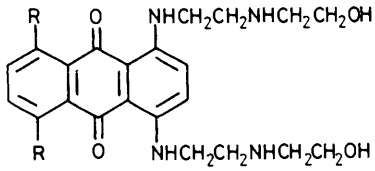
[a] *Pharmaceutical Chemistry, Heriot-Watt University, Edinburgh EH1 2HJ, U.K.*
[b] *School of Chemistry, University of Bradford, Bradford BD7 1DP, U.K.*

1,4-Diaminoanthraquinone [leuco derivative (**4**)] with aldehydes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in dimethyl formamide afforded (after aerial oxidation) 2-(hydroxyalkyl)-1,4-diaminoanthraquinones in good yields; reaction of (**4**) with 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylopentodialdo-1,4-furanose (**8**) gave, stereospecifically, the hydroxyglycityl derivative (**9**) which was readily transformed into the novel 6,11-diaminoanthracyclinone (**12**).

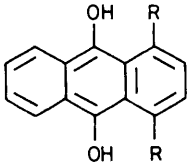
The anthracycline antibiotics, primarily adriamycin and daunomycin, have well established roles in the treatment of human cancer.[1] A new class of synthetic, relatively simple, aminoanthracenedione DNA-intercalating agents, superficially related to the anthracyclines, also possess outstanding antineoplastic activity, notably mitoxantrone (**1**)[2] and ametantrone (**2**).[3]

In recent publications[4,8,10] we have shown that novel anthracyclinones, *e.g.* (**5**), possessing a 1,4-dihydroxyanthraquinone chromophore and uniquely substituted at all four positions of ring A, may be synthesised from leucoquinizarin (**3**) and chiral templates derived from carbohydrates using a modification of the Marschalk reaction.[5] Anthracyclinone (**5**) and related compounds have shown interesting anti-tumour properties associated with the nature and stereochemistry of ring A substituents.[4] Subsequently, we have been interested in the preparation of compounds analogous to (**5**) containing the 1,4-diaminoanthraquinone chromophore. There have been no previous reports of anthracyclines possessing amino functions in the aglycone, but the 5-imino derivatives of adriamycin and daunomycin have been demonstrated to display less cardiotoxicity than the parent compounds.[6] We report here a general route to 6,11-diaminoanthracyclinones.

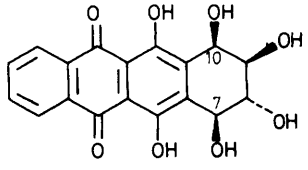
The Marschalk reaction of aldehydes with the leuco



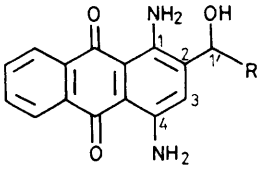
(1) R = OH
(2) R = H



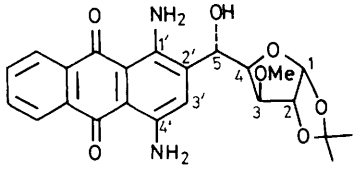
(3) R = OH
(4) R = NH_2



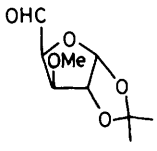
(5)



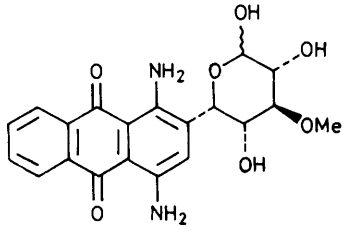
(6) R = Et
(7) R = C_6H_4F-*p*



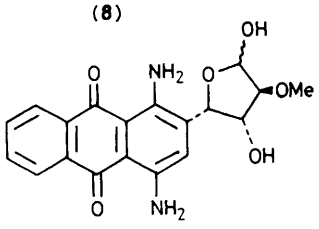
(9)



(8)



(10)



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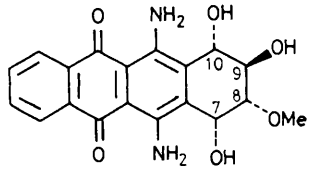
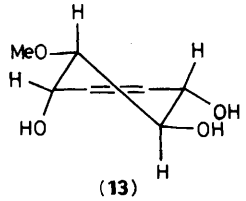


(12)



(13)

derivatives of 1-hydroxy-, 1-amino-, and 1,4-dihydroxyanthraquinones results in nuclear alkylation at the 2-position in high yields, but fails completely with leuco-1,4-diaminoanthraquinone (**4**) owing to quantitative conversion of (**4**) into quinizarin under the reaction conditions.[7]

We now report that hydroxyalkyl groups may be successfully introduced into the 2-position of leuco-1,4-diaminoanthraquinone by reaction with aldehydes (including aldehydo sugars). Thus, reaction of propanal (5 equiv.) with (**4**) in dry dimethylformamide (DMF) at room temperature under nitrogen in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[8] (3 equiv.), followed by aerial oxidation, gave 1,4-diamino-2-(1-hydroxypropyl)-anthraquinone (**6**) (needles from ethanol) in 48% yield, m.p. 211 °C.† Similarly reaction of (**4**) with 4-fluorobenzaldehyde gave crystalline (**7**) (needles from ethanol) in 69% yield, m.p. 230 °C.

Furthermore, under identical conditions, when treated with 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylopentodialdo-1,4-furanose (**8**),[9] (**4**) gave the hydroxyglycitylanthraquinone (**9**) in good yield (58%) in crystalline form (from ethanol) after a single chromatographic purification on silica gel (toluene–ethyl acetate eluant), m.p. 194 °C. The structure assigned to (**9**) was confirmed by elemental analysis, its i.r. [*e.g.* $\nu_{max.}$ 1380 cm^{-1} (CMe_2)], ^1H n.m.r. (200 MHz $CDCl_3$) [*e.g.* absence of signal for 2′-H; δ 2.8 (d, 5-OH), 3.67 (s, OMe), 4.96 (dd, 5-H), 6.92 (s, 3′-H); full assignment of all other protons], and desorption chemical ionisation (d.c.i.) mass [*e.g.* *m/z* 441 (M^+ + 1), 425 (M − Me)] spectra. By direct analogy with our earlier findings on the stereospecific condensation of leucoquinizarin with dialdofuranose sugars,[10,11] the spectroscopic data and homogeneity of compound (**9**) on t.l.c. in several solvent systems suggested that it was a single diastereoisomer. This was confirmed by ^1H n.m.r. spin-decoupling experiments (*e.g.* double irradiation of the signal for 5-H, centred at δ 4.96, produced collapse of the hydroxy proton doublet centred at δ 2.8 to a singlet). Although we have not established the chirality of the new asymmetric centre at C-5, it probably has the 5*S* configuration.[10,11]

Treatment of (**9**) with aqueous acetic acid readily removed the isopropylidene group to afford an almost quantitative yield of the crystalline D-xylopyranose derivative (**10**) (from ethanol), m.p. 205 °C. Reaction of (**10**) with sodium metaperiodate (1.1 equiv.) in aqueous methanol at room temperature gave the D-threose (**11**), m.p. 197 °C, quantitatively.

Compound (**11**) was reduced to the leuco form with powdered zinc in ethanol–acetic acid under nitrogen. The reduced product was subsequently treated with DBU in dry dimethylformamide at room temperature for 3 h, whereupon (after aerial oxidation) t.l.c. indicated complete disappearance of the starting material and the presence of a major product spot in addition to traces of other compounds. After a single chromatography on silica gel (toluene–ethyl acetate eluant), the major product (**12**) crystallised from propan-2-ol as violet platelets [m.p. 268 °C (decomp.); 68% yield from (**11**)]. Compound (**12**) was identified as the 6,11-diaminoanthracyclinone by its mass spectra [*e.g.* d.c.i. mass spectra showed *m/z* 371, (M^+ + 1); electronic impact (e.i.) mass spectra showed *m/z* 296, characteristic retro-Diels–Alder fragment: diagnostic for the tetracyclic system possessing hydroxy functions at C-7 and C-10] and by its 300 MHz ^1H n.m.r. spectrum [$(CD_3)_2SO$] [*e.g.* absence of signal for 3′-H, confirming cyclisation; 3 hydroxy proton signals (δ 2.82, 3.01, 3.13) all of which exchanged with D_2O; δ 3.46 (3H, s, OMe); full assignment of all other protons]. Furthermore, the spectroscopic data suggest that cyclisation to the anthracyclinone system had taken place stereospecifically to afford a pure chiral centre at C-7. Based on the values of coupling constants, the conformation of ring A is probably that shown in structure (**13**) [$J_{7,8}$ 3.7, $J_{9,10}$ 8.9, $J_{8,9}$ 10.4 Hz].

† Satisfactory analytical, t.l.c. and spectral data were obtained for all new compounds.

The reactions outlined clearly demonstrate that direct nuclear alkylation of 1,4-diaminoanthraquinone is possible by substantial modification of Marschalk conditions. This method offers advantages over previous indirect routes to such compounds based on the unreliable reaction of ammonia (or amines) with 2-alkylquinizarins.[12] In addition, successful intramolecular alkylation provides access to a wide range of novel chiral anthracyclinones.

The results of the biological evaluations of aminoanthracyclinone (**12**) and its derivatives will be reported elsewhere.

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